Psychiatric Drugs in Children and Adolescents

Basic Pharmacology and Practical Applications

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Editors
Manfred Gerlach, PhD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
Laboratory for Clinical Neurobiology and Therapeutic Drug Monitoring
University of Würzburg
Würzburg
Germany

Andreas Warnke, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
University of Würzburg
Würzburg
Germany

Laurence Greenhill, MD
NYS Psychiatric Institute
New York Presbyterian Hospital
New York, NY
USA

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Preface

This comprehensive book combines the scientific bases of psychopharmacology and the methods of the application of psychotropic drugs in the treatment of psychiatric disorders in children and adolescents. It is focused on up-to-date knowledge necessary for state-of-the-art practice in pediatric psychopharmacology. This volume that uses numerous tables, schemata, and illustrations is both a textbook and a reference book for drug treatment of psychiatric disorders in children, adolescents, and young adults. Our goal has been to achieve the most integrated flow possible throughout the book, to move seamlessly between basic psychopharmacology and the care of vulnerable, suffering children and adolescents.

Psychotropic drug therapy in childhood and adolescence is always part of an individual treatment program that is adapted to the personal development of the patient, which also includes psychoeducation, psychotherapy, physical interventions, and sociotherapeutic and rehabilitation measures. The experience gained from adult psychiatry is only partially transferable to pediatric psychopharmacology, because young patients have special pharmacokinetic and pharmacodynamic characteristics during their development as well as a significantly higher vulnerability to adverse drug reactions (ADRs). Thus pediatric psychopharmacology is "developmental psychopharmacology" and requires a specific curriculum.

When prescribing psychotropic drugs, there are a lot of questions being raised. Is there a pharmacological treatment indication for the present mental disorder? If so, what drugs are available for treatment? According to which criteria the selection of the active substance is to be taken? Is there empirical evidence for the efficacy of a drug? Before prescribing drugs what has to be taken into account diagnostically? What are the requirements for medical information and compliance? How to dose, how long and when can the desired effect and ADRs be expected? What drug interactions are to be observed in combination treatments? To what extent can the monitoring of the desired effect and ADRs be backed up in outpatient therapy? Is the medication in the acute phase of the disease different than used in the subsequent course of the disease? Are short-term effects and ADRs identical to those which can be expected during long-term treatment? When is a change of medication indicated and how is this change to be carried out? When is the discontinuance of the drug indicated and how should it be handled? What laboratory tests are required during an increase of the dose and during prolonged medication? How is the medication to be integrated into the overall design of the treatment? What are the legal and ethical issues that should be respected?

These are some of the questions that this book tries to answer by providing systematic drug-specific (Part II, Chaps. 4, 5, 6, 7, and 8) and disorder-specific or symptom-specific (Part III, Chaps. 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27) responses. The first part of the volume provides in a compact form a foundation of psychopharmacology upon which the rest of the book builds. The first chapter includes information on neurotransmitters and signal transduction pathways, and molecular brain structures as targets for psychotropic drugs. The second and third chapters focus on age-specific differences relevant to psychotropic drug actions, including variations in response or ADR profiles as well as regulatory issues pertaining to children and adolescents, and the pharmacotherapy in the outpatient setting.

The second and longest part reviews the current knowledge of the various psychotropic drug classes routinely used in children and adolescents. The chapters provide sufficient background material to understand more easily how these drugs work, and why, when, and in whom should they be used. For each drug within a class, data on potential mechanisms of action, clinical pharmacology, indications, dosages, and other related topics are reviewed.

In the third part, the disorder-specific and symptom-oriented medication is described and discerningly evaluated from a practical point of view, providing physicians with precise instructions on how to proceed. In this part, chapters are also included that address psychotropic drug therapy in children and adolescents with co-morbid intellectual disability and in psychiatric emergency. The chapters include the attention to the importance of careful diagnostic assessment, the therapeutic framework, the choice of pharmacotherapy, and treatment strategies. Each of these chapters is in turn related back to the underlying drug-specific principles previously presented.

Who will benefit from this book? Child and adolescent psychiatrists, psychotherapists and psychologists, pediatricians, general practitioners, psychologists, nurses, teachers, social workers, and students of medicine and pharmacy can all use it as a guide about medications and a guideline for applying them to help their patients. We intend to provide a current, multidisciplinary and comprehensive overview of this field of knowledge.

We would first like to thank the authors who, with great commitment and professional knowledge – complemented by a lively academic exchange – have contributed their clinical experience to this book. We want to thank Springer publishing house and in particular Ms. Barbara Zöhrer and Mr. Claus-Dieter Bachem for their trustful and fruitful cooperation in the formal design and the publication of the book.

We would like to thank Paul Foley for language editing and Christian von Grafenstein for proofreading the manuscript. We are grateful to the Verein zur Durchführung Neurowissenschaftlicher Tagungen for an unrestricted grant which has made possible the work on this volume. And finally, our special thanks go to our wives and families who have always lovingly supported our work.

We hope that this book finds positive feedback and would appreciate any advice on errors, suggestions for improvement and completion.

Würzburg, Germany — Manfred Gerlach, PhD
Würzburg, Germany — Andreas Warnke, MD
New York, NY, USA — Laurence Greenhill, MD

Contents

Contributors

Tobias Banaschewski, MD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Mannheim, Mannheim, Germany

Karin Egberts, MD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany

Christine M. Freitag, MD, MA Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Goethe-Universität Frankfurt am Main, Frankfurt, Germany

Manfred Gerlach, PhD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Laboratory for Clinical Neurobiology and Therapeutic Drug Monitoring, University of Würzburg, Würzburg, Germany

Laurence Greenhill, MD NYS Psychiatric Institute, New York Presbyterian Hospital, New York, NY, USA

Beate Herpertz-Dahlmann, MD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, RWTH Aachen University, Aachen, Germany

Tomasz A. Jarczok, MD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Goethe-Universität Frankfurt am Main, Frankfurt, Germany

Claudia Mehler-Wex, MD Department of Child and Adolescent Psychiatry and Psychotherapy, University of Ulm, Ulm, Germany

HEMERA-Klinik, Bad Kissingen, Germany

Veit Roessner, MD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, TU Dresden, Dresden, Germany

Marcel Romanos, MD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany

Aribert Rothenberger, MD Clinic for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany

Silke Rothenhöfer, MD Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Köln, Germany

Jürgen Seifert, MD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany

Benno G. Schimmelmann, MD University Hospital of Child and Adolescent Psychiatry, University of Bern, Bern, Switzerland

Klaus Schmeck, MD Child and Adolescent Psychiatry Hospital, University of Basel, Basel, Switzerland

Rudolf Stohler, MD Substance Use Disorders, Treatment and Research, Psychiatric University Hospital, Zurich, Switzerland

Regina Taurines, MD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany

Alexander von Gontard, MD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Saarland University Medical Center and Saarland University Faculty of Medicine, Homburg, Germany

Susanne Walitza, MD Department of Child and Adolescent Psychiatry, University of Zurich, Zurich, Switzerland

Andreas Warnke, MD Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany

Christoph Wewetzer, MD Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Köln, Germany

Gerhard A. Wiesbeck, MD University Hospital of Psychiatry, University of Basel, Basel, Switzerland

Part I

Essential Psychopharmacology

Fundamentals of Neuropsychopharmacology

1

Manfred Gerlach

Contents

1.1 Definitions

Pharmacology is the science concerned with the interactions between chemical substances and living creatures. A chemical substance that interacts with animals is termed a "pharmacological agent"; it is also referred to colloquially as a "drug." **Psychopharmacology** is the branch of neuropharmacology concerned more specifically with pharmaceutical agents that exert an effect on the central nervous system (CNS) and modify mental processes. Their specific purpose is the abolition or amelioration of psychopathological syndromes and mental disorders.

Pharmaceutical agents and poisons are pharmacological agents that at appropriate dosage either benefit or harm people. Pharmaceutical agents prevent, heal, ameliorate, or assist in the diagnosis of disease. "Pharmaceutical agent," in contrast to "pharmacological agent," is thus a judgmental term. Psychopharmaceutical agents are classified according to their intended therapeutic effect: antidepressants, anxiolytic-hypnotic, antipsychotic agents, psychostimulants, and

M. Gerlach, PhD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Laboratory for Clinical Neurobiology and Therapeutic Drug Monitoring, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: manfred.gerlach@uni-wuerzburg.de

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mood stabilizers. The classification of psychopharmaceutical agents is thus based upon the modulation of psychopathological symptoms, regardless of the different neuropsychiatric disorders in which they occur.

Chemically defined pharmaceutical agents are identified internationally by generic names (synonym: international nonproprietary name, INN) determined by the World Health Organization (WHO). These generic names are usually employed in scientific discussions and will also be generally used in this book. Pharmaceutical firms also employ legally protected brand names that are indicated by the symbol ® (for "registered trade mark").

Medications, **medicinal agents**, **or medicines** are pharmaceutical agents prepared with pharmaceutical technology in a form suitable for administration to patients (including tablets, injection solutions, salves); their production, distribution, and employment are subject to both national and international legal regulation. **Proprietary medical products** that are produced in advance and marketed to the end consumer in packaged form require registration approval (= licensing) by the appropriate local authority (in the USA: Food and Drug Authority [FDA]; in the European Union: European Medicines Agency [EMA]), which requires that the pharmaceutical quality of the medication, its therapeutic effectiveness, and its safety be demonstrated.

The effects of pharmaceutical agents vary between people. The action of an agent is the consequence of numerous, usually highly complex metabolic processes (Fig. 1.1) and results from the interaction between the effects of the pharmacological agent upon the animal (**pharmacodynamics**) and the effects of the animal upon the agent (**pharmacokinetics**). Pharmacokinetics encompasses the processes of resorption, distribution, and storage (together: invasion) as well as elimination by excretion and biotransformation. Pharmacodynamics comprises the interactions of the pharmaceutical agent with their molecular target structures in the animal as well as its concentration-dependent pharmacological effect (dose-response relationship).

The branch of pharmacology that investigates the effects of new or proprietary medicinal agents in humans is **clinical pharmacology**. It is concerned with the effects of medicinal agents in the broadest sense, thereby establishing the preconditions for rational pharmacotherapy and providing the bridge between experimental pharmacology and clinical medicine.

Clinical efficacy is defined as the degree of healing, improvement, amelioration, or prophylaxis of a disease that one can expect to achieve with a medicinal product in clinical studies. The **effect size** is the measure of efficacy (how much the group of patients improve), and it is calculated using the difference between the experimental group and the control group in the main measure of efficacy (the difference between the score at baseline and that at the end of the study) and dividing that value for the average of standard deviations. This measure is independent from the specific scales used and is not related to the number of samples studied, but it is sensitive to their heterogeneity. By convention (Cohen 1988), an effect size below or equal to 0.2 is considered insignificant, between 0.3 and 0.7 midsize, and higher than 0.8 significant. An epidemiological measure in assessing the **effectiveness** of a treatment with medication is the **number needed to treat** (Laupacis et al. 1988). Effectiveness is defined as the ability of an intervention to produce the desired beneficial effect in actual usage. The number needed to treat is the number of patients that need to be treated for one to benefit compared with a control in a clinical trial. It is calculated as the percentage difference between patients who respond to active drug treatment compared with placebo. The smaller the value of the number needed to treat, the greater the efficacy of treatment.

The specific elimination of a pathological condition with a medicinal product without also affecting other physiological functions is rarely possible. Almost all medicinal products are thus inevitably associated with the so-called side effects, that is, with effects other than the desired "main" effect. Since the term "side effect" is ambiguous, the term **adverse drug reaction** (ADR) is now generally employed. According to the definitions of the guideline on good pharmacovigilance practices (EMA 2012), an ADR (synonyms: adverse reaction, suspected adverse

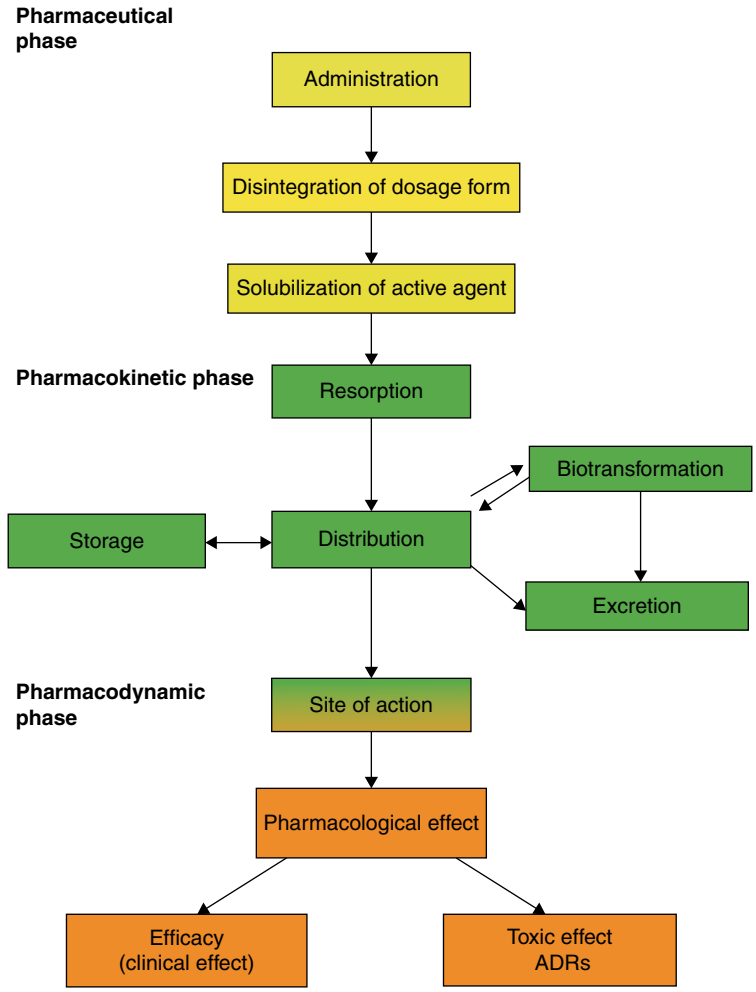

Fig. 1.1 Processes relevant to oral administration of a medication (adapted from Mutschler et al. 2008). *ADRs* adverse drug reactions

reaction, adverse effect, undesirable effect) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an ADR is at least a reasonable possibility. ADRs may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use (see Sect. 2.1.2), overdose, misuse, abuse, and medication errors. One can distinguish agent-specific, dose-dependent ADRs, explained by the pharmacological mode of action of the agent and thus foreseeable, and allergic reactions, largely dose independent and atypical for the pharmaceutical agent involved. Undesirable effects will be experienced by anyone at a sufficiently elevated dose (or overdose). On the other hand, the individual tolerance for a pharmacological agent varies markedly between people, so that there is always the possibility that even a dose tolerated by the majority of patients will elicit ADRs in others.

Both pharmacokinetics and pharmacodynamics are subject to significant developmental processes throughout infancy, childhood, puberty, and adolescence. Child and adolescent psychopharmacology makes it possible to distinguish special pharmacological features of these age groups (see Chap. 2), based on expectations of therapeutic efficacy upon normal development.

As each developmental stage possesses its own specific physiology and psychopathology, it is clear that pharmacotherapy must be related to the age of the child; the effect of an agent in an infant is not the same as in a 17-year-old youth. However, in long-term therapies and longitudinal investigations, maturational processes and unrecognized psychosocial factors may play a more significant role in the observed clinical changes than the action of the pharmaceutical agent.

Developmental psychopharmacology encompasses all the issues relevant to the employment of medicinal agents, including safety issues regarding its use in child and adolescent psychiatry. Special consideration is thereby accorded the specific developmental stage-related physiological and psychopathological characteristics of children and adolescents. This naturally also applies to the general circumstances in which pharmacological therapy is undertaken (see Chap. 2).

In order to reach their cellular and molecular targets in the CNS, psychopharmaceuticals must cross the so-called blood-brain barrier, a multilayered biological system that prevents the uncontrolled entry of blood components and substances carried in the blood. Once an agent accesses the CNS, it affects the transmission of information between neurons, or between neurons and other cell types by modifying the transmission pathways of chemical messengers (neurotransmitters), and normalizes dysfunctional signal transmission in various neurotransmitter systems in CNS disorders. Since as underlying mechanisms and many aspects of the brain function are not yet – or only partly – understood, the effects of many psychopharmaceuticals cannot be completely explained at the cellular and molecular levels. Furthermore, the causes of psychiatric disorders are in many cases unknown; pharmacological agents that effectively treat such disorders, or at least ameliorate serious symptoms, have nevertheless been discovered.

In the following two sections, the principles of neurotransmission and important neurotransmitter systems will be concisely presented. These are very important for understanding the molecular sites of action for psychopharmaceuticals (see Sect. 1.4). Readers with a particular interest in general and specific issues of pharmaceutical mechanisms and fundamental neuroscience are referred to textbooks summarized under further reading.

1.2 Principles of Neurotransmission

Neuroscience has made significant progress in the past three decades, particularly with regard to the elucidation of the brain structures and functions involved in the so-called mental activities, including consciousness. One outcome of this research is that the molecular sites of action and mechanisms underlying the effects of psychopharmaceuticals are now much better understood. The fundamental components of the brain are individual but interconnected specialized cells, including nerve cells (neurons) and nonneuronal cells (glia cells). There are approximately 1,000 billion cells in the CNS, of which 100 billion are nerve cells – this astronomic number is of the same order of magnitude as the number of stars in the Milky Way – with an incredible variety of different functions, forms, and molecular components. Although Rudolf Virchow recognized as early as 1846 that the nervous system essentially consists of two fundamentally different cell types, the nerve and glia cells, knowledge regarding the glia is today still quite limited in comparison with that concerning neurons. This is surprising, given that the vertebrate nervous system includes approximately 10–50 times as many glia as nerve cells, thereby constituting more than half the volume of the nervous system. This dearth of knowledge has resulted in a **nervous system concept** clearly dominated by the neurons, and in which the role of the glia cells is underappreciated. Two families of vertebrate glia cells are distinguished according to their size, the macroglia and the microglia. The macroglia include the astrocytes and oligodendrocytes of the CNS, and the Schwann cells of the peripheral nervous system, among others.

The neurons, unlike other vertebrate cell types, possess the unique capacity to exchange

information, quickly and precisely, over long distances. Each neuron is both a reception and transmission unit. The dendrites and the cell body (perikaryon) of the neuron present on their outer surface special proteins (neuroreceptors) that convert incoming signals into excitatory (depolarizing) or inhibitory (hyperpolarizing) membrane potentials. The spatial and temporal integration of these signals determines whether an action potential is triggered. Following this information processing step, the information to be conveyed is coded as a series of action potentials that is transmitted along the axon. In contrast to most other cell types, neurons have specific contacts to numerous other target cells, including other nerve cells and glia, but in other cases muscle or endocrine cells.

1.2.1 Synapses as Sites of Information Transmission

The synapse is the site at which information is transmitted between neurons. The synapse consists of three essential elements: the presynaptic nerve terminal, the postsynaptic receiving cell, and a contact zone. Each neuron conveys signals via an average of 1,000 synaptic connections, and receives signals from considerably more. The human brain, containing, as noted, approximately 100 billion neurons, thus includes around 10^{14} synapses. Despite this immense number of connections, synaptic transmission throughout the entire nervous system employs only **two significant mechanisms**: electrical and chemical synaptic transmission.

Chemical and electrical synapses differ morphologically. At chemical synapses there is no cytoplasmic connection between the nerve cells; the neurons are instead separated by a narrow gap (15–25 nm), the synaptic cleft. In contrast, electrical synapses exchange information directly between the cytoplasm of the two cells via special ion channels in the pre- and postsynaptic cell membranes, the gap junctions. Electrical information transmission is by its nature rapid and stereotypic. Electrical synapses primarily serve to conduct simple depolarizing signals further; alone they can neither exert inhibitory effects nor cause long-lasting changes in sensitivity. Chemical synapses, on the other hand, can convey both inhibitory and excitatory signals. They are thus more flexible than electrical synapses and therefore generally elicit more complex changes in behavior. Because the sensitivity of chemical synapses can be modulated, they exhibit a plasticity that is a prerequisite for memory and other higher cerebral functions. Chemical synapses can amplify neuronal signals, so that even a small presynaptic nerve ending can significantly alter the potential of a large postsynaptic cell; this is not possible at electrical synapses. As nerve impulses are transmitted in only one direction at chemical synapses, these synapses also function as signal rectifiers.

Information transmission between CNS neurons occurs primarily via chemical synapses. The mechanisms of chemical synaptic transmission are the basis for the mental functions of the brain, including intellect, consciousness, perception, emotion, motor control, memory, and learning.

1.2.2 Definition of a Neurotransmitter

Information transmission at chemical synapses is mediated by low molecular weight messengers, the (neuro)transmitters. According to **Dale's principle**, each neuron synthesizes only a single neurotransmitter; neurons are therefore classified according to the transmitter employed. A neuron that uses dopamine as its neurotransmitter, for example, is termed a dopaminergic neuron. Dale's principle, however, is no longer entirely valid, as it is now known that several neurotransmitters can be used by the one neuron, often a classical neurotransmitter and one or more neuropeptides.

The initial proof that a chemical substance is capable of mediating the transfer of an electrical impulse across the synaptic cleft has been provided in 1921 by the Graz pharmacologist and physiologist Otto Loewi, who demonstrated that the contraction frequency of the heart was centrally modulated by the vagus nerve. Loewi required a further five years to demonstrate that

the inhibitory chemical substance released by the vagus was identical with acetylcholine (ACh). Since this time numerous further substances that act as neurotransmitters have been discovered, but it has never been possible to achieve analogous results in brain and spinal tissue. As a result, concepts concerning neurotransmitters have been subject to constant change according to novel insights in neurobiology and receptor pharmacology.

In accordance with Loewi's findings, a **neurotransmitter** is a metabolic product that is released by a stimulated neuron into a synapse and exerts specific effects on a cell in the effector organ. Although it would appear straightforward to employ this definition to classify a chemical substance identified in the brain as a transmitter, it is quite difficult to prove in practice. This is partly because the anatomic complexity of the CNS renders extremely difficult the selective electrical stimulation of a homogenous group of neurons. Furthermore, the analytic techniques available are not sufficiently sensitive in order to quantitatively assess the local presynaptic release of potential neurotransmitters. Current analytic techniques permit the measurement of concentrations at the femtomolar level (10^{-15} M), but this is still insufficient to quantify the amount of presynaptically released neurotransmitters. One femtomole of a transmitter contains about 600 million molecules; but a presynaptic action potential at each nerve terminal elicits the release of only a few hundred synaptic vesicles, each of which contains around 10,000 transmitter molecules. The analytic problems are exacerbated by the fact that a neuron has about 1,000 synaptic connections on different parts of the nerve cell and is also part of a complex network of neuronal regulatory circuits. This all renders it practically impossible to selectively measure the release of specific neurotransmitters. Theoretically, it is possible that stimulation of a defined neuronal system does not elicit measurable neurotransmitter release, as it can be suppressed by feedback inhibition via a presynaptic autoreceptor.

In the face of all these problems, it is difficult to prove the neurotransmitter function of even those molecules generally recognized as neurotransmitters. For this reason, **four criteria** for the definition of a metabolite as a neurotransmitter were established:

- The metabolite is synthesized in neurons (**localization**). In postmortem investigations, for instance, characteristic regional distributions of metabolites regarded as neurotransmitters are found. Figure 1.2 depicts, as an example, the regional distribution of dopamine in the human brain.
- The metabolite is present in the presynaptic terminal at elevated concentrations and is released by a Ca^{2+}-dependent process in sufficient quantities to elicit a specific effect in the postsynaptic neuron or effector organ (**release**).
- Exogenous administration of the metabolite should elicit in a dose-dependent manner the same effect as the endogenously released neurotransmitter: that is, the same receptor ion channels or intracellular signal transduction cascades should be activated in the postsynaptic cell (**mimicry**).
- There must exist one or more specific mechanisms for removal of the metabolite from the synaptic cleft (**inactivation**).

1.2.3 Neurotransmitters

The most important CNS neurotransmitters are listed in Table 1.1. With two exceptions (adenosine triphosphate [ATP] and ACh), they fall into two groups: biogenic amines and amino acids. Under physiological conditions, all biogenic amines occur as small charged molecules and are synthesized from precursor molecules derived from intermediate metabolism. As with other intermediate metabolic pathways, the synthesis of these neurotransmitters is almost entirely catalyzed and regulated by cytosolic enzymes, whereby these are usually characteristic for a particular neuron type and are normally not present in others (Table 1.1).

1.2.4 Putative Neurotransmitters

Some substances that do not fulfill all four criteria for neurotransmitters are referred to as putative neurotransmitters or neurotransmitter candidates

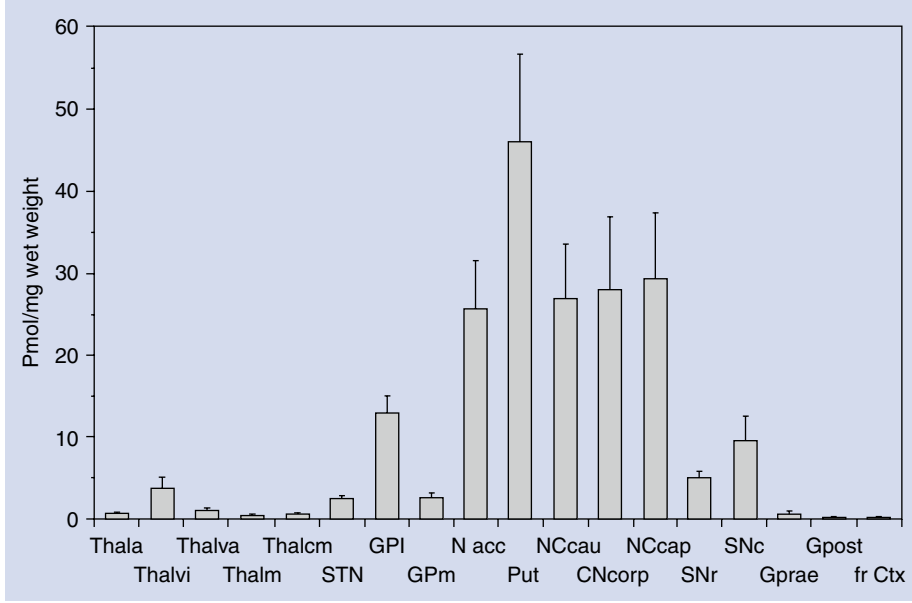

Fig. 1.2 Regional distribution of dopamine in postmortem human brain (from Gerlach et al. 1996). Mean values ± SEM are shown. fr Ctx frontal cortex, GPl globus pallidus pars lateralis, GPm globus pallidus pars medialis, Gprae gyrus praecentralis, Gpost gyrus postcentralis, N acc nucleus accumbens, NCcap caput nucleus caudatus, NCcau cauda nucleus caudatus, CNcorp corpus nucleus caudatus, Put putamen pars anterior, SNc substantia nigra pars compacta, SNr substantia nigra pars reticulata, STN nucleus subthalamicus, Thala nucleus anterior thalami, Thalcm nucleus centromedianus thalami, Thalm nucleus medialis thalami, Thalva nucleus ventralis anterior thalami, Thalvl nucleus ventralis lateralis thalami

Table 1.1 Neurotransmitters and their most important biosynthetic enzymes

Neurotransmitter	Enzyme
Acetylcholine	Choline acetyltransferase (specific)
ATP and metabolites	Energy metabolism: ATP synthase (specific path not known)
Biogenic amines	
Dopamine	Tyrosine hydroxylase (specific)
Noradrenaline	Tyrosine hydroxylase and dopamine β-hydroxylase (specific)
Adrenaline	Tyrosine hydroxylase, dopamine β-hydroxylase, and phenylethanolamine *N*-methyltransferase (specific)
Serotonin	Tryptophan hydroxylase (specific)
Histamine	Histidine decarboxylase (specificity uncertain)
Amino acids	
Glutamate	General metabolism (specific path unknown)
GABA	Glutamic acid decarboxylase (probably specific)
Glycine	General metabolism (specific path unknown)

ATP adenosine triphosphate, *GABA* γ-aminobutyric acid

(Table 1.2), the most important of which are the neuroactive peptides (neuropeptides). Some neuropeptides actually satisfy the four criteria, but are nonetheless classified only as neurotransmitter candidates because their metabolism and release mechanisms differ from those of the classical neurotransmitters. Neuropeptides occur in some neurons at relatively high

Table 1.2 Examples of putative neurotransmitters

Neuroactive peptides
Gastrins (gastrin, cholecystokinin)
Insulins (insulin, insulin-like growth factors I and II)
Neurohypophyseal peptides (vasopressin, oxytocin, neurophysins)
Opioids (enkephalins, dynorphin, β-endorphin)
Secretins (growth hormone releasing factor [GHRH], somatoliberin)
Somatostatins
Tachykinins (substance P, substance K, neurokinin A)
Other low molecular weight metabolites
Aspartate
Carbon monoxide (CO)
L-3,4-Dihydroxyphenylalanine (L-DOPA)
Phenethylamine
Nitric oxide (NO)

concentrations, but are synthesized only in the cell body, as ribosomes are required for polypeptide synthesis. Low molecular weight neurotransmitters, in contrast, can be synthesized locally in the synaptic nerve terminal. Precursors of the peptide transmitters are produced on free polysomes in the cell body, but are only distributed throughout the entire neuron by slow axoplasmic transport in the so-called vesicles (bubble-shaped, membrane-bound structures, visible only under the electron microscope). Some neuropeptides can also be released by a Ca^{2+}-dependent mechanism into the synaptic cleft, but this probably differs quite significantly from the release of low molecular weight neurotransmitters: sustained, rapid release of the latter is possible because the vesicles can be very quickly replenished with neurotransmitter synthesized in the nerve terminal or removed from the synaptic cleft by specific transport mechanisms (see the following section); neuropeptides, in contrast, must be freshly produced in the cell body and again transported to the synapse before they can be released.

A number of short chain peptides are pharmacologically active in the CNS, divided into families according to analogies in their amino acid sequences (Table 1.2). Neuropeptides can be inhibitory, excitatory, or both, depending upon the target neuron with which they interact. Some peptides, such as angiotensin and gastrin, were previously identified as hormones with known targets outside the brain or as products of neuroendocrine secretion (e.g., oxytocin, vasopressin, somatostatin). These peptides can act as chemical transmitters in certain tissues, quite distinct from their hormonal function, when released in sufficient proximity to their target receptors.

Nitric oxide (NO), a gaseous radical, was initially identified as the physiological messenger EDRF (endothelial-derived relaxing factor) that regulates the tone of vascular tissue and macrophage function. Subsequent investigations demonstrated that NO is also produced in the brain, and it has since been established that it acts in the CNS as a nonclassical neurotransmitter that modulates glutamatergic neurotransmission. NO activates intracellular guanylate cyclase by binding to its heme groups, so that guanosine triphosphate (GTP) is converted to the intracellular hormone cyclic guanosine monophosphate (cGMP).

Carbon monoxide (CO) is another gaseous neurotransmitter, produced by heme oxygenase-2, and similarly acts as an activator of guanylate cyclase. Gaseous neurotransmitters do not conform to classical concepts of vesicular release and recognition by specific neuroreceptors in the plasma membrane of the receptive nerve cell. In contrast to classical neurotransmitters, they can also act in a retrograde fashion and over longer distances; also in contrast to the classical transmitters, the short-lived molecule NO requires no specific inactivation mechanism.

1.2.5 Individual Stages of Synaptic Chemical Transmission

The arrival of an action potential triggers the Ca^{2+}-dependent release of neurotransmitter from the presynaptic nerve terminal in discrete amounts (quanta). The neurotransmitter then diffuses across the synaptic cleft and binds specific neuroreceptors, located in the membrane of the adjacent postsynaptic receiving cell (Fig. 1.3). This binding leads directly either to a change in electrical potential across the postsynaptic membrane (**ionotropic receptors**) or to a guanosine triphosphate protein (G protein)-mediated

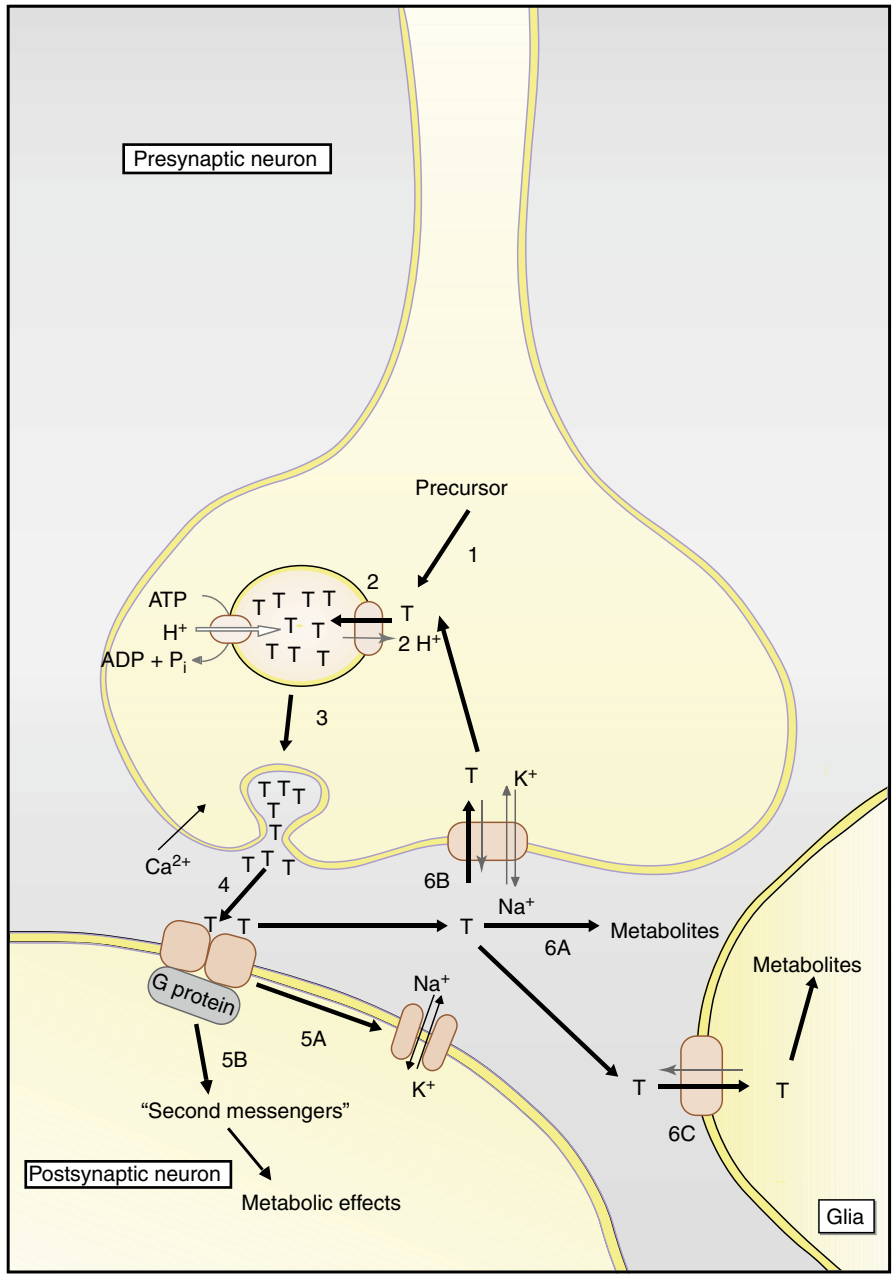

Fig. 1.3 Schematic depiction of the individual steps of signal transmission across a chemical synapse. T, neurotransmitter. (*1*) Synthesis of neurotransmitter in the cytoplasm of the nerve terminal. (*2*) Uptake by specific transport systems and storage of neurotransmitter in synaptic vesicles. Preparation for release; concentration and protection from further metabolism. (*3*) Depolarization-induced, Ca^{2+}-dependent fusion of the vesicle with the presynaptic membrane; release of neurotransmitter into the synaptic cleft (exocytosis). (*4*) Diffusion to postsynaptic membrane. (*5*) Recognition and binding of neurotransmitter by a specific receptor. The consequence of the formation of a reversible neurotransmitter-receptor complex, depending upon receptor type, is either a direct effect upon the permeability of the postsynaptic membrane for specific ions (*5A*: should the resulting depolarization exceed a certain threshold value, an action potential is triggered; that is, the chemical signal is again converted into an electrical nerve impulse) or an intracellular metabolic change, that is, G protein-mediated activation of intracellular signal transduction cascades (*5B*). (*6*) Inactivation of the neurotransmitter in synaptic cleft by enzymatic degradation (*6A*), reuptake into the presynaptic neuron via specific transport proteins (*6B*), or uptake into glia cells (*6C*)

activation of intracellular signal transduction cascades (**metabotropic receptors**) that can indirectly also elicit in a change in electrical potential across the postsynaptic membrane (Fig. 1.4). Ionotropic receptors all produce fast (<10 ms) synaptic conductances, whereas metabotropic receptors influence synaptic transmission over a slower timescale (sub-seconds to minutes). The neuroreceptors are the sites of action for psychopharmaceuticals. The binding properties of receptors thereby provide the basis for the action and specificity of pharmacological agents (see Sect. 1.4.2.1).

1.2.6 Intracellular Signal Transduction

Signal transduction refers to the entire complex mechanism of signal transmission from the membrane-bound receptor to the cytoplasm and cell nucleus by means of various biochemical reactions, whereby intracellular metabolic pathways are modified (hence, the term metabotropic receptors) and extracellular signals are not simply relayed, but also amplified, classified, and integrated. Only a few signal transduction pathways have thus far been identified: the processes of intracellular signal transduction appeared to be markedly similar for a range of different neuroreceptors.

The **family of metabotropic receptors** includes the α- and β-adrenergic receptors; dopaminergic receptors; muscarinic ACh receptors; the $GABA_B$ receptor; subtypes of the glutamate, serotonin, and purine receptors; and receptors for neuropeptides. It also includes the so-called orphan receptors, receptors for which the endogenous agonists are unknown. In sensory systems, G protein-coupled receptors also mediate the signal transmission initiated by extracellular signals, such as photons, and gustatory or odorous substances (odorants), and they serve in nonneuronal cell types as receptors for different proteinaceous hormones (such as the cytokines and growth factors).

G protein-coupled receptors possess seven coiled transmembrane segments, for which reason they are also termed heptical or serpentine receptors. This receptor type is generally coupled with intracellular, membrane-bound heterotrimeric G proteins (Gα, Gβ, Gγ) that activate or inhibit the actual effector proteins (ion channels or enzymes) and mediate a variety of cellular processes (Fig. 1.5). Through activation of enzymes, such as adenylate cyclase and phospholipase C, the synthesis of diffusible **second messengers**, including cyclic adenosine 3′,5′-monophosphate (cAMP), diacylglycerol, and inositol-1,4,5-triphosphate (IP_3), is increased (Fig. 1.6). These second messengers can also regulate ion channels or activate specific protein kinases that phosphorylate serine and threonine residues on further target proteins, once again including ion channels, thereby altering their activity and function. Through the intracellular production of second messengers, such as IP_3, **third messengers**, such as Ca^{2+}, can in turn be released from intracellular storage proteins. Neurotransmitter receptors are, however, also linked via protein kinases with gene-regulatory processes in the cell nucleus, as these kinases are able to move from the cytoplasm into the cell nucleus, where they phosphorylate transcription factors and in this manner regulate gene expression (Fig. 1.7).

By means of these complex signal transmission pathways, various receptive cell types have the possibility to respond to similar extracellular signals with completely different reactions, utilizing a varying repertoire of receptors, G proteins, and effectors. A receptive cell possesses considerably more G protein than receptor molecules, and a single receptor molecule can therefore activate several G proteins during the period in which it is bound to its ligand: following dissociation of the activated G protein from the ligand-receptor complex, it can activate further Gα proteins. A single bound neurotransmitter molecule can thus contribute to the activation of several G proteins. The ligand-receptor complex functions as a catalyst and is in certain respects comparable with an enzyme. As the effectors regulated by G proteins are also enzymes (apart from the ion channels), this multiple catalytic mechanism is an extremely efficient signal

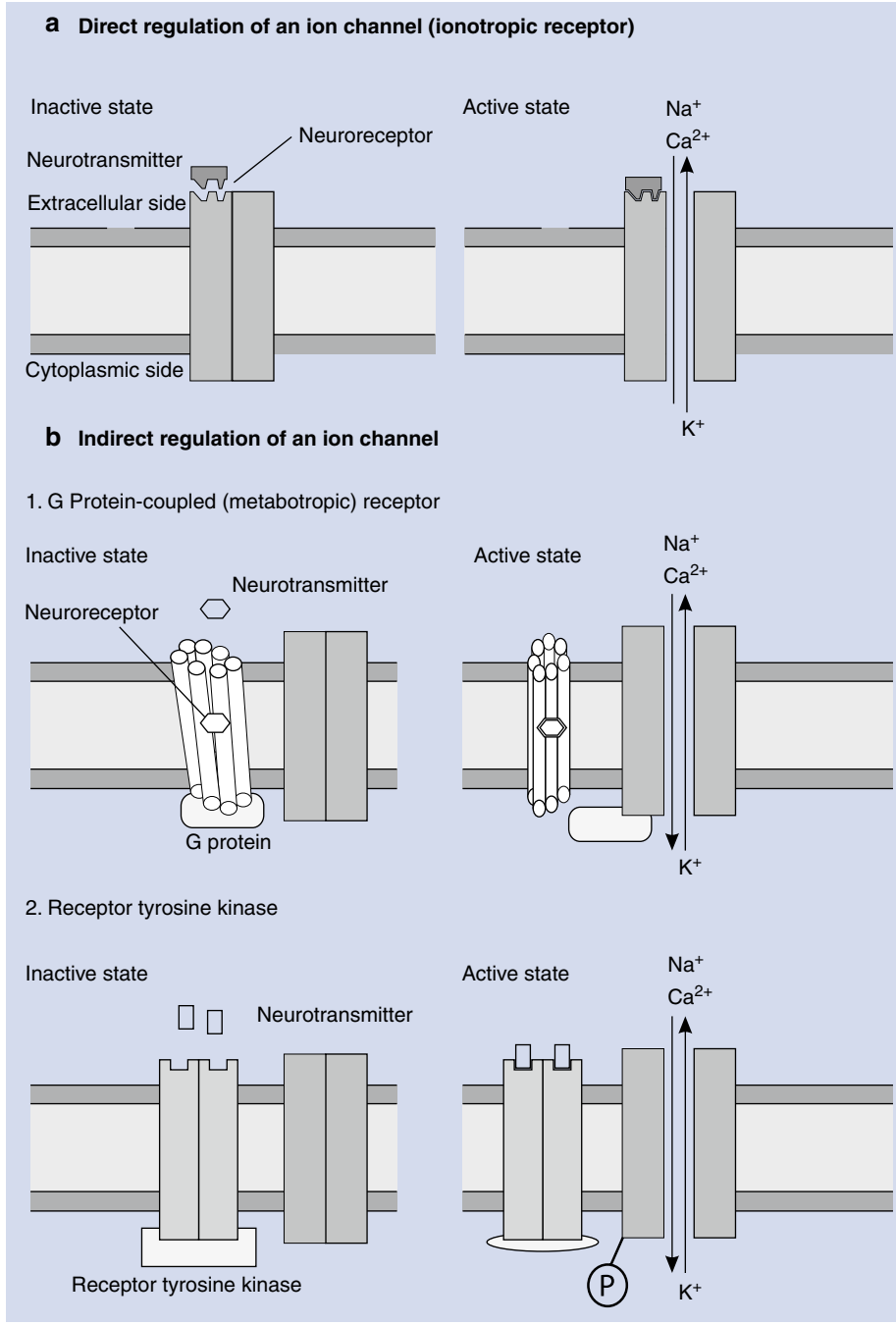

Fig. 1.4 Classification of neuroreceptors according to their coupling with ion channels. (**a**) Ligand-gated ion channels (ion channel receptors, ionotropic receptors). The receptor on the exterior of the neuronal membrane and the ion channel in the membrane are components of the same protein. Ion channel receptors usually operate rapidly and typically mediate synaptic communication between nerve cells. (**b**) Receptors that regulate ion channels indirectly are divided into two major families: 1. G protein-coupled receptors initiate metabolic reactions and are therefore termed metabotropic receptors. They regulate ion channels and other effectors indirectly by activating a G protein, which in turn activates a second messenger enzyme. By means of metabotropic receptors on their target cells, neurons can elicit regulatory effects of longer duration, but also permanent functional changes through specific modulation of gene expression. 2. Receptor tyrosine kinases indirectly modulate the activity of ion channels via a cascade of protein phosphorylations, commencing with the autophosphorylation of their own tyrosine residue

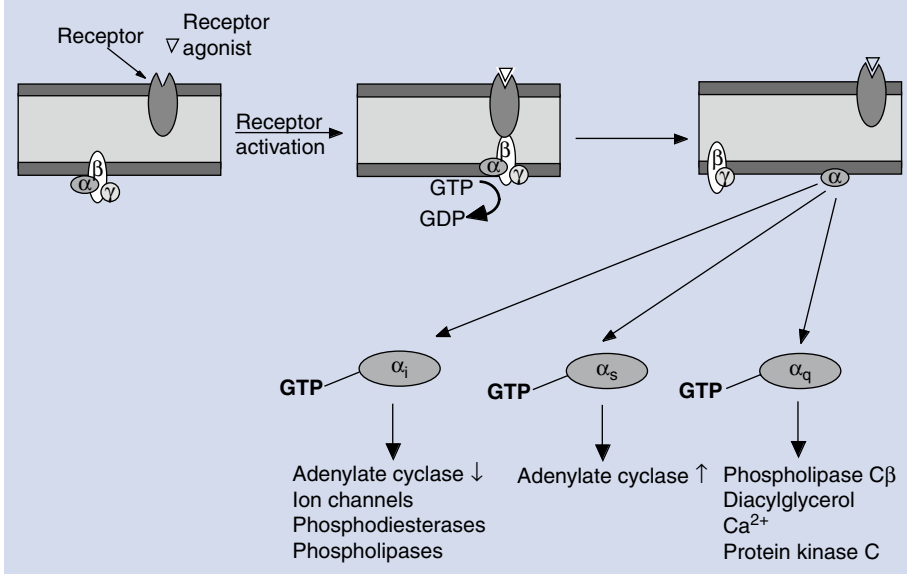

Fig. 1.5 Possible interactions between G proteins, the receptors with which they are coupled, their agonists, and various signal transduction pathways (based on Dean 2002). G proteins exist in two conformations: an inactive state, in which the α-subunit has bound guanosine 3′,5′-diphosphate (GDP) and is associated with the βγ-subunit; and an active state, in which the α-subunit has bound guanosine 3′,5′-triphosphate (GTP) and is not associated with the βγ-dimer. The alternation of the G protein between these two conformations is the basis of the GTPase or G protein cycle. When a neurotransmitter binds its receptor, the G protein binding site for GDP changes from a high-affinity, closed conformation to a low-affinity, open form, the result of which is the release of GDP from the α-subunit; as the cellular concentration of GTP is significantly higher than that of GTP, GDP is exchanged for GTP. This step is the rate-limiting step of the G protein cycle. The exchange also occurs to a limited extent even in the absence of receptor stimulation, but in these conditions, the process is so slow that 99 % of G protein is in the inactive form. Only the ligand-receptor complex functions as the catalyst that drastically accelerates GDP/GTP exchange and thus increases the amount of active G protein: with maximal stimulation of all receptors, as much as 60 % of G protein can be in the active conformation. α_i inhibitory α-subunit of the G protein G_i, which is coupled with acetylcholine and noradrenaline receptors, α_s stimulatory α-subunit of the G protein G_s, coupled with adrenaline and noradrenaline receptors, α_q -subunit of the G protein G_q, coupled with acetylcholine and noradrenaline receptors

amplifier, so that even a few neurotransmitter molecules can elicit an effective cellular response. The greatest amplifier effect has been measured in the photoreceptor cells of the retina: a single photon-stimulated rhodopsin molecule suffices for the activation of around 3,700 Gα proteins, so that the energy of a lone absorbed photon elicits for 1 s a change in current of 1 pA (10^{-12} A), corresponding to a 100,000-fold amplification. For neurons, the ratio of bound ligand to activated G proteins lies in the range 1:10 to 1:20.

As one receptor can activate several Gα proteins and the number of the latter greatly exceeds that of the receptors, maximum effector activation can be reached when only a fraction of the receptors have bound ligand. The result is that the concentration of agonist that achieves half the maximum effect (EC_{50}) can be significantly lower than the actual binding constant of the receptor for the ligand (K_D, see Sect. 1.4.2.1). It is thus possible for the signal-receiving cell to regulate its sensitivity to the transmitter by modulating the number of receptors.

Receptors, G proteins, and effectors constitute a complex information processing network in the receiving cell (Fig. 1.6). Inhibitory and stimulatory extracellular signals can be integrated via G proteins. Neurotransmitters or hormones that bind different receptors can activate the same effector if their receptors are coupled with the

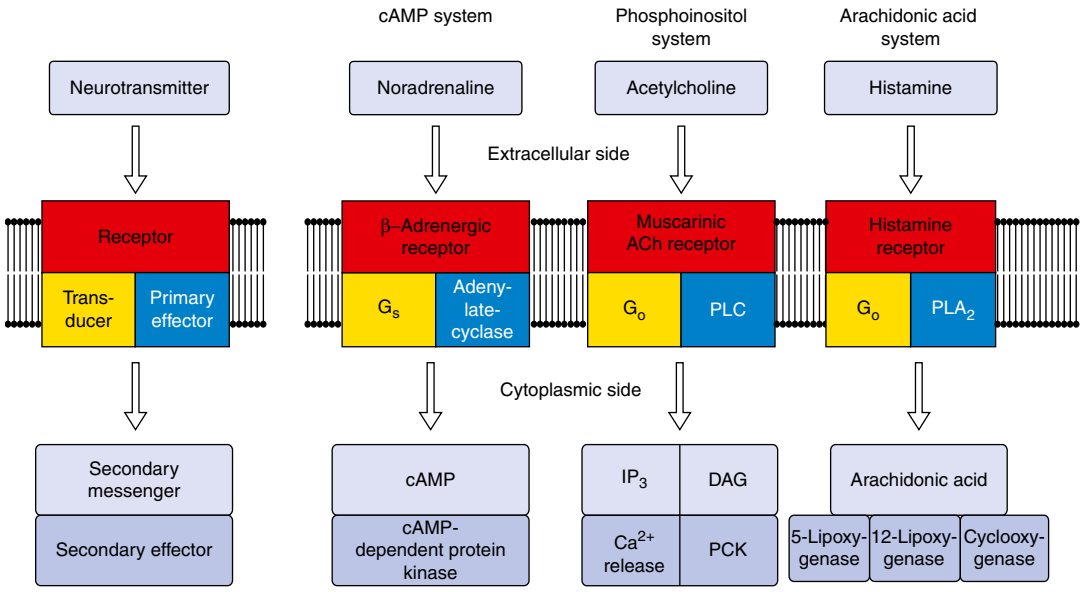

Fig. 1.6 Schematic overview of G protein-activated intraneuronal second messenger pathways (modified from Kandel et al. 1996). The cases depicted here all follow a common sequence of individual steps, summarized on the left side of the diagram. By binding a G protein-coupled receptor, neurotransmitters activate enzymes that synthesize a second messenger, which in the second step activates a secondary effector. In the first example, the secondary messenger cAMP (cyclic adenosine 3′,5′-monophosphate) is produced by activation of adenylate cyclase; the G protein involved is termed G_s because it stimulates adenylate cyclase. Other receptors activate the G protein G_i, which inhibits adenylate cyclase. In the second example, neurotransmitter activates a further specific G protein, G_o, which then stimulates phospholipase C (PLC). This enzyme catalyzes production of the second messengers diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP_3). In the following step, IP_3 liberates a further second messenger, Ca^{2+}, from intracellular storage proteins. In the final case, the arachidonic acid signal pathway is stimulated by activation of phospholipase A_2 (PLA_2). Three of the key enzymes in the transduction path are 5- and 12-lipoxygenase and cyclooxygenase

same G protein subtype. It has been shown in adipocytes, for instance, that five different receptors activate adenylate cyclase via $G\alpha_s$. Activation of an effector by different signals can also be achieved where the effector is regulated by several G protein subtypes. Phospholipase C, for example, can be activated by at least five different Gα subtypes that receive signals from different receptors.

A G protein subtype can, however, respond to different receptor-mediated signals with varying sensitivity. Signals that reach the cell via one receptor type can elicit multiple cellular effects through activation of several different effectors. This can occur where a G protein subtype is coupled with several effectors; in this manner, $G\alpha_s$ regulates not only adenylate cyclase but also Ca^{2+} channels. On the other hand, as discussed previously, a receptor also has the possibility of activating several Gα proteins after binding a neurotransmitter; they need not necessarily be Gα proteins of the one subtype, but rather G proteins coupled with a variety of effectors.

1.2.7 Second and Third Messengers

In contrast to the G protein-coupled receptors, the effector proteins are a quite heterogeneous group, possessing no common structural characteristics. The known effectors are either enzymes that synthesize or catabolize second messenger molecules or ion channels that alter the cellular membrane potential or regulate the concentration of Ca^{2+}, which also acts as a second messenger. The same G protein subtype can regulate both an

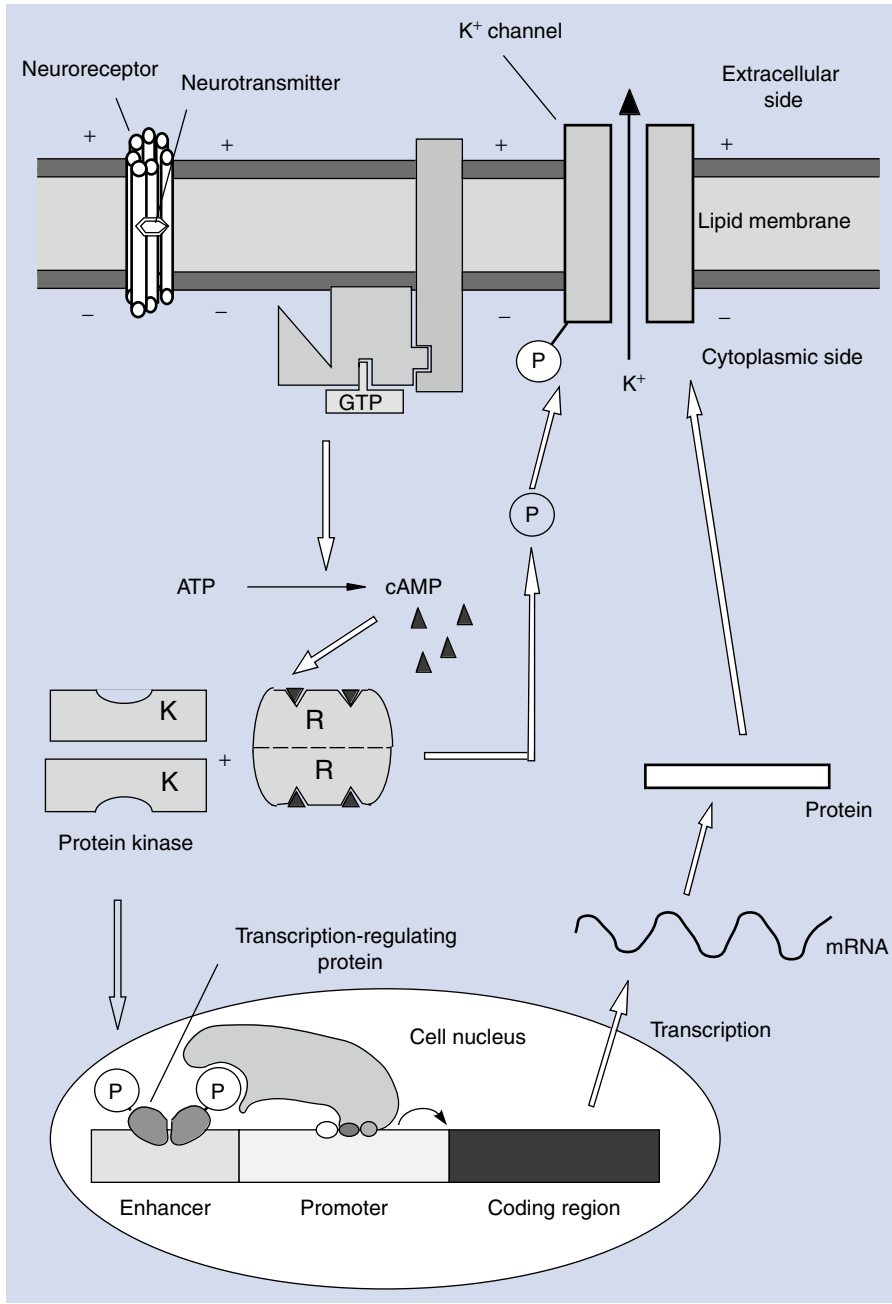

Fig. 1.7 Activation of a G protein-coupled receptor can elicit synaptic reactions with differing time courses (modified from Kandel et al. 1996). In this example, the binding of a neurotransmitter activates the cyclic adenosine 3′,5′-monophosphate (cAMP) system, leading to stimulation of the cAMP-dependent protein kinase A, which in turn phosphorylates a K^+ channel. The resultant change in synaptic potential modifies neuronal excitability for several minutes. Following repeated receptor stimulation, however, the cAMP-dependent protein kinase also phosphorylates one or more transcription-regulating proteins that induce gene expression of a protein that causes longer-term alterations of the channel. It is consequently closed for longer periods, the altered excitability of neuronal excitability persist for days or even weeks. R, K, regulatory, or catalytic subunit of the protein kinase

enzyme and an ion channel, so that G protein activation can simultaneously elicit changes in membrane permeability and in the concentration of intracellular secondary signal molecules.

The number of substances known to function as secondary messengers in synaptic signal transmission is much smaller than the number of neurotransmitters. There are approximately 100 different metabolic products that act as neurotransmitters and activate a variety of different cell surface receptors, but only a few second messengers have been well characterized, the best investigated to date being **cAMP**. Scientific findings concerning cAMP have essentially shaped our general concepts regarding the mechanisms that second messengers employ. A further class of second messengers are generated by the hydrolysis of cell membrane phospholipids: IP_3 and diacylglycerol are released through the activity of phospholipase C, and arachidonic acid, on the other hand, through that of phospholipase A_2 (Fig. 1.6). A third class of second messengers includes highly diffusible gases, such as NO and CO, that activate guanylate cyclase, leading to the production of a third messenger, cGMP.

Second messenger molecules can, in turn, activate a special class of enzymes, the so-called **protein kinases** that phosphorylate various target proteins, altering their activity. Although these cascades of biochemical reactions are available in every cell of the body, the degree of complexity and integration reaches its zenith in the neuron, a degree of organization comparable with that of the nervous systems itself.

1.3 Neurotransmitters and Neurotransmitter Receptors

Neuroreceptors are membrane-bound proteins and are the molecular targets for neurotransmitters and psychopharmaceutical agents. The binding characteristics of the receptors are in this regard the basis for the efficacy and specificity of neurotransmitters and psychopharmaceuticals. Neuroreceptors consist of a recognition and a binding component that receives the signal and an effector component that converts the signal into an intracellular effect. "**Agonists**" is the term used in pharmacology to denote substances that mimic the effect of a neurotransmitter at the neuroreceptor or that augment its effect. **Antagonists**, in contrast, inhibit or oppose the effect of a neurotransmitter. Neuroreceptors are classified as pharmacological subtypes on the basis of the specific effects of selective agonists and antagonists.

In the next section, the most important neurotransmitters and their receptors will be discussed in more detail.

1.3.1 Acetylcholine

Neuroanatomical Location and Function

Because of the easy accessibility of its site of release, the motor endplate, ACh is the best-investigated neurotransmitter. Apart from neuromuscular junctions, ACh is also active presynaptically on spinal cord motoneurons and in postganglionic neurons of parasympathetic fibers. In the brain, it is utilized by a number of projection neurons, the most important of which include those that originate in the so-called nucleus basalis of Meynert and project to the entire cortex as well as to subcortical regions of the cerebral hemispheres. Others originate in the *septum* and project primarily to the hippocampus. The *diagonal band of Broca* sends fibers to the entire cortex, whereas the pons mainly innervates the thalamus. Finally, there are cholinergic interneurons in the cortex as well as in the striatum.

Biosynthesis and Inactivation Mechanisms

ACh is synthesized from choline by choline acetyltransferase, which occurs fairly selectively in cholinergic neurons, in both cytosolic and membrane-bound forms (Fig. 1.8). The affinity of choline acetyltransferase for choline and its only moderate saturation with acetyl CoA in the nerve cell mean that ACh regulation can be regulated via both substrates.

The effect of ACh at cholinergic synapses is terminated by the metabolic inactivation of ACh

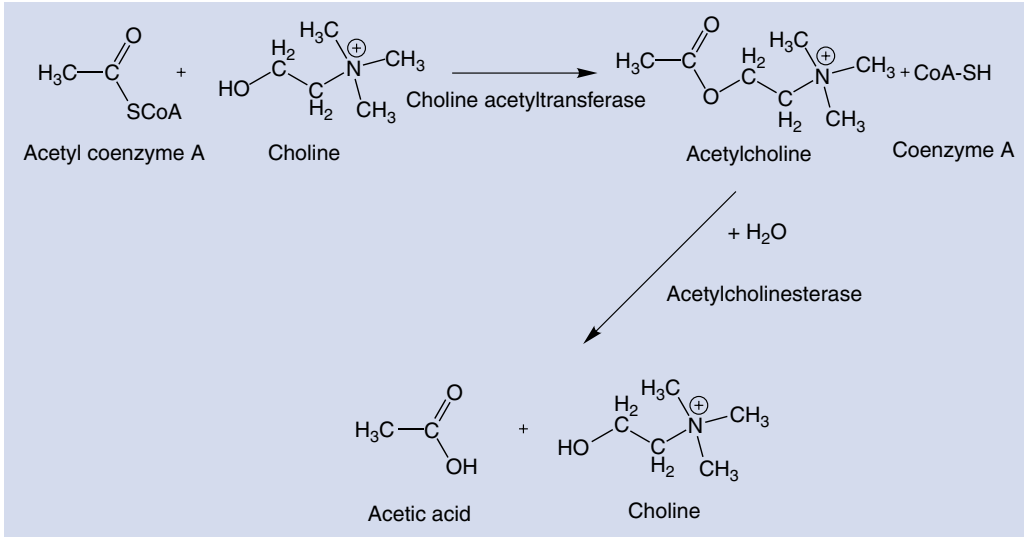

Fig. 1.8 Metabolism of acetylcholine

by acetylcholinesterase in the synaptic gap (Fig. 1.8) and not by presynaptic reuptake (a mechanism that plays an important role in the inactivation of other neurotransmitters). The resulting choline, however, is removed from the synaptic cleft into the presynaptic neuron by two separate transport systems:

- A low-affinity, high-capacity transport system that compensates the extremely low neuronal synthesis of choline.
- A high-affinity, Na^+-dependent transport system, localized in the presynaptic membrane, that ensures the rapid and provision of choline for the fresh synthesis of ACh.

Acetylcholinesterase is irreversibly inhibited by nerve gases (such as tabun and sarin), by various organophosphates (such as E605 = parathion), by other insecticides, and by diisopropyl fluorophosphate. These compounds, often designated nerve poisons, bind the active serine center of the enzyme, causing a massive synaptic accumulation of ACh and consequently sustained excitation at cholinergic synapses, leading ultimately to death by asphyxiation and cardiac arrest.

ACh Neuroreceptors

ACh receptors (cholinoceptors) were originally divided into two families on the basis of differing electrophysiological and pharmacological properties: nicotinic ACh (nACh) and muscarinic ACh receptors (mACh) (Fig. 1.9). **nACh receptors** are ligand-gated ion channels and are selectively stimulated by nicotine, an alkaloid that occurs in the tobacco plant. **mACh receptors** are, in contrast, G protein-coupled receptors that are selectively stimulated by the alkaloid muscarine, found in the fly agaric (a mushroom: *Amanita muscaria*). The division of ACh receptors into two groups occurred, however, long before the structures of these naturally occurring alkaloids had been elucidated. Later investigations employing synthetic agonists and antagonists necessitated further subclassification (Fig. 1.9). Molecular biological techniques finally identified further subtypes that could be differentiated according to their primary structures as well as their signal transduction mechanisms (Tables 1.3 and 1.4).

Most knowledge regarding the structure and mode of operation of ionotropic receptors derives from investigations of nACh receptors, primarily because it was possible to isolate large quantities of this protein from the electrical organs of the electric eel (*Electrophorus electricus*) and the torpedo. Assisted by electron microscopy, its three-dimensional structure in both its open and closed states has been elucidated, its genes cloned, and its coded amino acid sequence

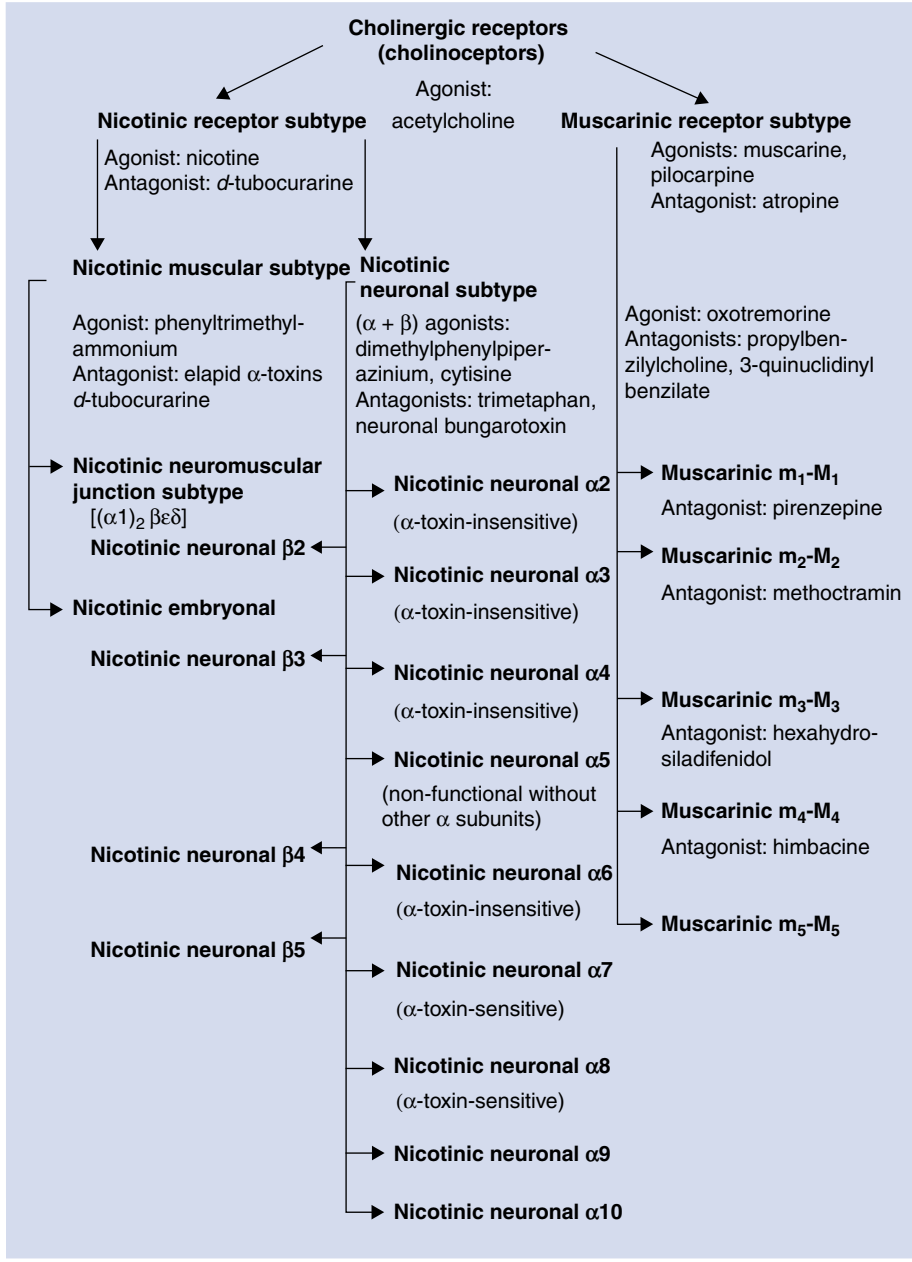

Fig. 1.9 Classification of cholinergic receptors (Modified from Taylor and Brown 2005). The figure shows the original pharmacological division based upon differing reactions to the naturally occurring alkaloids nicotine and muscarine (stage 1), the finer classification of receptor subtypes based upon the pharmacological activity of selective synthetic agonists and antagonists (stage 2), and the classification into subtypes on the basis of molecular biological distinguishing features (stage 3)

determined. The nACh receptor is a hetero-oligomeric protein (Fig. 1.10), consisting of four polypeptide chains differentiated by their migration velocity in polyacrylamide gel electrophoresis into α, β, γ, and δ-subunits (α has the highest, δ the lowest migration speed). Two α-subunits and one each of the β, γ, and δ-subunits constitute the typical nACh receptor/ion channel

Table 1.3 Classification, nomenclature, and characteristics of nicotinic cholinoceptors (nACh receptors)

Standard designation	Neuronal (CNS), α-bungarotoxin-insensitive nACh receptor	Neuronal (ANS), α-bungarotoxin-insensitive nACh receptor	Neuronal (CNS and ANS), α-bungarotoxin-sensitive nACh receptor	Neuromuscular nACh receptor
Subunits (arranged as pentamers)	α4β2 (predominant) α3β4 α6β2β3 α2	α3α5β4 α3α5β2β4	α7-Homomers (predominant) α3α5β2β4	$(\alpha1)_2\beta1\delta\gamma$ (during development/ extrasynaptic) $(\alpha1)_2\beta1\delta\gamma$ (endplate)
Receptor subtype-selective agonists	(β2 >β4 >α7) (–)-Nicotine Cytisine (+)-Anatoxin-a Epibatidine RJR-2403 ABT-418 A-85380	(–)-Nicotine Epibatidine SIB-1553A DMPP	α7: DMAC, GTS-21, AR-R17779, choline α9, α10: carbachol, DMPP, oxotremorine	Epibatidine (+)-Anatoxin-a TMA
Receptor subtype-selective antagonists	Mecamylamine (β2, β4 >α4) Dihydro-β-erythroidine (β2 >β4) Chlorisondamine (α3β4) α-Conotoxin MII (α3/α6β2) α-Conotoxin PIA (α6β2)	Mecamylamine (β2, β4 >α4) Hexamethonium Neuronal bungarotoxin α-Conotoxin AuIB (α3β4) Chlorisondamine	α7: α-bungarotoxin, methyllycaconitine α7 >α6 >α3 >α4 = α1: α-Conotoxin ImI α9, α10: α-bungarotoxin, D-tubocurarine, nicotine, atropine, muscarine, strychnine, bicuculline, tropisetron	α-Bungarotoxin D-Tubocurarine α-Conotoxin GI α-Conotoxin MI α-Conotoxin SI
Signal transduction mechanism	$N^+/K^+/Ca^{2+}$ conductance	$N^+/K^+/Ca^{2+}$ conductance	$N^+/K^+/Ca^{2+}$ conductance	$N^+/K^+/Ca^{2+}$ conductance
Tissue expression	α4, β2: widely distributed in CNS, particularly high levels in thalamus α2: nucleus interpeduncularis, reticularis system, colliculus inferior, septum α3: thalamus, LC, retina, medial habenula α5: hippocampus, SN, VTA α6: SN, VTA, LC β3: SN, VTA, LC, retina β4: medial habenula, nucleus interpeduncularis, retina	Sympathetic ganglia Sensory ganglia Chromaffin cells Fibroblasts Keratinocytes	α7: widely distributed in CNS, especially in cortex, hippocampus, hypothalamus, amygdala; autonomic nervous system, glia α9: cochlea, sensory neurons	Skeletal muscle
Physiological function	Postsynaptic receptors: synaptic neurotransmission (rare) Presynaptic receptors: modulation of synaptic neurotransmission	Synaptic neurotransmission (sympathetic ganglia) Presynaptic receptors: modulation of synaptic neurotransmission	α7: postsynaptic receptors: synaptic neurotransmission (rare: e.g., hippocampus) Presynaptic receptors: modulation of glutamate and GABA release, synaptic plasticity, gene regulation	Neuromuscular neurotransmission

Table 1.4 Classification, nomenclature, and characteristics of muscarinic cholinoceptors (mACh receptors)

Standard designation	M_1-ACh receptor	M_2-ACh receptor	M_3-ACh receptor	M_4-ACh receptor	M_5-ACh receptor
Molecular biological classification	m1	m2	m3	m4	m5
Receptor subtype-selective agonists	McN-A-343 (ganglion) Pilocarpine (relative to M_3- and M_5-ACh receptor) L-689,660 Xanomeline CDD-0097 AC-42	Bethanechol (relative to M_4-ACh receptor)	L-689,660 Xanomeline	McN-A-343 (relative to M_2-ACh receptor)	None known
Receptor subtype-selective antagonists	Pirenzepine Telenzepine	Methoctramine AF-DX 116 Gallamine (allosteric) Himbacine Tripitramine	Hexahydro-sila-difenidol p-Fluorohexahydro-sila-difenidol 4-DAMP	Tropicamide AF-DX 384	Himbacine
Signal transduction mechanism	$G_{q/11}$ (increase IP_3/DAG) NO	G_i (cAMP modulation) Increase K^+ (G)	$G_{q/11}$ (increase IP_3/DAG) NO	G_i (cAMP modulation) Increase K^+ (G)	$G_{q/11}$ (increase IP_3/DAG) NO
Tissue expression	Brain	Heart Smooth muscle	Endocrine and exocrine glands	Brain	Brain
Physiological function	Neuromodulation	Bradycardia, contraction	Secretion	Autoreceptors	Heteroreceptors

Modified from Watling (2006)

cAMP cyclic adenosine 3′,5′-monophosphate, *DAG* diacylglycerol, *IP_3* inositol-1,4,5-triphosphate, *K^+ (G)* G protein-coupled potassium channel, *NO* nitric oxide

Chemical abbreviations: *AC-42* 4-n-butyl-1-[4-(2-methylphenyl)-4-oxo-1-butyl]-piperidine hydrochloride, *AF-DX 116* 11-([2-[(diethylamino)methyl]-1-piperidinyl]acetyl)-5,11-dihydro-6-pyridol[2,3-b][1,4]benzodiazepin-6-one, *AF-DX 384* 5,11-dihydro-11-[2-[2-[(*N*,*N*-dipropylaminomethyl)piperidin-1-yl]ethylamino]-carbonyl]6H-pyridol[2,3-b][1,4] benzodiazepin-6-one, *CDD-0097* 5-Propargyloxycarbonyl-1,4,5,6-tetrahydropyrimidine, *L-689,660* 1-azabicyclo[2,2,2]octan-3-(6-chloropyrazinyl) maleate, *McN-A-343* 4-(*N*-[3-chlorophenyl]carbamoyloxy)-2-butynyltrimethylammonium chloride, *4-DAMP* 4-diphenylacetoxy-*N*-methylpiperidine methiodide

Modified from Watling (2006)

ANS autonomic nervous system, *GABA* γ-aminobutyric acid, *LC* locus caeruleus, *SN* substantia nigra, *VTA* area tegmentalis ventralis, *CNS* central nervous system

Chemical abbreviations: A-*85380* 3-(2[S]-azetidinylmethoxy)pyridine, *ABT-418* (S)-3-Methyl-5-(1-methyl-2-pyrrolidinyl) isoxazole, *AR-R17779* (–)-spiro[1-azabicyclo[2.2.2]octane-3,5′-oxazolidin-2′-one (4a), *DMAC* 3-(4)-dimethylaminocinnamylidine anabaseine, *DMPP* *N*,*N*-dimethyl-*N*′-phenyl-piperazinium iodide, *GTS-21* [3-(2,4-dimethoxybenzyliden) anabaseine, *RJR-2403* *N*-methyl-4-(3-pyridinyl)-3-buten-1-amine, *SIB-1553A* 4-[[2-(1-methyl-2-pyrrolidinyl)ethyl]thio] phenyl hydrochloride, *TMA* tetramethylammonium chloride

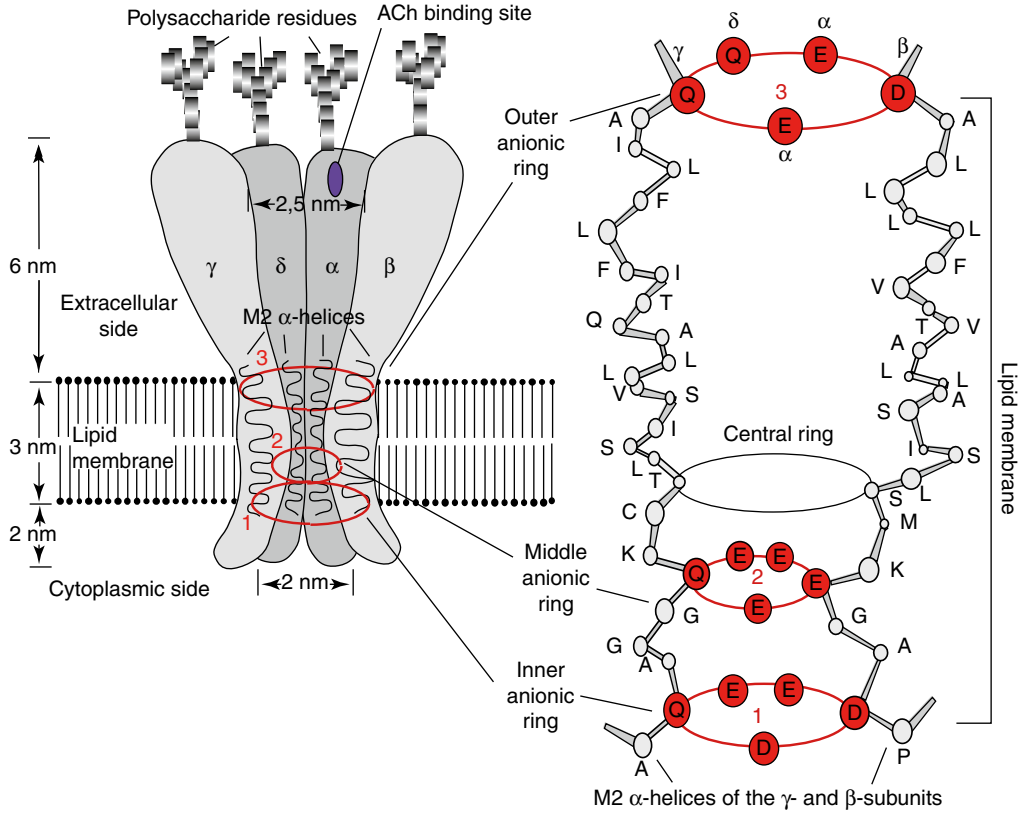

Fig. 1.10 Structural model of a nicotinic acetylcholine (nACh) receptor from the electric organ of the torpedo, showing the membrane topography of the subunits, the position of the α-helical M2 transmembrane domains of the subunits surrounding the channel pore as well as the three anionic rings and central ring of amino acids (modified from Zimmermann 1993). For reasons of clarity, one of the α-subunits that also has an ACh binding site has been omitted. *A* alanine, *C* cysteine, *D* aspartate, *E* glutamate, *F* phenylalanine, *G* glycine, *I* isoleucine, *K* lysine, *L* leucine, *M* methionine, *P* proline, *Q* glutamine, *S* serine, *T* threonine, *V* valine

pentamer (about 2,380 amino acids; relative molecular mass: approximately 270 kDa). nACh receptors, however, occur as a variety of subtypes that differ with respect to both their structure (combinations of subunit types) and their function (pharmacological and ion channel characteristics). The structure of the most important ganglion ACh receptor, for instance, is probably $(\alpha 3)_2(\beta 4)_3$, and two important nACh receptors of the mammalian CNS have the composition $(\alpha 4)_2(\beta 2)_3$ or $(\alpha 7)_5$ (Bertrand et al. 1993).

Activation of nACh receptors by ACh or nicotine leads to opening of the channel pore. The findings in mutagenesis experiments suggest that leucine molecules located in the middle of the M2 helix of each polypeptide chain are responsible for the opening and closing of the channel (Labarca et al. 1995). In the closed state of the ion channel, the side chains of these leucine residues project so far into the pore that it hinders ion flow. Binding of the agonist elicits a slight rotation of the N-terminals, the extracellular domains of the individual subunits, which in turn induce rotation of the M2 α-helices, screwing the leucine side chains out of the pore. This allows Na^+ and, to a lesser extent, Ca^{2+} to flow along their electrical gradients into the cell, while K^+ flows in the opposite direction. The cell interior is negatively charged, so that Na^+ and Ca^{2+} are driven outward by the electrical gradient when the channel is open; intracellular K^+ concentrations are 30 times higher than the extracellular level, so that osmotic forces play the dominant role for this ion and the flow direction is reversed. The net effect of nACh receptor activa-

tion is accordingly an inward ion flow, depolarizing the nerve cell and eliciting an excitatory effect.

Postsynaptic nACh receptors in the neocortex and hippocampus play a central **role in learning and memory processes**. This is suggested by the fact that a low nicotine dose improves learning and new memory acquisition in experimental situations and also by the fact that this brain region is neuropathologically altered in Alzheimer's disease, accompanied by parallel functional deficits in the cholinergic system. Centrally active reversible acetylcholinesterase inhibitors, such as donepezil and tacrine, that compensate the ACh deficit by inhibiting ACh catabolism are for this reason deployed in the therapy of dementia of this type.

Unlike nACh receptors, the mACh receptors are members of the G protein-coupled receptors family, which exhibit structural similarities as well as varying degrees of amino acid sequence homology in their transmembrane domains. The **mACh receptor group** includes five members, m1–m5 (Fig. 1.9, Table 1.4), with molecular masses between 55 and 70 kDa (Waxham 2003): The m1-, m3-, and m5-mACh receptors are predominantly coupled to G proteins that activate phospholipase C (Fig. 1.6); m2 and m4 receptors are coupled with G proteins that both inhibit adenylate cyclase as well as directly regulating K^+ and Ca^{2+} channels. The m1, m3, and m4 subtypes predominate in the brain, where they are widely distributed, both pre- and postsynaptically. It is probable that the effects mediated by mACh receptors involve modulation of the characteristics of ionotropic receptors (Waxham 2003). Presynaptic mACh receptors form part of important neuronal feedback circuits that regulate ACh release: depending upon which subtype is stimulated, release is either inhibited – the usual effect – or increased, as in the case of m5-ACh receptors.

1.3.2 Catecholamines

The neurotransmitters dopamine, noradrenaline, and adrenaline all share a catecholamine structure: that is, a 3,4-dihydroxylated benzene ring (Fig. 1.11). The starting point for the **biosynthesis** of these neurotransmitters is in each case the amino acid tyrosine, which is synthesized in the liver but also contained in the normal diet, and it can cross the blood-brain barrier into the brain. The synthesis of catecholamines from tyrosine involves the following enzymes:

- Tyrosine hydroxylase
- DOPA decarboxylase (aromatic amino acid decarboxylase)
- Dopamine β-hydroxylase
- Phenylethanolamine *N*-methyltransferase

The amino and nucleic acid sequences of tyrosine hydroxylase, dopamine β-hydroxylase, and phenylethanolamine *N*-methyltransferase are quite similar, evidence of their close evolutionary relationship. All four enzymes are present together only in adrenergic neurons; in dopaminergic neurons, synthesis ends at the level of dopamine, and in noradrenergic neurons, it proceeds only as far as noradrenaline (Fig. 1.11), whereby the **rate-limiting enzyme** in each case is **tyrosine hydroxylase**. Regulation of this enzyme at the level of the nerve terminals plays an important role in the short-term modulation of catecholamine synthesis, which is harmonized with changes in neuronal activity by end-product inhibition.

1.3.2.1 Dopamine

Neuroanatomical Distribution and Function

Although the proportion of dopaminergic neurons in the CNS is low (< 1/100,000 brain neurons) (Girault and Greengard 2004), they play an important role in the regulation of a number of fundamental brain functions (Björklund and Dunnett 2007; Bromberg-Martin et al. 2010). Dopamine concentrations (Fig. 1.2) and dopamine receptor density exhibit a characteristic distribution pattern in the brain that indicates the existence of specific dopaminergic systems, three of which are particularly important (Fig. 1.12):

- In the **nigrostriatal system**, neurons project from the substantia nigra pars compacta to the striatum, consisting of the nucleus caudatus and putamen. The nigrostriatal dopaminergic system is primarily involved in the **control of voluntary motor activity**. The substantia

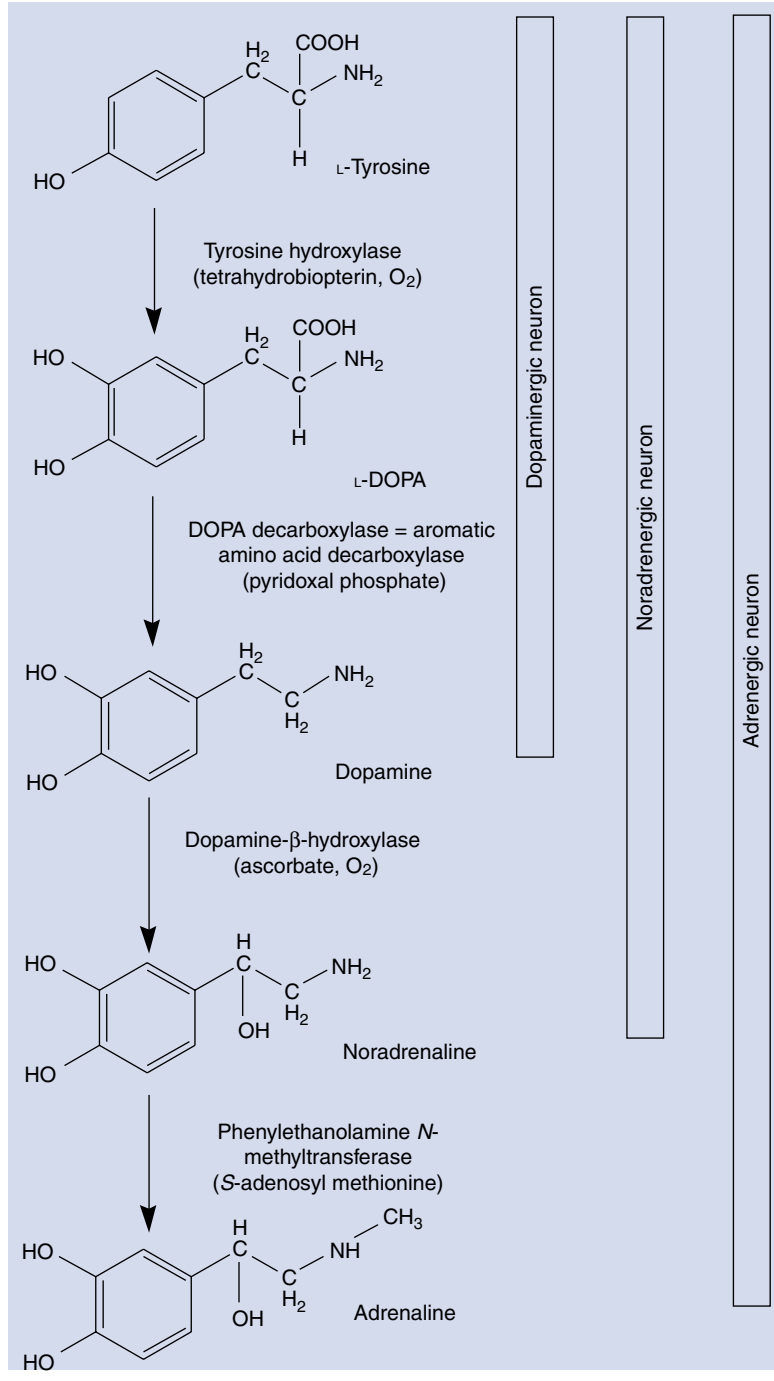

Fig. 1.11 Biosynthesis of the catecholamines dopamine, noradrenaline, and adrenaline

nigra (synonym: *nucleus niger*) received this designation because of the dark color of the neuromelanin found in many of its dopaminergic neurons; this is the major cell type that degenerates in Parkinson's disease. There are also indications, however, that this system is involved in the pathogenesis of attention deficit/hyperactivity disorder (ADHD). The importance of the nigrostriatal dopaminergic system for motor control was first recognized

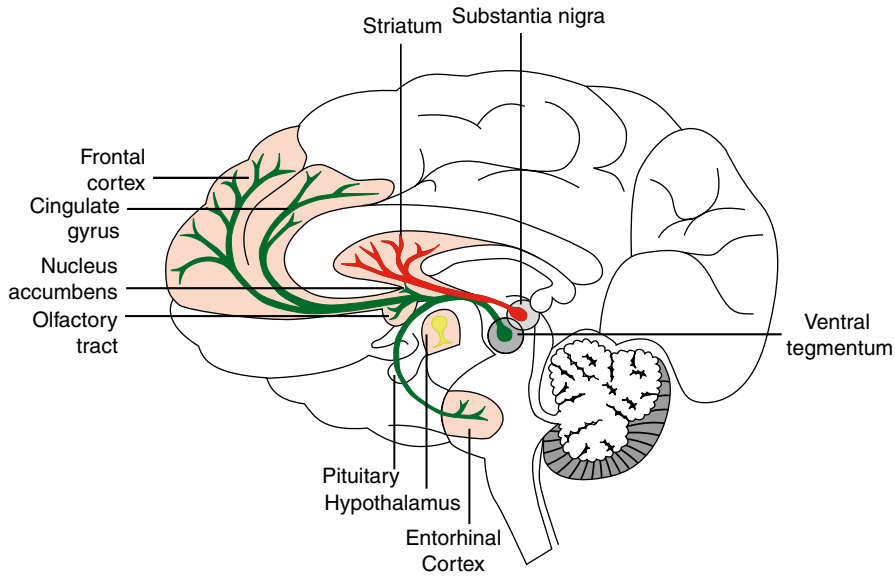

Fig. 1.12 The most important dopaminergic systems in the human brain

in the clinical practices when the administration of the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA), which, unlike dopamine itself, can cross the blood-brain barrier, was successfully used to ameliorate the symptoms of Parkinson's disease (Barbeau et al. 1962; Birkmayer and Hornykiewicz 1961).

- In the **mesolimbic and mesocortical system**, dopaminergic neurons of the area tegmentalis ventralis (ventral, VTA) innervate the mesolimbic (nucleus accumbens, septum, olfactory tract, amygdala, nucleus septi lateralis) and mesocortical brain regions (frontal and entorhinal cortex, cingulate gyrus). The mesolimbic-mesocortical system is involved in **motivation** and the **control of goal-directed behavior** and probably also in **learning and memory functions**. Disturbances in this system are thought to play a decisive role in development of alcohol and drug addiction; a pathogenetic role in ADHD has also been discussed. Hyperfunction of this dopaminergic system is also regarded as a possible cause of endogenous (such as schizophrenia) and pharmacotoxic psychoses (including those that can arise in the long-term dopaminergic therapy of Parkinson's disease). These conditions are rationally treated with dopamine receptor antagonists (neuroleptics = antipsychotics, see Chap. 5), which dampen the effect of dopamine, but at higher doses can also elicit a Parkinsonian syndrome as they also reduce activity of the nigrostriatal system.
- In the **tuberoinfundibular system**, dopaminergic neurons of the arcuate nucleus project to the hypothalamus and regulate the **release of pituitary hormones**. The best-investigated D_2 dopamine receptor-mediated effect (classification of **dopamine receptor subtypes**: Sect. Dopamine Receptors) in this system is the control of the synthesis and release of **prolactin** from the anterior pituitary. Hormonal disorders subsequent to hyperprolactinemia caused by inhibition of these receptors are possible ADRs of antipsychotic therapy.

Biosynthesis and Inactivation Mechanisms

Dopamine is synthesized by the decarboxylation of L-DOPA, which in turn is synthesized from the amino acid tyrosine by tyrosine hydroxylase (Fig. 1.11). Tyrosine hydroxylase is the rate-limiting enzyme in this pathway; it requires the cofactor sapropterin(5,6,7,8-tetrahydrobiopterin),

Table 1.5 Molecular and pharmacological characteristics of human catecholamine transporters

	DAT	NET	SERT	VMAT-2
Mechanism	Na^+/Cl^- dependent	Na^+/Cl^- dependent	Na^+/Cl^- dependent	$H^\pm$ dependent
Transmembrane segments	12	12	12	12
Amino acids	620	617	630	514
Chromosome	5	16	17	10
Inhibitors (examples)	β-CIT	Citalopram	β-CIT	Tetrabenazine
	Bupropion	Cocaine	Clomipramine	
	Cocaine	Desipramine	Cocaine	
	GBR-12909	Duloxetine	Fluoxetine	
	GBR-12935	Imipramine	Fluvoxamine	
	Indatraline	Mazindol	Imipramine	
	Mazindol	Nomifensine	Paroxetine	
	Nisoxetine	Nortriptyline	Reserpine	
	Nomifensine	Reboxetine	Sertraline	
		Tomoxetine	Trazodone	
		Venlafaxine	Venlafaxine	

Adapted from Kuhar et al. (2005), Watling (2006)
DAT dopamine transporter, *NET* noradrenaline transporter, *SERT* serotonin transporter, *VMAT-2* vesicular membrane transporter
β-*CIT* 2β-carbomethoxy-3β-(4-iodophenyl)tropane, *GBR-12909* 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine, *GBR-12935* 1-(2-[diphenylmethoxy]ethyl)-4-[3-phenylpropyl]-piperazine

synthesized in a three-step enzymatic process from guanosine triphosphate (GTP, and also involved in the synthesis of serotonin (5-hydroxytryptamine, 5-HT) and NO. Tyrosine hydroxylase activity is regulated through phosphorylation of multiple serine residues and stimulated by activity of the dopaminergic neuron; phosphorylation of Ser40 by a cAMP-dependent kinase reduces feedback inhibition by catecholamines. The second enzyme involved in dopamine biosynthesis is aromatic amino acid decarboxylase, which converts L-DOPA to dopamine. There is molecular biological and pharmacological evidence that this enzyme also catalyzes the decarboxylation of 5-hydroxytryptophan (see Sect. 1.3.3.2).

Termination of the action of synaptic dopamine of the nigrostriatal system chiefly occurs through **reuptake of dopamine** by specific transport proteins (**dopamine transporter**, DAT) into presynaptic dopaminergic nerve endings (see also Sect. 1.4.3). This reuptake is energy-dependent and saturable; the velocity of reuptake can be described by Michaelis-Menten enzyme kinetics. DAT belongs to a family of neurotransporters that share a number of structural features (Table 1.5). DAT and the noradrenaline transporter (plasma membrane transporters, plasmalemma transporters) are found primarily in the presynaptic membranes of the corresponding neurons, while the vesicular membrane transporter (VMAT-2) is found intraneuronally in vesicular membranes that protect the neurotransmitter from enzymatic degradation. Plasma membrane transporters are substrates for protein kinase C-dependent phosphorylation, which reduces its activity.

In addition, dopamine is **metabolically inactivated** by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) (Fig. 1.13). This inactivation mechanism is particularly important in the mesocortical system, where DAT density is very low. COMT is a cellular enzyme, occurring predominantly in soluble form that catalyzes the transfer of a methyl group from *S*-adenosyl-L-methionine to one of the two catecholamine hydroxyl groups. MAO is located on the outer mitochondrial membrane of neurons, glia, and other cell types and catabolizes relatively nonspecifically monoaminergic neurotransmitters, including dopamine, noradrenaline, and 5-HT; neuromodulators

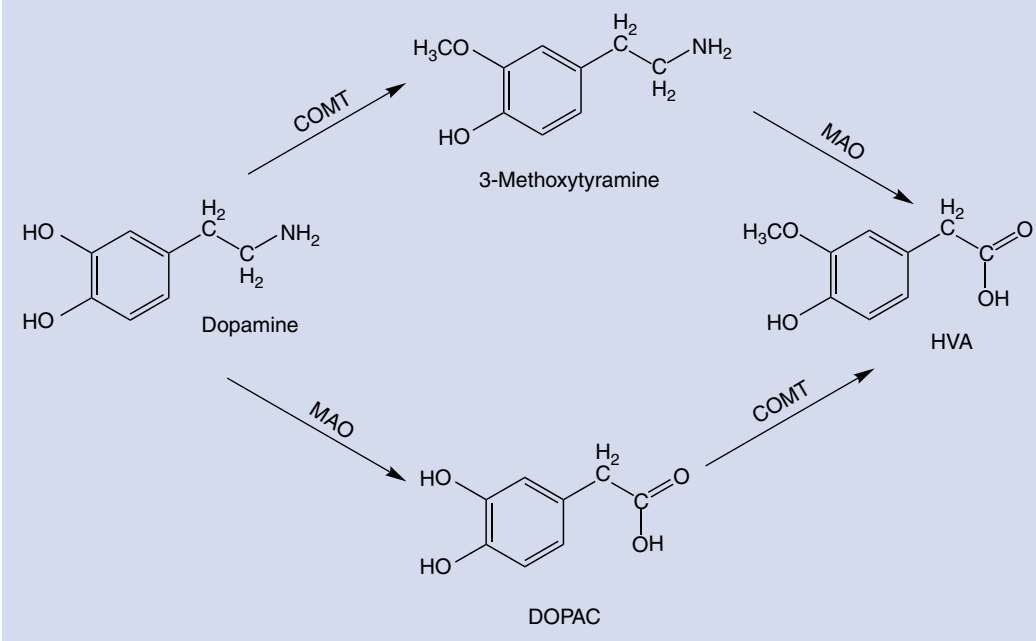

Fig. 1.13 Enzymatic degradation of dopamine. *COMT* catechol-*O*-methyltransferase, *DOPAC* dihydroxyphenylacetic acid, *HVA* homovanillic acid, *MAO* monoamine oxidase

such as β-phenethylamine; other endogenous and exogenous monoamines such as tyramine; but also tertiary amines, including the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Pharmacological findings underlay the identification of two isoforms with differing substrate specificity and sensitivity to inhibitors: the enzyme form more sensitive to clorgyline was designated MAO-A, while the less sensitive was dubbed MAO-B. The existence of the two isoforms, differing in their primary structure, was confirmed by molecular biological and immunocytochemical investigations. The amino acid sequences derived from cDNA exhibit 70 % homology. In the rat brain, MAO-A is predominant in many regions, but both forms occur in many areas of the human brain at roughly similar levels, although MAO-B is the major form in the striatum (Riederer and Youdim 1986). It is believed that dopamine in the human brain is metabolized by MAO-B; noradrenaline and 5-HT, on the other hand, are for the most part degraded by MAO-A (see also Sect. 1.4.1).

Dopamine Receptors

Dopamine receptors are G protein-coupled receptors. They were originally classified (Jaber et al. 1996) according to their effects upon adenylate cyclase into D_1 (activate cAMP synthesis) and D_2 subtypes (inhibit cAMP synthesis). Although molecular biological characteristics allow differentiation of at least five dopamine receptor subtypes (Table 1.6), the significance of the $D_{3–5}$ subtypes for dopamine-mediated effects in the CNS is unknown, principally because selective agonists and antagonists for these subtypes are not available, so that relevant behavioral-pharmacological investigations cannot be conducted. Furthermore, no clear indications of specific functions have emerged from transgenic animal models, in which individual specific genes are inactivated. For this reason, the subtypes are still pharmacologically allocated to the *D1* (D_1,D_5) and *D2 families* (D_2, D_3, D_4). The high density of D_3 subtype receptors in the mesolimbic system is regarded as evidence for implicating this subtype in the effects of antipsychotic and antidepressant agents as well as on the

Table 1.6 Criteria for the differentiation of dopamine receptors

1. Original pharmacological classification		
	D_1 receptors	**D_2 receptors**
Act via G proteins	Yes	Yes
Effect on adenylate cyclase	Stimulation	Inhibition
Selective agonist	SKF-38393	Fenoldopam
Selective antagonist	SCH-23390	(–)-Sulpiride Domperidone Raclopride
Function	Synergistic modulation of D_2 dopamine receptor-mediated motor effects	Mediation of motor effects Reduce prolactin release
2. Molecular biological classification		
$D_{1–5}$ and further subtypes defined according to differences in amino acid sequence		
Pharmacological and functional differentiation of the individual subtypes, however, is not possible		
3. Pharmacological classification		
D1 (D_1, D_5) and D2 ($D_{2–4}$) families		

SCH-23390 7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, *SKF-38393* (±)-1-Phenyl -2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrobromide

development of drug addiction. Dopaminergic receptors occur both pre- and postsynaptically, whereby the presynaptic D_2 receptors are termed autoreceptors.

1.3.2.2 Noradrenaline and Adrenaline

Neuroanatomical Distribution and Function

In the peripheral nervous system, noradrenaline (synonym: norepinephrine) is the neurotransmitter used by almost all terminals of sympathetic postganglionic fibers, through which it stimulates increases in blood pressure and heart rate. In the CNS, noradrenaline is used by neurons with cell bodies in the **locus caeruleus**, a **brainstem** nucleus with a number of complex regulatory functions. The locus caeruleus contains more noradrenergic neurons than any other CNS nucleus and is one of the most remarkable structures in the human brain. The small nucleus, named for its blue color (*caeruleus*: Latin for deep blue), contains only around 20,000 neurons – not many, when one considers the billions of nerve cells in the cerebral cortex – but the axons of these few neurons stretch over very long distances, projecting to nearly every region of the brain (exception: nigrostriatal dopaminergic system). It is therefore believed that this nucleus is involved in the regulation of a range of brain faculties, including perception, intellect, and memory formation. There is some evidence that disturbances of this system underlie the symptoms of ADHD. Noradrenergic activation at the great majority of CNS synapses leads to inhibition of synaptic signal transmission; in some synapses, however, it promotes (or even amplifies) transmission, with a consequent elevation of the signal-to-noise ratio for neuronal activity in these structures. Apart from these short-term effects of noradrenergic stimulation, there are findings suggesting that it also leads to longer-term effects, such as synaptic plasticity.

Further brain structures with noradrenergic neurons include the medulla oblongata (brain region that merges directly with the spinal cord) and the pons (the bridge to the brainstem), which inhibit, among other areas, the hypothalamus. In this manner, noradrenaline amplifies sympathetic activation.

CNS neurons that utilize **adrenaline** (synonym: epinephrine) occur in much fewer numbers than those that use noradrenaline and dopamine; it is more prominent as one of two transmitters (with noradrenaline) of the sympathetic peripheral nervous system. There is much more adrenaline in the adrenal medulla as in the CNS; the ratio of adrenaline to noradrenaline levels in the former is approximately 4:1. The most important group of CNS adrenergic nerve fibers are located in the rostroventrolateral medulla oblongata, a vasomotor control center mediating baroreceptor reflexes. In comparison with noradrenaline, however, adrenaline plays only a minor role in the central nervous regulation of autonomic functions.

Biosynthesis and Inactivation Mechanisms

The starting point for the biosynthesis of noradrenaline and adrenaline is the amino acid tyrosine, the first step being the synthesis of dopamine

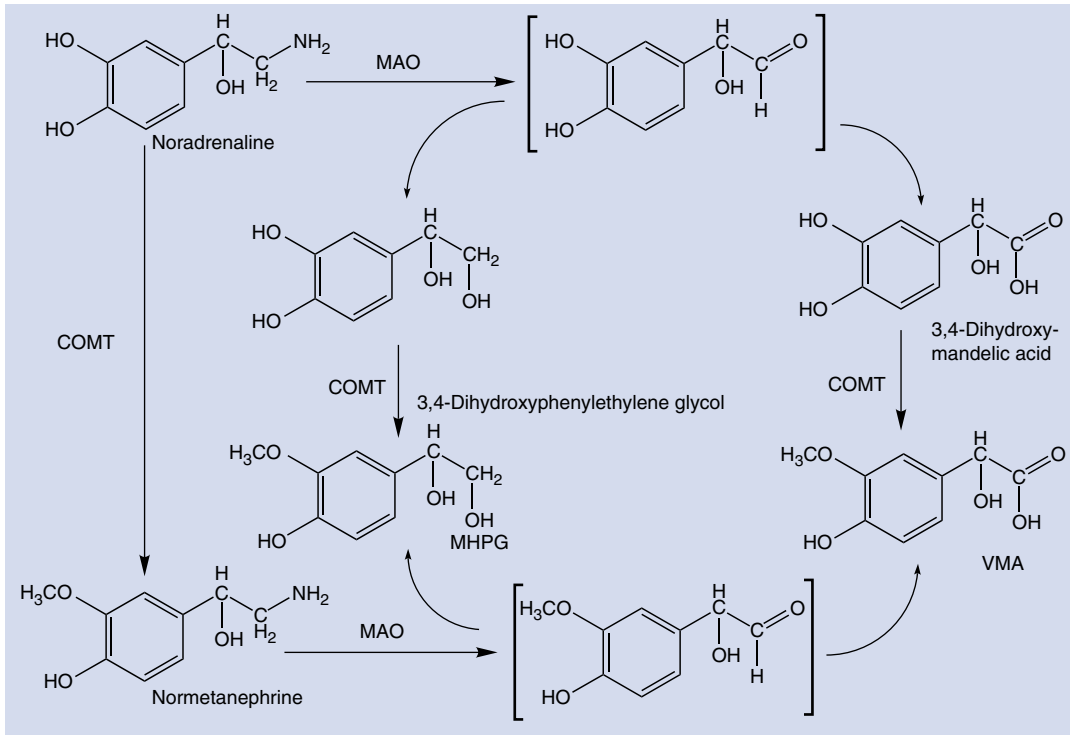

Fig. 1.14 Enzymatic degradation of noradrenaline. *COMT* catechol-*O*-methyltransferase, *MAO* monoamine oxidase, *MHPG* 3-methoxy-4-hydroxy-phenylglycol, *VMA* 3-methoxy-4-hydroxymandelic acid = vanillylmandelic acid

(Fig. 1.11). This is then taken into vesicles by noradrenergic neurons, where it is converted by dopamine β-hydroxylase to noradrenaline. The further transformation to adrenaline is possible in nerve terminals only in the CNS, as sympathetic nerve terminals do not contain phenylethanolamine *N*-methyltransferase for the methylation of noradrenaline, using S-adenosyl methionine (SAM) as the methyl donor. This is the biochemical reason for the fact that only noradrenaline, and not adrenaline, occurs in sympathetic nerve endings.

The most important **inactivation pathway** for released noradrenaline and adrenaline is the **reuptake by specific transporters** into presynaptic nerve terminals or other nearby cells (e.g., into glia via extraneuronal noradrenaline transporters). The noradrenaline transporter, like DAT, is a member of a family of neurotransporters that share structural features (Table 1.5); the transporter for adrenaline, however, has not yet been identified, but is assumed to be distinct from that for noradrenaline. Experimental data suggests that more than 80 % of noradrenaline released into the synaptic cleft is inactivated by reuptake mechanisms, with the consequence that most of the transmitter becomes available for renewed release. Some tricyclic antidepressants, such as desipramine and atomoxetine (the latter is also employed in the therapy of ADHD), possess a high affinity for the noradrenaline transporter (see Sect. 1.4.3). Cocaine also inhibits reuptake of noradrenaline; but it also inhibits to a similar degree the uptake of dopamine and 5-HT into their respective neurons.

A further inactivation pathway is the **metabolic transformation** into inactive metabolites by enzymes already discussed in connection with dopamine inactivation, COMT, and MAO (Fig. 1.14). Trace noradrenaline is also transported in the blood, some of which is metabolized in the liver, similarly by COMT and MAO.

Adrenoceptors

Noradrenaline and adrenaline stimulate the so-called adrenoceptors, which, like dopamine

Table 1.7 Classification, nomenclature, and characteristics of human α_1-adrenoceptors

Standard name	**α_{1A}**	**α_{1B}**	**α_{1D}**
Other name	α_{1a}, α_{1c}	α_{1b}	α_{1d}, $\alpha_{1a/d}$
Receptor subtype-selective agonists	SKF-89748 A-61603	None known	None known
Receptor subtype-selective antagonists	(+)-Niguldipine 5-Methylurapidil RS-17053	(±)-Cyclazocine L-765,314	BMY 7378
Signal transduction mechanism	$G_{q/11}$ (increase IP_3/DAG)	$G_{q/11}$ (increase IP_3/DAG)	$G_{q/11}$ (increase IP_3/DAG)
Tissue expression	Heart Liver CNS Smooth muscle in urogenital tract	Pancreas Kidney	Aorta Bladder CNS
Physiological function	Contraction of smooth muscle Myocyte hypertrophy	Contraction of smooth muscle CNS stimulation	Contraction of smooth muscle Locomotor activity

Modified from Watling (2006)
DAG diacylglycerol, *IP_3* inositol-1,4,5-triphosphate
Chemical abbreviations: *A-61603* N-[5-(4,5-dihydro-1H-imidazol-2-yl)-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]methanesulphonamide, *BMY 7378* 8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4,5]decane-7,9-dione, *L-765,314* 4-amino-2-[4-[1-(benzyloxycarbonyl)-2(S)-[[(1,1-dimethylethyl)amino]carbonyl]-piperaziny]-6,7dimethoxyquinazoline, *RS-17053* (*N*-[2-(2-Cyclopropylmethoxyphenoxy)ethyl]-5-chloro- α,α -dimethyl-1H-indole-3-ethanamine

receptors, belong to the G protein-coupled receptor family. On the basis of the selective effect of the synthetic agonist isoproterenol, adrenoceptors were originally divided into α (isoproterenol-insensitive) and α-adrenergic receptors (isoproterenol sensitive). The **α-adrenoceptors** were later divided into two subtypes (α_1, α_2) on the basis of their molecular biological characteristics, each of which includes three species of receptors (α_{1A}, α_{1B}, α_{1D} and α_{2A}, α_{2B}, α_{2C}) (Tables 1.7, 1.8, and 1.9). Both subtypes share structural features with dopamine receptors, and all subtypes within each adrenoceptor family appear to be coupled with the same primary signal transduction mechanism (Tables 1.7, 1.8, and 1.9), raising the question of whether these receptors are redundant or can be associated with different functions.

Receptor binding studies have demonstrated the presence of α_1 and α_2-adrenoceptors in peripheral organs as well as their widespread distribution in the CNS. The proportions of the two subtypes in different brain regions vary significantly: the α_{1A} and α_{1B}-receptor subtypes generally occur at higher levels than the α_{1D}-subtype; α_{2A} and α_{2C}-adrenoceptors are found in almost all brain regions, while the α_{2B} subtype is predominantly found in the thalamus (Pupo and Minneman 2001). The physiological significance of brain α_1 and α_2-adrenoceptors is unclear, as there are no subtype-selective agonists and antagonists that cross the blood-brain barrier. Many antipsychotics and antidepressants displace radioactively labeled antagonists of α_1-adrenoceptors from their binding sites in brain homogenate preparations (Snyder 2002). α_1-Adrenergic antagonists are highly efficacious antihypertensive and sedative pharmaceutical agents, so that the antihypertensive and sedative ADRs associated with many antipsychotics and antidepressants are probably caused by their blockade of α_1-adrenoceptors. Recent evidence suggests that depression is associated with an increase in the high-affinity conformation of α_2-adrenoceptors in human brain (see Muguruza et al. 2013). Therefore, α_2-adrenoceptors antagonists were developed as potential antidepressant drugs.

Stimulation of α_2-adrenoceptors, like that of D_1 dopamine receptors, leads to inhibition of

Table 1.8 Classification, nomenclature, and characteristics of human α_2-adrenoceptors

Standard name	**α_{2A}**	**α_{2B}**	**α_{2C}**	**α_{2D}**
Other name	–	–	–	α_{2A}
Receptor subtype-selective agonists	Oxymetazoline (partial agonist)	None known	None known	None known
Receptor subtype-selective antagonists	BRL 44408	Prazosin ARC 239 Imiloxan Rauwolscine	Prazosin ARC 239 MK-912	BRL 44408
Signal transduction mechanism	G_i (cAMP modulation)	G_i (cAMP modulation)	G_i (cAMP modulation)	G_i (cAMP modulation)
Tissue expression	CNS Lung Vasculature Skeletal muscle	Thalamus Lung Kidney	CNS Lung	Aorta
Physiological function	Inhibition of neurotransmission Vasoconstriction	Contraction of smooth muscle Thermoregulation	Modulation of neurotransmission Vasoconstriction	Inhibition of neurotransmission

Modified from Watling (2006)
cAMP cyclic adenosine 3′,5′-monophosphate
Chemical abbreviations: *ARC 239* 2-[2-[4-(o-methoxyphenyl)piperazin-1-yl]ethyl]4,4-dimethyl-1,3-(2H,4H)isoquinolinedione, *BRL 44408* (2-[2H-(1-methyl-1,3-dihydroisoindole)methyl]-4,5-dihydroimidazole, *MK-912* ((2S,12bS)1′,3′-dimethylspiro(1,3,4,5′6,6′,7,12b-octahydro-2H-benzo[b]furo[2,3a]quinazoline)-2,4′-pyrimidin-2′-one

Table 1.9 Classification, nomenclature, and characteristics of human β-adrenoceptors

Standard name	**β_1**	**β_2**	**β_3**
Other name	–	–	Atypical β
Receptor subtype-selective agonists	Noradrenaline Xamoterol Denopamine T-0509	Procaterol Salbutamol Fenoterol	BRL 37344 CL 316243 SB-226552
Receptor subtype-selective antagonists	CGP20712A Betaxolol Atenolol	ICI-118,551 Butoxamine α-Methylpropanolol	SR 58894 SR 59230A
Signal transduction mechanism	G_s (increase cAMP)	G_s (increase cAMP)	G_s (increase cAMP)
Tissue expression	Coronary artery Kidney Heart CNS	Kidney Lung Heart CNS	Fat tissue Gastrointestinal tract Vascular endothelium
Physiological function	Cardiac stimulation Coronary vasodilatation	Contraction of smooth muscle	Adipocyte lipolysis Bladder relaxation Thermogenesis

Adapted from Watling (2006)
cAMP cyclic adenosine 3′,5′-monophosphate
Chemical abbreviations: *BRL 37344* (±)-(R*,R*)-(4-[2-(3-chlorophenyl)-2-hydroxyethyl]amino)propyl)phenoxy)acetic acid, *CGP20712A* (±)-2-hydroxy-5-[2-[[2-hydroxy-3-[4-[1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl]phenoxy]propyl]-amino]ethoxy]-benzamide methanesulfonate, *CL 316243* (R,R)-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]-propyl]1,3-benzodioxole-2,2-dicarboxylate, *ICI-118*551, (±)-1-[2,3-(dihydro-7-methyl-1H-inden-4-yl)oxy]3-[(1-methylethyl)amino]-2-butanol, *SB-226552* (S)-4-{2-[2-hydroxy-3-(4-hydroxyphenoxy)propylamino]ethyl}-phenoxymethylcyclohexylphosphinic acid, *SR 58894* 3-(2-allylphenoxy)-1-[(1S)-1,2,3,4-tetrahydronaphth-1ylamino-(2S)-2-propanol hydrochloride, *SR 59230A* 3-(2-ethylphenoxy)-1[(1S)-1,2,3,4-tetrahydronaphth-1-ylamino)-(2S)-2-propanol oxalate, *T-0509* [(–)-(R)-1-(3,4-dihydroxyphenyl)-2-[(3,4-dimethoxyphenethyl)-amino]ethanol

adenylate cyclase and consequently to opening of K^+ channels and closing of Ca^{2+} channels. CNS α_2-adrenoceptors mediate a reduction of sympathetic tone. For example, the selective α_2-adrenergic agonist clonidine reduces blood pressure. Presynaptic inhibitory autoreceptors on noradrenergic neurons are also of the α_2-adrenergic subtype. Investigation of postmortem tissue has found that high densities of α_2-adrenergic receptors are found in the cortex, globus pallidus, nucleus accumbens, and thalamus (Nicholas et al. 1996), that is, brain regions, implicated in neuronal circuits concerned with the initiation and execution of motor behaviors as well as with the mediation of cognitive processes. It is therefore thought that these receptors modulate motor performance, influence attention and cognition, and are involved in the pathogenesis of dyskinesias.

β-Adrenergic receptors are divided into three subtypes (Table 1.9) of major pharmacological significance. β_1 and β_2-adrenoceptors are widely distributed, whereby the β_1 subtype is most common in heart and cerebral cortex, and the β_2 subtype dominates in lung and cerebellum. In many cases, however, both subtypes are found together in the same tissue and appear to elicit the same physiological effect. Both subtypes are found in the brain, and differences in their physiological function have not been detected. The third β-adrenergic receptor subtype is distinguished from the other two on the basis of pharmacological criteria. In contrast to the first two subtypes, the β_3-receptor occurs only at very low levels in the CNS (Pupo and Minneman 2001). Altered function of this subtype has been associated in humans with hereditary obesity (adipositas), regulation of lipid metabolism, and the genesis of diabetes.

1.3.2.3 Serotonin

Neuroanatomical Distribution

Most 5-HT in the human body is not located in the brain, but in enterochromaffin cells and platelets. Nearly all serotonergic neurons in the brain project from a group of nuclei in the midline of the brainstem, the **raphe nuclei**, a name derived from Greek meaning seam or suture. The projection area of these neurons, similar to that of the noradrenergic nerve cells of the locus caeruleus, stretches across the entire brain and spinal cord. The limbic system, septum, hippocampus, and hypothalamus are all chiefly innervated by nerve fibers from the median raphe nucleus, while the dorsal raphe nucleus projects to the basal ganglia (Wallman et al. 2011), where it exerts an inhibitory effect. The neocortex is innervated by fibers from both nuclei.

There appear to be morphological differences between various serotonergic nerve terminals. Serotonergic axons of the median raphe nuclei appear quite rough under the light microscope and are characterized by spherical varicosities, whereas those of the dorsal raphe nuclei are much finer and typically have pleomorphic varicosities. Furthermore, serotonergic dorsal raphe neurons are more vulnerable than median raphe nerves to the neurotoxic effects of 3,4-methylene-dioxy-N-methylamphetamine (MDMA), highly popular in the nightclub scene for its mood-elevating effect under the vernacular name **ecstasy**. Its abuse can lead to severe mental problems (including depression, anxiety, and memory disorders) and to degeneration of serotonergic and also dopaminergic neurons. Its effects are at least partially attributable to its inhibition of the uptake of 5-HT into serotonergic nerve terminals, resulting in elevated synaptic 5-HT levels.

Serotonergic synapses are not present in all projection areas of the raphe nuclei, despite measurable 5-HT release in these targets. It is presumed that 5-HT acts as a dynamic, **hormone-like modulatory function** in such areas.

5-HT has been implicated in almost every aspect of behavior (appetitive, emotional, motoric, cognitive, and autonomic); it is nevertheless unclear whether 5-HT specifically modulates these behaviors or whether it rather more generally modulates CNS activity, in particular by influencing the tone of cerebral activity with respect to vigilance. CNS serotonergic neurons are involved in the regulation of the sleep-wake cycle, appetite, body temperature, the development of drug addiction, and mood

(Wallman et al. 2011). It is therefore presumed that disturbances of the serotonergic systems are etiologically relevant for affective disorders (such as anxiety and compulsive disorders). Dysfunction of the serotonergic system is, however, also thought to be involved in schizophrenia and depression.

Biosynthesis and Inactivation Mechanisms

5-HT is synthesized from the amino acid tryptophan by the enzymes tryptophan hydroxylase (L-tryptophan 5-monooxygenase) and aromatic amino acid decarboxylase (Fig. 1.15). The first step in 5-HT biosynthesis is the transport of tryptophan from the blood into the brain via a specific transport mechanism. The availability of tryptophan limits the rate of synthesis. Because tryptophan is an essential amino acid – the major source of this amino acid is dietary protein – synthesis increases when the diet is rich in tryptophan. This has been exploited in the therapy of sleep disorders and depression, although tryptophan supplementation has not been marked by unambiguous success. Other neutral amino acids, such as phenylalanine, leucine, and methionine, compete with tryptophan for the transporter protein, which means that when reduced dietary tryptophan is accompanied by the administration of other amino acids that compete with tryptophan for uptake, reduced brain 5-HT concentration ensues, altering behaviors subject to the influence of 5-HT. The rate-limiting enzyme in the biosynthesis of 5-HT is probably tryptophan hydroxylase, found only in serotonergic neurons, which exhibits a 50 % amino acid sequence homology with tyrosine hydroxylase, the rate-limiting enzyme for catecholamine synthesis; the homologous sequences probably represent the active centers of the two enzymes. Two forms of tryptophan hydroxylase can be distinguished: tryptophan hydroxylase-1 (found primarily outside the CNS and in the pineal gland) and, the CNS form, tryptophan hydroxylase-2. The second enzyme involved in 5-HT biosynthesis is aromatic amino acid decarboxylase, which can be identified in both serotonergic and catecholaminergic neurons.

Termination of the action of 5-HT in serotonergic synapses primarily involves **reuptake of 5-HT** into the presynaptic nerve terminal by a Na^+-/Cl^--dependent transport system (Table 1.5). This transport system is a member of a family of structurally similar, ATP-dependent transporters that move dopamine, noradrenaline, or 5-HT against concentration gradients (Table 1.5).

Agents have been identified that selectively block transmitter transporters (Table 1.10). For example, secondary amines, including the tricyclic antidepressant desipramine, block transport of noradrenaline more effectively than that of 5-HT. Some of the more recent antidepressants, the selective 5-HT serotonin reuptake inhibitors (SSRIs), such as paroxetine, inhibit the transport of 5-HT more than that of noradrenaline.

The gene that codes the human 5-HT transporter exhibits a functional polymorphism within the promoter region, which modulates the transcription and therefore the expression and function of the 5-HT transporters. Compared with the short (s/s) and heterozygous (s/l) forms, the long variant (l/l) is associated with greater expression and function of the transporter, with implications for serotonergic neurotransmission. These expectations motivated a variety of investigation that led to the identification of an association between this genetic polymorphism and certain aspects of personality (such as anxiety and negative emotionality), various neuropsychiatric disorders (including depression, anxiety disorders, autism, eating disorders), and differential responsiveness to psychopharmaceuticals, especially SSRIs (Murphy et al. 2001).

Apart from its recycling by serotonergic neurons, 5-HT is also **enzymatically metabolized,** primarily by MAO-A (serotonergic neurons contain both MAO-A and MAO-B) and aldehyde dehydrogenase (Fig. 1.15). The resulting 5-hydroxyindoleacetic acid (5-HIAA) is expelled in the urine. Selective MAO-A inhibitors, such as moclobemide and tranylcypromine, increase 5-HT levels and slow its conversion to 5-HIAA, explaining their antidepressive efficacy, and consistency with the 5-HT deficit hypothesis of depression.

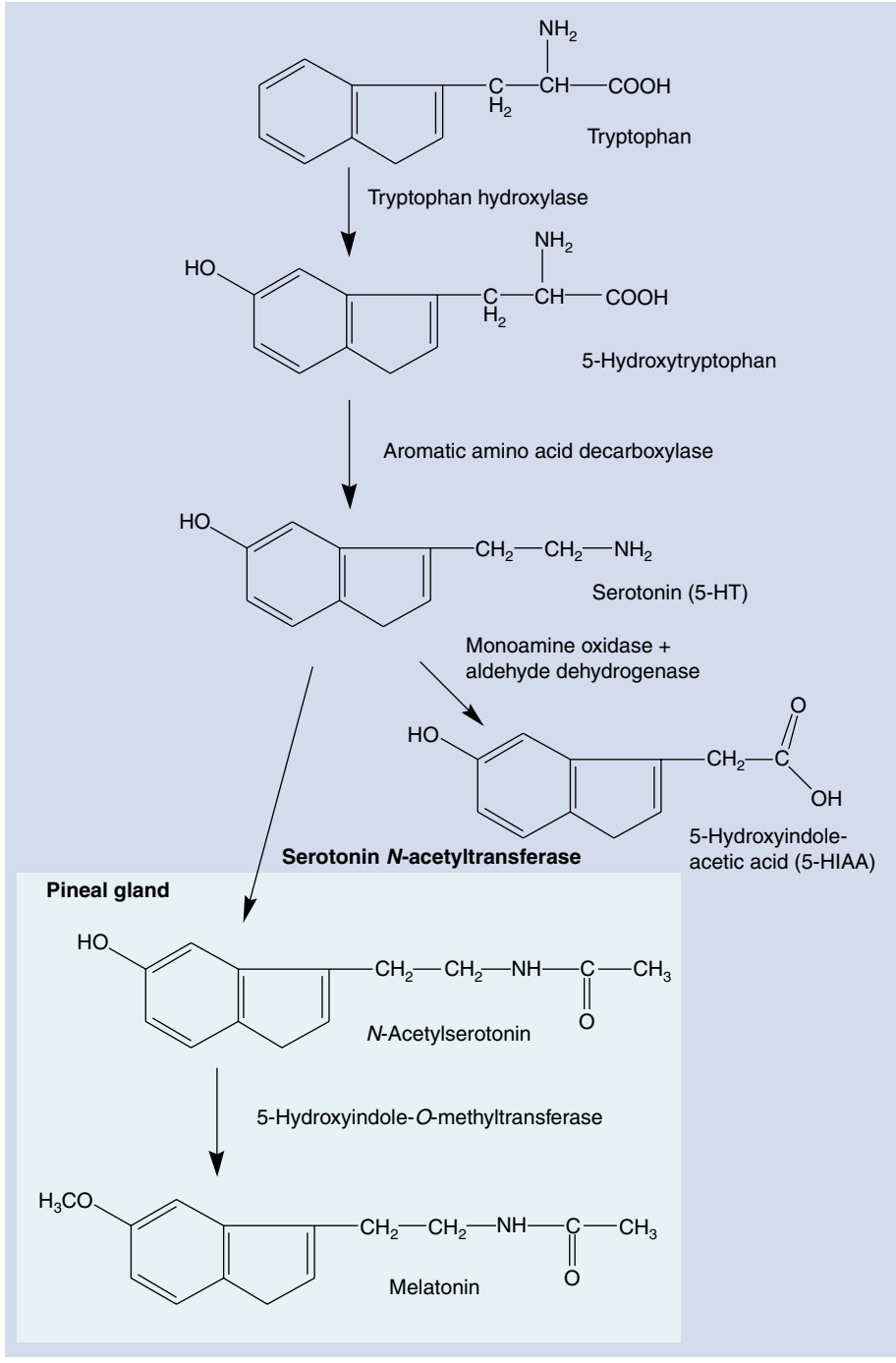

Fig. 1.15 Serotonin (5-HT) metabolism

In the pineal gland (epiphysis, an end organ of the photo-neuroendocrine system, lying between the cerebral hemispheres outside the blood-brain barrier), 5-HT is additionally converted to the hormone melatonin by 5-HT *N*-acetyltransferase and 5-hydroxyindole-*O*-methyltransferase (Fig. 1.15).

Table 1.10 Dissociation constants (K_i values; nM) for synthetic inhibitors of plasma membrane monoamine transporters

Inhibitor	Dopamine transporter	Noradrenaline transporter	Serotonin transporter
Cocaine	267	872	392
GBR 12935	21.5	225	6,514
Bupropion	2,784	1,389	45,026
Nisoxetine	477	5.1	383
Desipramine	78,720	4	61
Nortriptyline	13,920	3.4	161
Mazindol	27.6	3.2	153
Imipramine	24,576	67	7.7
Amitriptyline	3,000	100	14.7
Citalopram	10,000	>1,000	5.4
Paroxetine	–	312	0.25

Modified from Torres et al. (2003)
The smaller K_i, the more effective the inhibition of the transporter
– not determined

Melatonin synthesis is dependent upon the sleep-wake cycle, being produced only at night or during darkness.

Serotonin Receptors

Pharmacological, electrophysiological, biochemical, and molecular biological investigations have demonstrated that 5-HT exerts its effects in the CNS and peripheral tissues through a variety of neuroreceptors. **Thirteen human subtypes** have been distinguished on the basis of pharmacological and structural criteria as well as according to their modes of signal transduction; these subtypes have been collated into **seven structural classes**, **5-HT$_1$–5-HT$_7$** (Tables 1.11, 1.12, and 1.13). There are also receptor subtypes for which only the genes have been identified and have not been unambiguously associated with particular physiological functions; these are listed in the table in lower case type (5-ht). With the exception of the 5-HT$_3$ receptor, an ionotropic receptor, 5-HT receptors belong to the family of G protein-coupled receptors.

For many of the 5-HT subtypes, there are no selective agonists or antagonists, hampering investigation of their physiological functions. As there are few selective radioligands and no specific antibodies, the regional distribution of 5-HT receptor subtypes and their subcellular localization in the human brain are also largely unexplored. Much of what is currently known about their regional distribution in the CNS derives from gene expression investigations in rodents; these studies have revealed different regional distributions of the 5-HT receptor subtypes, suggesting that these receptors exercise different functions in the CNS.

5-HT receptors have commonly been attributed **physiological significance** in pain perception, but also in anaphylactic shock and in allergic reactions in general, in the activation of thromboxane A_2 prior to irreversible platelet aggregation, in the genesis of migraine, in gastrointestinal tract motility abnormalities, in the regulation of the sleep-wake cycle and of appetite, as well as in the control of blood pressure and body temperature. These conclusions rest largely upon the fact that serotonergic raphe neurons maintain numerous intensive contacts with blood vessels and this neurovascular contact represents a form of communication channel for neuroendocrinologically active substances.

Attempts to **elucidate the physiological functions** of individual 5-HT receptor subtypes has in some cases employed the **gene-knockout strategy**, in which mice with a clearly defined genetic defect are produced by inactivation or removal of the gene. Mice that lack, for example, the 5-HT$_{1B}$ receptor apparently develop in a normal manner but in a behavioral test prove to more aggressive than wild-type mice. In behavioral experiments with wild-type animals, the presence of antiaggression effects could be demonstrated for a series of 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor agonists. Because of their selective ability to tone down aggressive behavior without sedating the animal, such agonists are also termed "serenics." These findings and the results of gene-knockout experiments suggest that 5-HT$_{1B}$ receptors modulate aggressive behavior. Although similar experiments will contribute further to the elucidation of the specific functions of the various receptor classes and subtypes in the mammalian brain, these investigations are subject to certain limitations. Firstly, it is conceivable that under certain conditions another subunit or receptor subtype is

Table 1.11 Classification, nomenclature, and characteristics of human 5-HT_1 receptors

Standard name	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-ht_{1e}	5-ht_{1f}
Other names	~	5-HT_{1D}	5-HT_{1D}	5-HT_{1E}	5-HT_{1E} 5-HT_6
Receptor subtype-selective agonists	R(+)-8-OH-DPAT U-92016A R(+)-UH-301	Sumatriptan Zolmitriptan L-694,247 CGS12066	Sumatriptan Zolmitriptan L-694,247	BRL 54443	LY-334370 LY-344864 BRL 54443
Receptor subtype-selective antagonists	WAY 100635 S(–)-UH-301 NAN-190 S(–)-pindolol Spiperone	GR 55562 SB-216641 GR 127935 SB-224289	GR 127935 BRL 15572	None known	None known
Signal transduction mechanism	$G_{i/o}$ (cAMP modulation)	$G_{i/o}$ (cAMP modulation)	$G_{i/o}$ (cAMP modulation)	$G_{i/o}$ (cAMP modulation)	$G_{i/o}$ (cAMP modulation)
Tissue expression	Hippocampus Corpus amygdaloideum Raphe nuclei Myenteric plexus	Striatum Hippocampus Raphe nuclei Sympathetic neurons Vascular smooth muscle	Striatum Hippocampus Dorsal raphe nuclei Trigeminal ganglion Vascular smooth muscle	Parietal cortex Striatum Olfactory bulb Amygdala Glial cells	Cortex Thalamus Hippocampus Uterus
Physiological function	Somatodendritic autoreceptor in raphe nuclei and hippocampus Somatodendritic heteroreceptor in myenteric plexus	Presynaptic autoreceptor in hippocampus and sympathetic neurons Contraction of smooth muscle	Somatodendritic autoreceptor in raphe nuclei and hippocampus Presynaptic autoreceptor on sympathetic nerve terminals	None known	Inhibition of trigeminal ganglion

Modified from Watling (2006)
cAMP cyclic adenosine 3′,5′-monophosphate
Chemical abbreviations: *BRL 15572* 3-[4-(3-chlorophenyl)piperazine-1-yl]-1,1-diphenyl-2-propanol, *BRL 54443* 3-(1-methylpiperidin-4-yl)-1H-indol-5-ol; CGS12066, 7-trifluoromethyl-4-(4-methyl-1-piperazinyl)pyrrolo[1,2-a]quinoxaline, *GR 55562* 3-[3-dimethylamino)propyl]-4-hydroxy-*N*-[4-pyridinyl)phenyl]benzamide, *GR 127935* *N*-[methoxy-3-(4-methyl-1-piperizinyl)phenyl]-2′-methyl-4′(5-methyl-1,2,4-oxadiazol-3-yl)[1,1-biphenyl]-4-carboxamide, *L-694*247, 2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]1H-indol-3-yl]ethanamine, *LY-334370* 4-fluoro-*N*-[3-(1-methyl-4-piperidinyl)-1H-indol-5-yl]-benzamide, *LY-344864* (R)-*N*-[3-dimethylamino-2,3,4,9-tetrahydro-1H-carbazol-6-yl]-4-fluorobenzamide, *NAN-190* 1-(2-methoxyphenyl)-4-(4-[2-phthalimido]butyl)-piperazine, *SB-216641* *N*-[3-(2-dimethylamino)ethoxy-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadizaol-3-yl)-(1,1′-biphenyl)-4-carboxamide, *SB-224289* 2,3,6,7-tetrahydro-1′-methyl-5-[2′-methyl-4′(5-methyl-1,2,4-oxadiazol-3-yl) biphenyl-4-carbonyl]furo[2,3f]indole-3-spiro-4′ piperidine hydrochloride, *U-92016A* (+)-R-2-cyano-*N*, *N*-dipropyl-8-amino-6,7,8,9-tetrahydro-3H-benz[e]indole, *UH-301* 5-fluoro-8-hydroxy-2-dipropylamino-1,2,3,4-tetrahydronaphthalene, *WAY 100635* *N*-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-*N*-(2-pyridyl)-cyclohexanecarboxamide trichloride, *8-OH-DPAT* 8-hydroxy-2-(di-*n*-propylamino)tetralin

capable of compensating for the loss of a gene coding for a related subtype or part of a related subtype. In this situation it is possible that no detectable change in phenotype (external appearance of the organism, as opposed to genotype) occurs. Secondly, it is also possible that the

Table 1.12 Classification, nomenclature, and characteristics of human 5-HT_2 receptors

Standard name	**5-HT_{2A}**	**5-HT_{2B}**	**5-HT_{2C}**
Other name	D 5-HT_2	5-HT_{2F}	5-HT_{1C}
Receptor subtype-selective agonists	α-Methyl-5-HT DOI DOB	α-Methyl-5-HT BW723C86	α-Methyl-5-HT m-CPP YM348 Tegaserod (partial agonist)
Receptor subtype-selective antagonists	Ketanserin AMI-193 ML 100907 R102444	SB-204741 RS 127445 EGIS-7625 LY 272015	RS 102221 SB-242084
Signal transduction mechanism	$G_{q/11}$ (increase IP_3/DAG)	$G_{q/11}$ (increase IP_3/DAG)	$G_{q/11}$ (increase IP_3/DAG)
Tissue expression	Cortex Hippocampus Striatum Platelets Vascular and nonvascular smooth muscle	Vascular and gastrointestinal smooth muscle Stomach fundus Uterus Vascular endothelium	Choroid plexus Striatum Hippocampus Hypothalamus
Physiological function	Probably inhibitory effect Activation of platelets Contraction of smooth muscle	Contraction of smooth muscle NO-dependent vasorelaxation	Regulation of cerebrospinal fluid

Modified from Watling (2006)
DAG diacylglycerol, *IP_3* inositol-1,4,5-triphosphate, *NO* nitric oxide
Chemical abbreviations: *AMI-193* 8-[3-(4-fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, *BW723C86* 1-[5(2-thienylmethoxy)-1H-3-indolyl]propan-2-amine hydrochloride, *DOB* 2,5-dimethoxy-4-bromo-amphetamine, *DOI* 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, *EGIS-7625* 1-benzyl-4-[2-nitro-4-methyl-5-amino)-phenyl]-piperazine, *LY 272015* 6-methyl-1,2,3,4-tetrahydro-1-[3,4-dimethoxyphenyl)methyl-9H-pyrido[3,4b] indole] hydrochloride, *m-CPP* 1-(m-chlorophenyl)piperazine, *ML 100907* (±)-2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol], *R 102444* (2R,4R)-4-lauroyloxy-2-[2-[2-[2-(3-methoxy)phenyl]ethyl]phenoxy]ethyl-1-methylpyrrolidine hydrochloride, *RS 102221* 8-[5-(5-amino-2,4-dimethoxyphenyl)-5-oxopentyl]-1,3,8-triazaspiro[4,5]decane-2,4-dione, *RS 127445* 2-amino-4-(4-fluoronaphthyl-1-yl)-6-isopropylpyrimidine, *SB-204741* *N*-(1-methyl-5-indolyl)-*N*-(3-methyl-5-isothiazolyl) urea, *SB-242084* 6-Chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl-carbamoyl]indoline, *YM348* *S*-2-(7-ethyl-1H-furo[2,3-g]indazol-1-yl)-1-methylethylamine

homozygotic loss of a gene product could prove lethal at an early developmental stage, in which case investigation of the consequences of this loss for a later stage, such as adulthood, cannot be undertaken.

All 5-HT receptor subtypes can, in principle, occur both pre- and postsynaptically. 5-HT_{1A} and 5-HT_{1D} receptors appear to be mostly located presynaptically on cell bodies and dendrites (as somatodendritic autoreceptors) of the dorsal raphe nuclei (Table 1.11). The 5-HT_{1B} receptor, on the other hand, is predominantly located presynaptically on serotonergic nerve terminals. The major role of **5-HT autoreceptors** is in the negative feedback modulation of serotonergic neurotransmission. Activation of these receptors opens presynaptic Ca^{2+} channels, causing hyperpolarization of the nerve cell, the consequence of which is inhibition of the spontaneous activity of serotonergic neurons and of 5-HT release. Application of small doses of the selective 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) in the rat dorsal raphe nuclei leads to a reduction of the firing rate of serotonergic neurons and to a reduced 5-HT release in the striatum; higher concentrations also

Table 1.13 Classification, nomenclature, and characteristics of additional human 5-HT receptor classes

Standard name	5-HT$_3$	5-HT$_4$	5-ht$_5$	5-ht$_6$	5-HT7
Other name	M	–	5-HT$_{5a}$ 5-HT$_{5b}$	–	5-HT$_1$-like 5-HTY
Receptor subtype-selective agonists	SR 57227A 2-Methyl-5-HT 1-m-Chlorophenyl-biguanide 5-HTQ	BIMU 8 RS 67506 ML 10302 SC 53116	LSD	LSD 5-CT	5-CT
Receptor subtype-selective antagonists	Granisetron Ondansetron Tropisetron	GR 113808 SB-204070 RS 100235	None known	Ro 04-6790 Ro 63-0563	SB-258719 Clozapine
Signal transduction mechanism	Ion channel receptor	G_s (increase cAMP)	None known	G_s (increase cAMP)	G_s (increase cAMP)
Tissue expression	Striatum Substantia nigra Hippocampus Autonomic nervous system nerve terminals Sensory neurons	Striatum Substantia nigra Brainstem Cardiac muscle Smooth muscle	Hippocampus Cortex Cerebellum Spinal cord Habenula	Striatum Nucleus accumbens Hippocampus	Hippocampus Hypothalamus Raphe nuclei Vascular and gastrointestinal smooth muscle Sympathetic ganglion cells
Physiological function	Stimulation of sympathetic and parasympathetic nerve cells	Relaxation of smooth muscle Cardiac contraction Excitatory cholinergic effect	None known	Modulation of cholinergic neurons in CNS (probable)	Relaxation of smooth muscle Neuromodulation in CNS

Modified from Watling (2006)

cAMP cyclic adenosine 3′,5′-monophosphate

Chemical abbreviations: *BIMU 8* (endo-*N*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-isopropyl-2-oxo-1H-benzimidazol-1-carboxamide hydrochloride, *GR 113808* [1-2[(methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl-1-methyl-1H-indole-3-carboxylate, *LSD* lysergic acid diethylamide, *ML 10302* 2-(1-piperidinyl)ethyl-4-amino-5-chloro-2-methoxybenzoate, *Ro 04-6790* 4-amino-*N*-(2,6-bis-methylamino-pyrimidin-4-yl)-benzene-sulfonamide, *Ro 63-0563* 4-amino-*N*-(2,6-bis-methylamino-pyridin-4-yl)-benzene-sulfonamide, *RS 67596* 1-(4-amino-5-chloro-2-methoxyphenyl)-3-(1-*n*-butyl-4-piperidinyl)-1-propanone, *RS 100235* 1-(8-amino-7-chloro-1,4-benzodioxan-5-yl)-5-((3-(3,4-dimethoxyphenyl)prop-1-yl)piperidin-4-yl)propan-1-one, *SB-204070* 1-butyl-4-piperidinylmethyl-8-amino-7-chloro-1,4-benzoioxane-5-carboxylate, *SB-258719* (R)-3,*N*-dimethyl-*N*-[1-methyl-3-(4-methylpiperidin-1-yl)propyl]benzene-sulfonamide, *SC 53116* (1*S*-*cis*)-4-amino-5-chloro-*N*-[(hexahydro-1H-pyrrolizin-1-yl)methyl]-2-methoxybenzamide, *SR 57227A* 4-amino-(6-chloro-2-pyridyl)-1-piperidine hydrochloride, *5-CT* 5-carboxamidotryptamine, *5-HTQ N*,*N*,*N*-trimethylserotonin iodide

elicit a depolarizing effect on postsynaptic receptors. In contrast, application of selective 5-HT$_{1B}$ and 5-HT$_{1D}$ receptor agonists to 5-HT-innervated brain areas induces both synthesis and release of 5-HT, but not a reduced firing rate. Inhibition of somatodendritic 5-HT$_{1A}$ autoreceptors has only a minor effect upon extraneuronal 5-HT concentration in rodents, but it potentiates the increase elicited by selective 5-HT reuptake inhibition. It is therefore thought that desensitization of these autoreceptors explains the observation that synaptic 5-HT concentrations are elevated by chronic, but not acute, therapy with 5-HT reuptake inhibitors.

The **5-HT$_{1A}$ receptor** occurs at high levels in the brain in cortical and limbic structures (includ-

ing the hippocampus, entorhinal cortex, septum, amygdala, frontal cortex). This distribution pattern suggests that this 5-HT receptor subtype plays a role in cognitive or integrative functions, and also in emotional states. Activation of CNS 5-HT_{1A} receptors results in a series of physiological and behavioral reactions, leading, for example, to the release of adrenocorticotropic hormone (ACTH).

There is evidence that the 5-HT_{1A} receptor is **involved in affective disorders**, such as anxiety disorder and depression. Reduced 5-HT_{1A} receptor binding density have been measured in the hippocampus of deceased patients who had suffered depressive disorders, whereas in schizophrenics elevated densities were found in the frontal cortex and in Brodmann areas 10 and 11. Stimulation of 5-HT_{1A} autoreceptors exerts an anxiolytic effect in the rat; activation of the postsynaptic receptor subtype leads, in contrast, to increased anxiety. Newer anxiolytic agents, such as buspirone, have a high affinity for the 5-HT_{1A} receptor.

The highest CNS **5-HT_{1B} receptor** density is in the basal ganglia, particularly the striatum, indicative of a function related to motor control. Dysfunction of this receptor subtype in Parkinson's disease is therefore suspected. Stimulation of postsynaptic 5-HT_{1B} receptors modulates the release of other neurotransmitters, including ACh in the hippocampus and dopamine in the prefrontal cortex. Postsynaptic receptors are also found on cerebral arteries and other vascular tissues. Sumatriptan and zolmitriptan, agonists at the 5-HT_{1B} and 5-HT_{1D} receptors (Table 1.11), are employed clinically in the therapy of migraine. These agents cause constriction of meningeal blood vessels via stimulation of 5-HT_{1B} receptors. Activation of 5-HT_{1D} receptors is believed to act as an anti-inflammatory mechanism, in that they inhibit release of pro-inflammatory neuropeptides from vasculotrigeminal fibers in the meninges. Coronary arteries are, however, also equipped with 5-HT_{1B} receptors and can be caused to contract by these agents, for which reason they are contraindicated in patients with coronary heart disease.

It has been difficult to prove the presence of **5-HT_{1D} receptors** in the CNS, as there are no selective radioligands for this subtype. Gene expression investigations have found low mRNA levels in the basal ganglia, dorsal raphe nuclei, and locus caeruleus, indicating that these receptors occur chiefly on axonal nerve endings of both serotonergic and non-serotonergic neurons.

The **5-HT_{2A} receptor** subtype occurs as a postsynaptic receptor in both the peripheral nervous system and CNS, the highest density in the latter being those in the frontal cortex. High levels are also found in the claustrum, a region that has connections with the visual cortex, parts of the limbic system (e.g., the amygdala, hippocampus) and the basal ganglia. In the cortex, 5-HT_{2A} receptors are located on local GABAergic interneurons as well as on pyramidal glutamatergic projection neurons. The high density of this 5-HT receptor subtype in the cortex suggests that it plays a role in cognitive and integrative functions. Activation of CNS 5-HT_{2A} receptors results in elevation of body temperature and increased release of adrenocorticotropic hormone. The receptor has also been associated with the hallucinogenic effects of 5-HT_{2A} receptor agonists. Finally, this receptor subtype is of interest in connection with the action of **antipsychotic agents**; the so-called atypical antipsychotics (see Chap. 5), such as clozapine and olanzapine, are high-affinity antagonists of the 5-HT_{2A} receptor and dopamine D2 receptor family.

The **5-HT_{2B} receptor** occurs in humans primarily in peripheral tissues. Very high concentrations of 5-HT_{2B} mRNA in the placenta, lung, liver, kidney, heart, small intestine, and stomach have been measured. In contrast, only comparatively low levels in the brain have been found, in the cerebellum, cerebral cortex, amygdala, substantia nigra, nucleus caudatus, thalamus, hypothalamus, and retina. The functional role of 5-HT_{2B} receptors is little understood, as until recently there have been no selective agonists (Table 1.12). This 5-HT receptor subtype also occurs, however, in a number of blood vessels; contraction of the renal artery is controlled by the

5-HT_{2B} receptor. Antagonists of this receptor were developed for their potential clinical value in the treatment of migraine attacks.

The highest densities of the **5-HT_{2C} receptor** in the human and rat brain have been measured in the epithelial cells of the choroid plexus, leading to the proposal that activation of this subtype by 5-HT is involved in the regulation of the composition and volume of cerebrospinal fluid. Much lower levels of the 5-HT_{2C} receptor have, however, also been demonstrated in other regions of the brain, especially in parts of the limbic system (hypothalamus, hippocampus, septum, neocortex) and regions associated with motor control (substantia nigra, globus pallidus). The lack of selective 5-HT_{2C} receptor agonists and antagonists is the reason for the very limited knowledge of the function of this 5-HT subtype in the CNS.

As already noted, the **5-HT_3 receptor**, in contrast to the other 5-HT receptor subtypes, belongs to the receptor family of ligand-gated ion channels. Characteristic for this receptor family is that the receptor is modulated via pharmacologically distinct binding sites other than the actual ligand recognition site; alcohol and narcotics are examples for such modulatory agonists. The 5-HT_3 receptor is widely distributed in both the peripheral and CNS (Table 1.13). The highest binding site density is found in all levels of the area postrema, in the nucleus tractus solitarius, and in the substantia gelatinosa in the spinal cord as well as in lower brainstem nuclei (such as the nucleus trigeminalis and the dorsal vagal complex). The presence of these receptors in the spinal cord implies that they are involved in the modulation of nociceptive mechanisms; stimulation of 5-HT_3 receptors enables the release of substance P in the spinal cord. The localization of binding sites of this receptor in cortical and limbic regions of the brain is consistent with findings from animal investigations that suggest the anxiolytic, antidepressive, and cognitive potential of 5-HT_3 receptor antagonists. The observation that the activity of dopaminergic neurons in the VTA is modulated by 5-HT_3 receptors led to the hypothesis that 5-HT_3 receptor antagonists possess antipsychotic properties and the capacity to reduce the rewarding effect of alcohol and other drugs of abuse. The therapeutic efficacy of ondansetron, an antagonist of this receptor, in reducing emesis and nausea caused by chemotherapy of cancer is explained by its blockade of 5-HT_3 receptors in the intestinal mucosa.

The **5-HT_4 receptor** occurs at high density, as indicated by radioligand binding studies, in the striatum, substantia nigra, and tuberculum olfactorium, but also in the hippocampus. This postsynaptic receptor subtype modulates the release of various neurotransmitters, including ACh, dopamine, and GABA as well as, indirectly, that of 5-HT. Activation of this receptor in rats and apes brings about an enhancement of cognitive performance. Its enhancement of memory has, however, not yet been conclusively demonstrated in clinical studies.

The **5-HT_7 receptor** is the most recently identified G protein-coupled 5-HT receptor. In the absence of selective agonists and antagonists, little is known of the function and CNS distribution of this receptor. A role for this receptor in circadian rhythms has been discussed. There are, however, increasingly numerous suggestions that this receptor also plays a role in psychiatric disorders. Atypical antipsychotics, such as clozapine and risperidone, as well as some antidepressants exhibit high affinities for the 5-HT_7 receptor.

1.3.3 Amino Acid Neurotransmitters

ACh and the biogenic amines are generally synthesized only in certain neurons. The amino acid neurotransmitters, aspartate, GABA, and glutamate, are, in contrast, intermediate **metabolites of general biochemical pathways**. L-Asparagine and L-glutamic acid are proteinogenic amino acids, and thus building blocks of most proteins. Under physiological conditions, they exist as salts, for which reason the terms aspartate and glutamate are frequently used as synonyms. Glutamic acid is a key product in amino acid

metabolism, in that the degradation of amino acids commences with the catalyzed transfer of the amino group to the citric acid cycle intermediate α-ketoglutarate (oxoglutarate) or other α-ketoacids; where α-ketoglutarate accepts the amino group, glutamate is the amino acid product. In GABAergic neurons, moreover, glutamate is the precursor of GABA, to which it is decarboxylated.

1.3.3.1 Aspartate and Glutamate

Neuroanatomical Distribution

Glutamate is probably the most utilized excitatory neurotransmitter in the brain and spinal cord; 80–90 % of excitatory CNS synapses employ glutamate as neurotransmitter. The repolarization of membranes depolarized by glutamatergic activity accounts for around 80 % of energy consumption by the brain. The **excitatory action** of very low concentrations of aspartate and glutamate (ca. 10 fM) by almost all neurons has long been known through electrophysiological investigations. Although the unambiguous demonstration that they acted as neurotransmitters was difficult because both amino acids are involved in a number of other physiological processes (only around 30 % of assayed CNS glutamate is related to neurotransmission), there is no longer any doubt regarding the neurotransmitter function of glutamate. The status of aspartate remains unresolved, however. There is some evidence for a neuropeptide-like modulatory role for aspartate, in particular hippocampal synaptic populations where either glutamate or GABA serves as the principal neurotransmitter (Nadler 2011).

Many neurons that project from the cortex to the striatum, thalamus, brainstem, and spinal cord employ glutamate as neurotransmitter, as do afferent, intrinsic, and efferent neurons of the hippocampus. Different regional aspartate and glutamate concentrations are measured in projection areas, corresponding to the degree of innervation (Fig. 1.16). It is noteworthy that aspartate and glutamate occur at 1,000 times higher concentrations than those of biogenic amines such as dopamine (Fig. 1.1). It is believed that aspartate and glutamate play an important role in cognitive functions controlled by the cortex and hippocampus (learning and memory formation), in pyramidal and extrapyramidal motor functions (initiation of movements), and in synaptogenesis. Disturbances of glutamatergic neurotransmission are involved in the pathogenesis of epilepsy as well as in acute (stroke) and chronic neurodegenerative disorders (Alzheimer's disease, amyotrophic lateral sclerosis = ALS, Huntington's chorea, Parkinson's disease).

Biosynthesis and Inactivation Mechanisms

Aspartate and glutamate are nonessential amino acids that cannot cross the blood-brain barrier. Both amino acids are synthesized in the brain from circulating glucose (Fig. 1.17). The intermediate metabolite α-ketoglutarate is produced by glycolysis and the citric acid cycle (= tricarboxylic acid cycle), and glutamate is synthesized from this and other blood-brain barrier-permeable amino acids (probably leucine, isoleucine, valine). The concentrations of α-ketoglutarate, constantly metabolized by the citric acid cycle, are in a steady state relationship with those of glutamate. Aspartate is produced by the reversible aspartate transaminase-catalyzed transfer of the amino group from glutamate to the citric acid cycle intermediate oxaloacetate, the other product being a further citric acid cycle intermediate, α-ketoglutarate.

Glutamate and aspartate are transported into separate populations of synaptic vesicles by **vesicular glutamate transporters** (VGLUT) and sialin, respectively, and stored for release. Three vesicular glutamate transporters (VGLUT1–VGLUT3) have thus far been cloned. They are multimeric protein complexes that very efficiently transport glutamate against a concentration gradient into vesicles; the process is ATP and H^+ dependent. The concentration of glutamate in the vesicles is estimated at 60–250 mM, whereas the cytosolic level is only a few mM (Hassel and Dingledine 2005). Sialin is a member of the SLC17 anion transporter family and shares

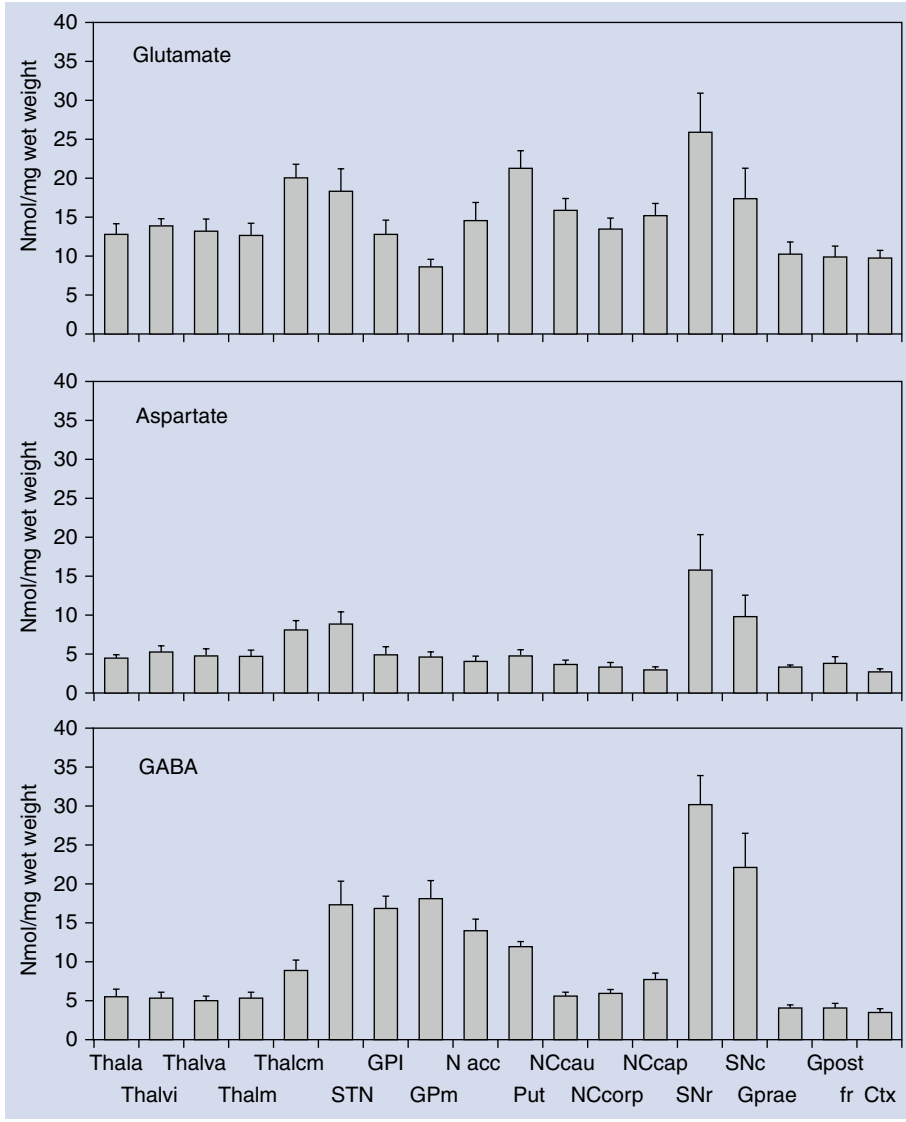

Fig. 1.16 Regional distribution of aspartate, glutamate, and GABA in postmortem human brain (mean values ± SEM; modified from Gerlach et al. 1996). *fr Ctx* frontal cortex, *GPl* globus pallidus pars lateralis, *GPm* globus pallidus pars medialis, *Gprae* gyrus praecentralis, *Gpost*, gyrus postcentralis, *N acc* nucleus accumbens, *NCcau* cauda nucleus caudatus, *NCcap* caput nucleus caudatus, *NCcorp* corpus nucleus caudatus, *Put* putamen pars anterior, *SNc*, substantia nigra pars compacta, *SNr* substantia nigra pars reticulata, *STN* nucleus subthalamicus, *Thala* nucleus anterior thalami, *Thalcm* nucleus centromedianus thalami, *Thalm* nucleus medialis thalami, *Thalva* nucleus ventralis anterior thalami, *Thalvl* nucleus ventralis lateralis thalami

considerable sequence homology with the VGLUTs (see Nadler 2011). In most cells of the body, including astrocytes and oligodendrocytes, sialin is expressed as a lysosomal transmembrane protein whose function is to transport sialic acid, along with H^+, out of the lysosome.

The larger fraction of released glutamate is probably taken up by glutamate transporter systems into astrocytes, where it is degraded to glutamine (Fig. 1.17). This is then taken up by glutamatergic neurons, available for renewed utilization in the glutamate and GABA neurotransmitter

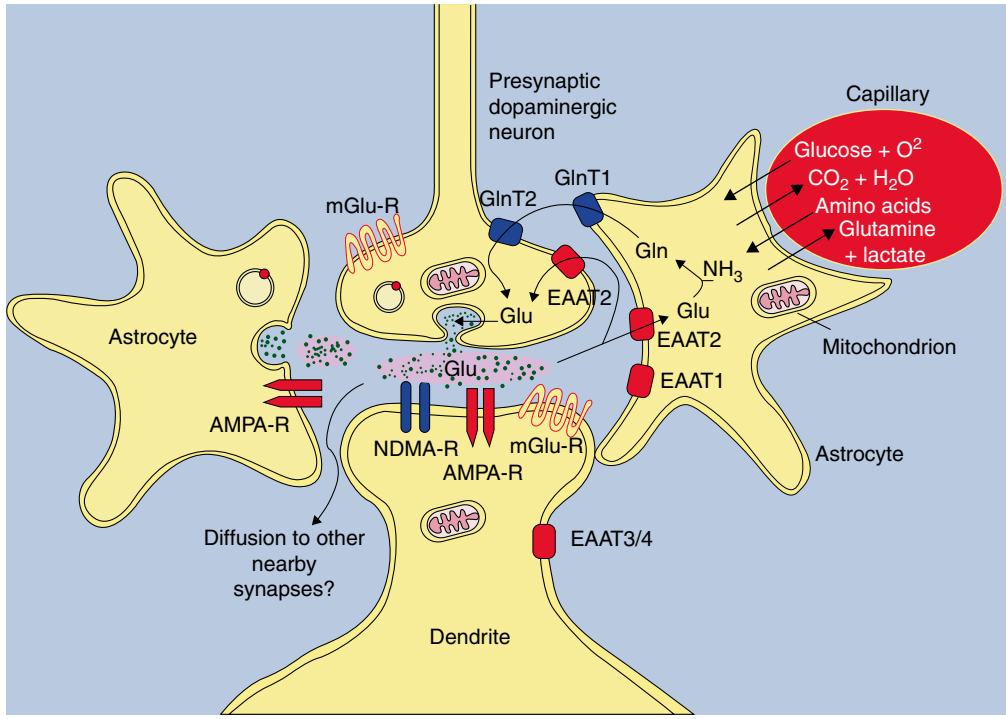

Fig. 1.17 Axodendritic synaptic glutamatergic neurotransmission (modified from Hassel and Dingledine 2005). *AMPA-R* 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propionic acid receptor, *EAAT1* excitatory amino acid transporter type 1, *EAAT2* excitatory amino acid transporter type 2 (synonym: glutamate-aspartate transporter), *EAAT3/4* excitatory amino acid transporter type 3 and 4, *Gl* glutaminase, *Gln* glutamine, *GlnT1*, *GlnT2* glutamine transporter, *Glu* glutamate, *mGlu-R* metabotropic glutamate receptor, *NMDA N*-methyl-D-aspartate receptor

pool. There is currently little evidence for extracellular metabolism of glutamate in the CNS.

As polar zwitterions, aspartate and glutamate are unable to diffuse across lipid bilayer membranes. **Na^+-dependent glutamate transporters** coupled with an electrochemical gradient are thus required to enable the movement of aspartate and glutamate against their respective concentration gradients (Fig. 1.17). There is strong evidence that their chief function is to maintain synaptic concentrations of aspartate and glutamate as low as possible and thereby to prevent excessive stimulation of glutamate receptors (see following section on excitotoxicity). L-Aspartate and L-glutamate have a similar affinity for this transporter and are therefore transferred with roughly the same velocity. As with many CNS transport systems, D-aspartate is transported with the same speed as the L-isomer, but this does not apply to D-glutamate. Several members of the Na^+-dependent glutamate transporter family have been cloned, and they exhibit differences in their regional and cellular distributions: the glutamate-aspartate transporter, corresponding to the human transporter EAAT1 (excitatory amino acid transporter), occurs almost only in astrocytes; glutamate transporter-1, corresponding to human EAAT2, occurs in both astrocytes and neurons, while EAAT3 and EAAT4 are primarily expressed in neurons. Unlike the biogenic amine transporter systems, the Na^+-dependent glutamate transporter family is not dependent upon Cl^-.

Glutamate Receptors

As aspartate and glutamate, and perhaps certain of their analogues, exert an excitatory effect upon postsynaptic receptors, these receptors are termed **excitatory amino acid receptors**. In this chapter, we follow the practice of naming this family of neuroreceptors after their most prominent

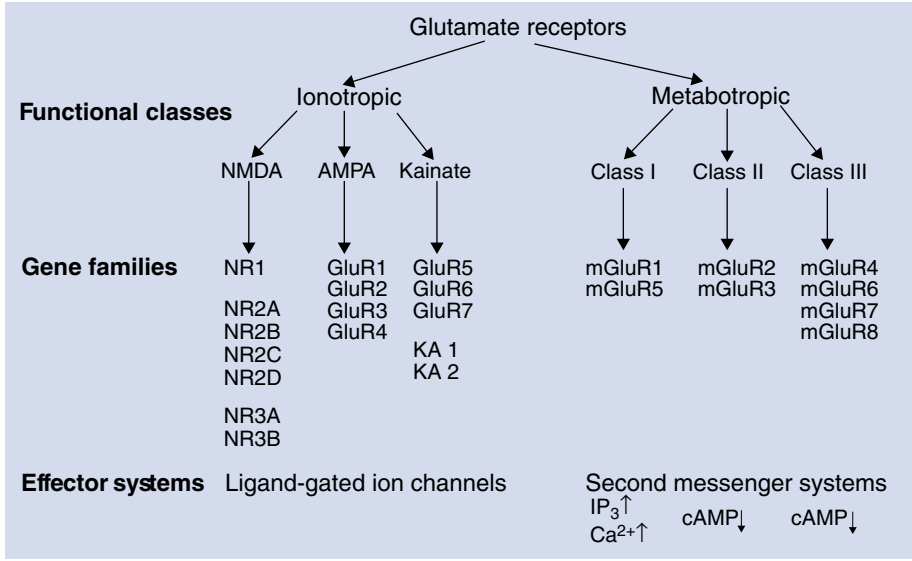

Fig. 1.18 Molecular classification of glutamate receptors (modified from Hassel and Dingledine 2005). *AMPA* 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propionic acid, *cAMP* cyclic adenosine 3′,5′-monophosphate, *Glu* glutamate, IP_3 inositol-1,4,5-triphosphate, *NMDA* *N*-methyl-D-aspartate

neurotransmitter agonist and so use the term "glutamate receptors" to refer to all excitatory amino acid receptors. Glutamate receptors are divided into ligand-gated (ionotropic) ion channels and G protein-coupled (metabotropic) receptors (Fig. 1.18). Ionotropic receptors all produce fast (<10 ms) synaptic conductances, whereas metabotropic receptors influence synaptic transmission over a slower timescale (sub-seconds to minutes). Each of these two receptor classes are subdivided into three functionally defined groups composed of members of different molecular families of receptor genes.

On the basis of analogies with other ligand-gated ion channels, it is thought that ionotropic glutamate receptors consist of heteromeric groups (probably tetrameric) of homologous receptor subunits, each coded by distinct genes (Fig. 1.18). One feature of these receptors is that different combination of subunits produces functionally different receptors, which implies the existence of a great variety of glutamatergic receptors in the brain (Paoletti 2011). For instance, the NMDA receptor (NMDA = *N*-methyl-D-aspartate) is composed of the NR1 receptor subunit and a combination of one or more NR2 receptor subunits (A–D) as well as a third NR3 subunit (A, B).

The **glutamatergic ion channel receptors** are divided into pharmacologically and functionally distinct receptors: the **NMDA**, **AMPA** (2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propionic acid), and **kainate receptors**. All of these receptors are permeable for Ca^{2+}, K^+, and Na^+, whereby the relative degree of permeability is determined by the subunit composition of the receptor. For example, the AMPA receptor that includes GluR2 subunits chiefly allows Na^+ to pass from the extracellular side to the intracellular space; for Ca^{2+}, in contrast, it is permeable to only a very limited degree.

The endogenous ligands for the NMDA receptor are glutamate and aspartate. The latter activates only this glutamate receptor subtype and exerts no effects upon other ion channel receptors. The NMDA receptor, one of the most tightly controlled neurotransmitter receptors, exhibits a number of special properties (Fig. 1.19): There are no less than six distinct binding sites for endogenous ligands that probably modulate

opening of the channel pore, including two binding sites for two different agonists, glutamate and glycine: the binding of both is required for the opening of the NMDA receptor channel. The glycine binding site differs pharmacologically from classical inhibitory glycine receptors in that it is not inhibited by strychnine, nor activated by β-alanine. As neither glycine nor glutamate alone can open the NMDA-coupled ion channel, they are termed co-agonists. There is also a polyamine binding site that also regulates activation as well as various further binding sites for Mg^{2+}, H^+, and Zn^{2+}, the role of which is to inhibit the ion flow elicited by the agonists. Finally, the redox state of the NMDA receptor influences the reaction elicited by its activation: one of three pairs of cysteine groups can be in either a reduced form (amplifying the activated NMDA receptor response) or an oxidized form (presence of disulphide bridges: reduces the activated NMDA receptor response). At normal resting potential, the NMDA receptor is closed by Mg^{2+}. The channel opens only following partial depolarization (including that elicited by activation of AMPA receptors), whereby the Mg^{2+} are driven out by electrostatic repulsion through the opening of the channel pore, so that Ca^{2+} can stream into the nerve cell. Other potential-dependent inhibitors of the NMDA receptor channel include MK-801 (dizocilpine); ketamine, a narcotic agent; phencyclidine (PCP), formerly employed as a narcotic agent but now a widely used designer drug (angel dust) that, among other effects, causes nightmarish hallucinations; and memantine, licensed for the therapy of Alzheimer's disease.

Autoradiographic receptor binding investigations indicate that ionotropic glutamate receptors are predominantly postsynaptic and that their **regional distribution** in the human brain is highly differentiated. The distribution pattern for

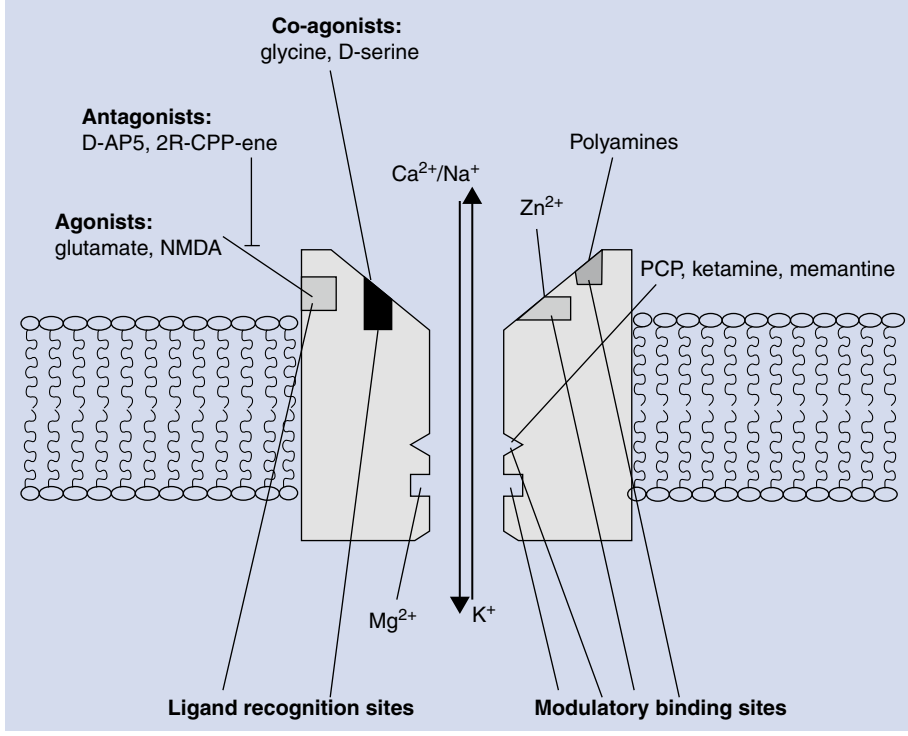

Fig. 1.19 Schematic representation of the NMDA receptor. At normal resting potential, it is closed by Mg^{2+}. Only a selection of the modulatory binding sites is shown. *D-AP5* 2-amino-5-phosphonopentanoic acid, *NMDA* N-methyl-D-aspartate, *PCP* phencyclidine, *2R-CPPene* 3-(2-carboxypiperazin-4-yl)1-propyl-1-phosphonic acid

NMDA and AMPA receptors are similar, but different to that of kainate receptors. High AMPA and NMDA receptor binding densities have been found in the cerebral cortex, hippocampus, lateral septum, striatum, amygdala, and the molecular layer of the cerebellum; high kainate receptor binding densities have been measured in the CA3 region of the hippocampus, the cortex, and the lateral septum.

The **physiological and pathophysiological function** of postsynaptic ionotropic glutamate receptors has been intensively investigated with molecular and pharmacological methods. The Ca^{2+} that streams together with Na^{+} into the postsynaptic nerve cell, following opening of the ion channel (Fig. 1.19), activates second messenger cascades that result in long-term metabolic and structural changes, as well as prolonged elevation of efficiency of the transmission. NMDA receptors play an important role in plasticity in both the developing and mature brain (Paoletti 2011). Postsynaptic AMPA receptors participate in signal transmission at most of the fast excitatory synapses in the CNS. Both glutamate receptor subtypes are involved in certain forms of plasticity, such as long-term potentiation (LTP) and long-term depression (LTD). LTP is electrophysiologically demonstrable, but only occurs if other synapses on the same neuron are activated at the same time. This creates the possibility for the logical associations required for learning processes. The role of kainate receptors is less clear, but there are indications that these receptors occur postsynaptically in the hippocampus and spinal cord and influence neurotransmitter release.

Excessive stimulation of ionotropic glutamate receptors also elicits, however, neurotoxic effects leading to the death of neurons bearing these receptors. The term for this phenomenon is **excitotoxicity**. The term implies two contradictory actions associated with the excitatory amino acids (glutamate, aspartate, NMDA, and kainate): a physiological, excitatory effect, and a nonphysiological neurotoxic action. The neurotoxic facet of these amino acids was first recognized in animal experiments by Olney (1978): oral administration of glutamate and chemically related substances to young animals leads to acute neuronal cell loss in brain regions not well protected by the blood-brain barrier, above all the nucleus arcuatus in the hypothalamus. Histological investigations showed that it was always the postsynaptic cell structures at glutamatergic synapses (dendrites and cell bodies) that were affected, while presynaptic nerve terminals and nonneuronal cells were unscathed. It is now thought that the neurotoxic action of excitatory amino acid is primarily the result of an uncontrolled Ca^{2+} influx into the nerve cell following extended stimulation of NMDA and AMPA receptors. This leads to unregulated activation on Ca^{2+}-dependent enzymes (such as Ca^{2+}-/calmodulin-dependent protein kinase II, protein kinase C, phospholipase A_2, NO synthetase, and endonucleases), causing lipid and protein degradation, the generation of free radicals, and ultimately irreversible damage to the nerve cell.

Elevated glutamate release, NMDA receptor and glutamate transporter dysfunction as well as characteristic cytopathological changes have been identified in a range of acute and chronic neurodegenerative disorders: those involving acute neuronal loss include stroke and epileptic fits, while Huntington's chorea, Alzheimer's disease, ALS, and Parkinson's disease are examples for chronic neurodegeneration.

Eight human **metabotropic glutamate receptor** subtypes (mGluR1–mGluR8) have been identified to date. The recombinant receptors are all stimulated by glutamate, but the efficacy varied widely, from 2 nM (mGluR8) to 1 mM (mGluR7). On the basis of amino acid sequence homology, pharmacology, and coupling with particular second messenger systems, they are divided into three groups (Fig. 1.18), for each of which there are now several selective agonists: 3,5-dihydroxyphenylglycine (DHPG) appears to be a selective group I agonist, 2R,4R-4-aminopyrrolidin-2-4-dicarboxylate (ADPC) is highly selective for group II receptors (440 nM), and L-amino-4-phosphonobutyrate (L-AP4) is a selective agonist for group III. An interesting development in the pharmacology of metabotropic glutamate receptors has been the discovery

of allosteric modulators of particular receptor subtypes. These agents bind to transmembrane domains, either positively or negatively influencing glutamate-mediated activation.

The lack of selective agonists and antagonists for the individual subtypes has hampered investigation of the physiological roles of the various metabotropic receptors. The regional distribution in human brain is similarly largely unexplored. Metabotropic glutamate receptors appear to be widely distributed in the CNS, both pre- and postsynaptically. Activation of presynaptic metabotropic glutamate receptors blocks the transmission not only of excitatory glutamatergic but also of inhibitory GABAergic neurotransmission, probably by an effect upon the voltage-gated Ca^{2+} channels. Postsynaptic receptors modulate the ion channel activity of a variety of ligand- and voltage-gated ion channels. Whether activation leads to inhibition or potentiation of the receptors depends upon the component of the signal transduction mechanism affected and the neuron type on which the receptors are located. Activation of metabotropic glutamate receptors on hippocampal pyramidal cells, for instance, enhances the effects elicited by activation of NMDA receptors. In cerebellar granule cells, in contrast, activation leads to an inhibition of the elevation of intracellular Ca^{2+} concentrations elicited by NMDA receptor activation. The results of investigations in genetically modified mice have suggested possible physiological functions of metabotropic glutamate receptors: mice lacking the mGluR1 gene exhibited symptoms of cerebellar dysfunction, such as ataxia, intention tremor, and dysmetria. Generally impaired motor coordination and LTP deficits were similarly described in these mice.

1.3.3.2 GABA

Neuroanatomical Distribution

GABA is the most important **inhibitory transmitter** in the mammalian brain, and the first amino acid for which a neurotransmitter function was suspected on the basis of electrophysiological findings. Maintenance of a physiological balance between inhibitory and excitatory neurotransmission in the CNS is critical in determining normal brain function and behavior. This relies on a functional interaction between GABA and glutamate, the major neurotransmitter involved in mediating excitatory synaptic activity.

The neuroanatomic distribution of GABAergic neurons in the human brain is still only **imperfectly known**, essentially because there are no sufficiently reliable or unambiguous methods for the mapping of GABAergic neuronal systems. The identification of the GABA-synthesizing enzyme glutamic acid decarboxylase by means of labeled antibodies cannot be employed in postmortem human tissue because the enzyme is oxygen dependent, so that its activity declines rapidly after death. Investigations of the reuptake sites with radioactively labeled GABA indicate that GABA is present in most brain regions, 25–45 % of nerve terminals using GABA as neurotransmitter, depending upon the region examined. The direct assay of GABA in postmortem tissue is similarly problematic: as GABA is also produced in the course of protein metabolism, it is difficult to determine what proportion of measured GABA is relevant to its role in neurotransmission. It is thought that 70–80 % of measured GABA can be attributed to the neurotransmitter pool, but the actual proportion may well be smaller, as GABA also occurs in glia (see Gerlach et al. 1996).

As for the amino acid neurotransmitter glutamate, GABA occurs at regionally different concentrations (Fig. 1.16), suggestive of a role in neurotransmission. Immunohistochemical investigations in rat brain indicate that not only are there GABAergic projection neurons, some with very long processes (e.g., cortico-nigral, striato-pallidal, nigro-thalamic), but also GABAergic interneurons (including the granulate cells of olfactory bulb, Purkinje cells, and cerebellar basket cells).

Biosynthesis and Inactivation Mechanisms

GABA is synthesized in the so-called **GABA shunt**, the closed-looped system that constitutes a side path to the citric acid cycle and is responsible for the synthesis, supply, and metabolism of GABA (Fig. 1.20). Glucose is the major source for GABA synthesis, although pyruvate and other amino acids can serve as precursor. The

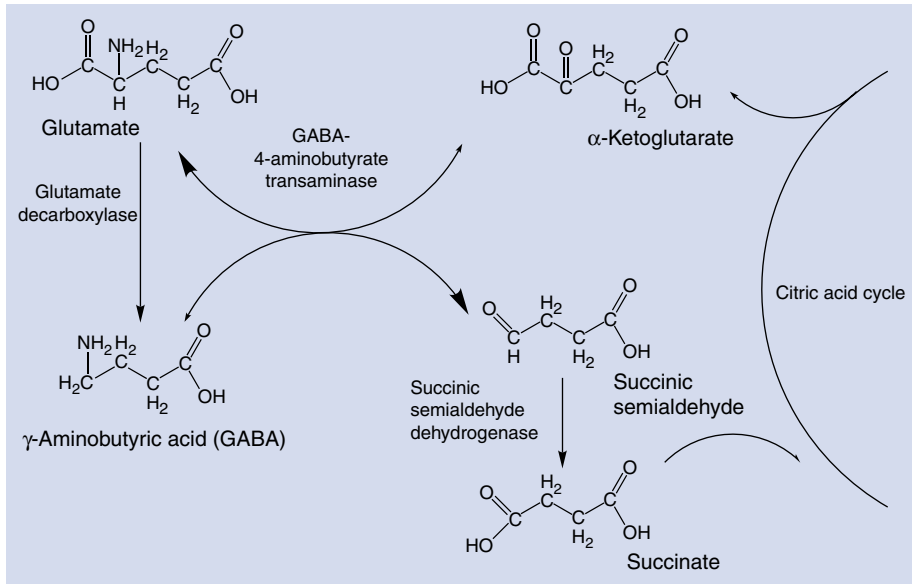

Fig. 1.20 The γ-aminobutyric acid (GABA) metabolic pathway

first step in the GABA shunt is the transamination by GABA oxaloacetate transaminase of α-ketoglutarate, an intermediate metabolite in the citric acid cycle, to glutamate; this is then converted by glutamate decarboxylase to GABA. Glutamate decarboxylase occurs presynaptically only in neurons that employ GABA as their neurotransmitter. GABA is catabolized by GABA oxaloacetate transaminase to succinic semialdehyde; in order to secure the availability of GABA, this transamination generally only occurs when the co-substrate α-ketoglutarate is available to accept the amino group removed from GABA. For this reason, a molecule of GABA can only be synthesized when one of its precursors is available. Succinic semialdehyde is then oxidized by succinic semialdehyde dehydrogenase to succinate, which is available for reinsertion into the citric acid cycle.

Termination of the synaptic action of GABA occurs principally through **reuptake** into presynaptic nerve terminals and nearby glia by specific transport systems, the membrane-bound GABA transporter (synonym: plasmalemma transporter). A variety of subtypes of this transporter have been cloned, all of which are both temperature and ion dependent and capable of facilitating the transport of GABA in both directions. The dependence upon extracellular Na^+ and also Cl^- is also critical. The family of membrane-bound GABA transporters includes glycoproteins with 12 transmembrane regions and molecular mass of 80 kDa; they share no amino acid sequence homologies with GABA receptors, but exhibit similarities to other Na^+-dependent transporters. The vesicular transporters differ from the membrane-bound GABA transporter in the number of transmembrane regions (ten) and the autonomy of transport from extracellular Na^+ concentration.

GABA taken up into the presynaptic nerve terminals can be used for renewed release; GABA transported into glia, however, is degraded by GABA oxaloacetate transaminase to succinic semialdehyde and thus cannot be immediately employed for the resynthesis of GABA, as glutamate decarboxylase is not present in glia. Only the digression via the citrate acid cycle and glutamate production enables resynthesis; the glutamate is then converted to glutamine, which is transported to neurons, where it is again converted by glutaminase to glutamate, which can then once more enter the neuronal GABA shunt.

GABA Receptors

The effects of GABA are mediated by at least **two classes** of GABA receptors, the $GABA_A$ and $GABA_B$ types, that are distinguished by their pharmacological, electrophysiological, and biochemical characteristics (Table 1.14). The GABA receptors are the **major targets for** a variety of **psychopharmaceuticals**, including the benzodiazepines, barbiturates, intravenous and gaseous narcotic agents, neurosteroids, and, possibly, also alcohol. Some of these agents have long been employed in the therapy of patients, without initially knowing their mechanism of action. Phenobarbital, for instance, has been used since 1912 in the therapy of epilepsy. Another example are the benzodiazepines, such as diazepam and chlordiazepoxide, introduced into the clinical practice more than 50 years ago, and today are among the most employed psychopharmaceuticals. They possess anxiolytic, sedative, muscle-relaxant, and anticonvulsive properties and are utilized above all in anxiety and stress conditions, depression, and sleep disorders. At higher doses, symptoms of the opposite type can arise: euphoria, agitation, and insomnia. Only elucidation of the mode of action of the $GABA_A$ receptor permitted understanding of the molecular site of action and mechanisms of barbiturates and benzodiazepines. Similar to ACh and glutamate, GABA utilizes both receptors that are coupled with ligand-gated ion channels ($GABA_A$ receptor class) as well as receptors that modulate G protein-regulated signal transduction cascades ($GABA_B$ receptor class).

The **$GABA_A$** receptor type is a **ligand-gated Cl^- channel** (the so-called $GABA_A$ receptor-chloride channel complex), activation of which by GABA and agonists such as muscimol (found in fly agaric, *Amanita muscaria*) leads to direct opening of the channel pore (Fig. 1.21). The classic antagonist is the anticonvulsive agent bicuculline, which reduces activity of the receptor by reduction of the channel opening frequency and the mean duration of opening. Electrophysiological investigations of this receptor type indicate that their activation results in elevated conductance: the equilibrium potential is close to the resting potential of −70 mV. This elevation of conductance is often associated with a membrane hyperpolarization, resulting in a higher firing rate threshold and a reduced probability of the occurrence of an action potential. The end result is neuronal inhibition. On the other hand, the increased permeability for Cl^- in case of elevated intracellular Cl^- concentrations can also depolarize the target cell. This can in turn cause the neuron to fire or to enable the entry of Ca^{2+} via voltage-gated channels, a mechanism that has been attributed physiological significance, particularly in embryonic neurons.

Similar to the nACh receptor (Fig. 1.10), for example, or the serotonergic 5-HT_3 receptor, the $GABA_A$ receptor is composed of different subunits. These subunits possess an amino acid sequence homology with subunits of other ligand-gated receptors and are coded by multiple genes. The $GABA_A$ receptor-chloride channel complex is a pseudo-symmetric pentamer that spans the double lipid membrane and forms the Cl^- channel. The binding of GABA and structural analogous with agonist activity (Table 1.14) to the GABA receptor recognition site (Fig. 1.21) opens this channel. Each $GABA_A$ receptor subunit includes four α-helical transmembrane domains (M1–M4) with mostly hydrophobic characteristics, of which one or more form the channel pore. At least 19 distinct but closely related polypeptides have been identified, from which these subunits can be assembled: α1–6, β1–3, γ1–3, δ, ε, ψ, π, and ρ1–3. The differing distribution of the corresponding mRNAs and polypeptides in the brain is consistent with data that indicate their regional diversity with regard to physiological function, pharmacology, and biochemistry. It may be assumed that combinations of different subunits occur with different pharmacological characteristics and Cl^- channel permeability in various neuronal populations, possibly even at different sites on the neuronal membranes. The ρ-subunits are expressed predominantly in the retina, where they probably form homomeric Cl^- channels with novel pharmacological characteristics. On the basis of their insensitivity to both bicuculline and baclofen these receptors have also been classified as type $GABA_C$, that is, non-A, non-B.

Table 1.14 Classification, nomenclature, and characteristics of human GABA receptor classes

Standard name	$GABA_A$		$GABA_B$
	Neurotransmitter recognition site	Allosteric modulatory site	
Agonists	Isoguvacine Muscimol THIP (gaboxadol) Piperidine-4-sulfonic acid	Not applicable	(R)-Baclofen 3-Aminopropylphospinic acid 3-Aminopropylmethylphosphinic acid
Antagonists	Bicuculline SR 95531	Ro 15-1788 (flumazenil) ZK 93426	Phaclofen 2-Hydroxy-saclofen CGP35348 CGP55845 SCH-50911
Indirect agonists	γ-Vinyl-GABA (vigabatrin)	Not applicable	Not applicable
Positive modulators	None known	Allopregnanolone Barbiturates (phenobarbital, pentobarbital, thiopental) Flunitrazepam Diazepam Alprazolam Zolpidem	CGP7930 CGP13501
Negative modulators	None known	Pregnenolone DMCM FG 7142	Not applicable
Partial modulators	None known	Bretazenil Imidazenil	Not applicable
Channel blocker	TBPS Picrotoxin	Not relevant	Not applicable
Signal transduction mechanism	Cl^- influx	Modulates $GABA_A$-activated Cl^- channels	G_s (increase cAMP) G_i (cAMP modulation) Increase K^+ (G) Increase Ca^{2+} (G)
Physiological function	Neuronal inhibition	Modulation of neuronal inhibition	Modulates slow inhibitory postsynaptic potentials Auto- and heteroreceptor-coupled neurotransmitter release Modulation of K^+ and Ca^{2+} conductance Inhibition of adenylate cyclase Stimulation of MAP kinase

Modified from Watling (2006)
cAMP cyclic adenosine 3′,5′-monophosphate, *Ca^{2+} (G)* G protein-coupled calcium channel, *K^+ (G)* G protein-coupled potassium channel, *MAP kinase* mitogen-activated protein kinase
Chemical names: *CGP13501* 3-(3′,5′-Di-tert-butyl-4′-hydroxy)phenyl-2,2-dimethylpropanal, *CGP35348* 3-aminopropyl-diethoxymethylphosphinic acid, *CGP55845* (3-*N*[[1-(*S*)-(3,4-dichlorophenyl)ethyl]amino-2(*S*)-hydroxypropyl)-benzyl-phosphinic acid, *CGP7930* 2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol, *DMCM* methyl-6, 7-dimethoxy-4-ethyl-β-carboline-3-carboxylate, *FG 7142* *N*-methyl-β-carboline-3-carboxamide, *SCH-50911* (+)-(S)-5,5-dimethylmorpholinyl-2-acetic acid, *SR 95531* 2-(3′-carboxy-2′-propyl)-3-amino-6-(4-methoxyphenyl)-pyridazinium bromide, *TBPS* t-butylbicyclophosphorothionate, *THIP* 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol, *ZK 93426* 5-isopropyl-4-methyl-β-carboline-3-carboxylate ethyl ester

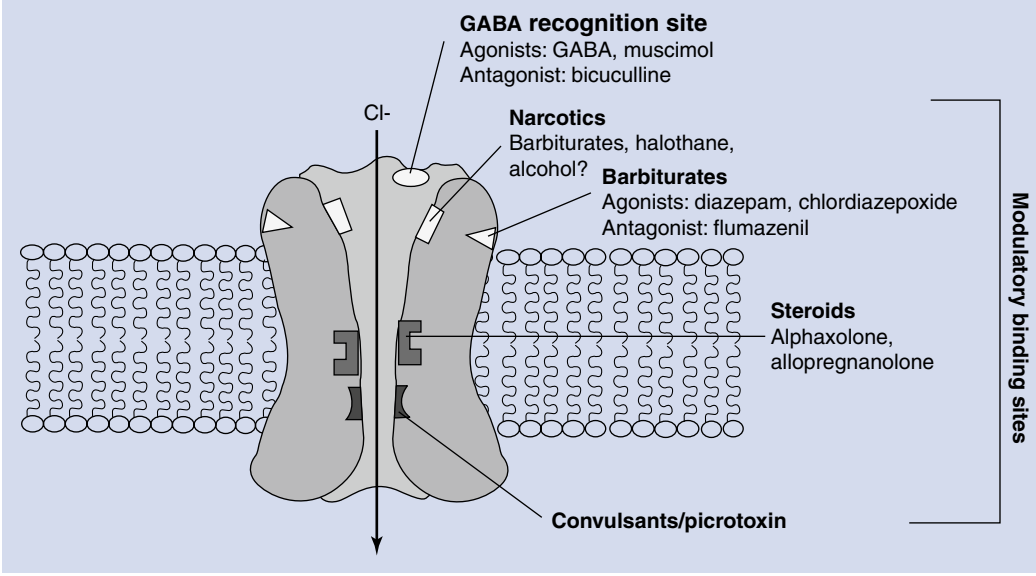

Fig. 1.21 Model of the structure of the $GABA_A$ receptor type. The cross section through the macromolecular protein complex illustrates the targets of a variety of psychopharmacological agents that influence channel activity

$GABA_A$ receptor possesses, in addition to the GABA recognition site at the interface of the α and β-units four further ligand-binding domains (Fig. 1.21) that allosterically modulate receptor activation (i.e., by modifying the conformation of the protein). Agents that bind these recognition sites are not themselves capable of opening the ion channel, but their binding elevates the affinity of GABA for the GABA recognition site and hence increases the permeability of the channel for Cl^-, amplifying the inhibitory function of GABAergic neurons.

Benzodiazepines and **barbiturates** (see Chap. 6) are agonists of the ligand-binding domains of $GABA_A$ receptors (Fig. 1.21); the affinity of benzodiazepines for these binding sites is tightly correlated with their clinical potency. The fact that the benzodiazepine binding site is evolutionarily conserved in all vertebrates has been interpreted as indicative of its physiological importance, motivating the search for endogenous agonists. It has been assumed that, in analogy to the mode of action of endorphins, benzodiazepine-like metabolites are synthesized in the body and act as regulatory factors in the CNS. Thus far, however, neither endogenous agonists nor antagonists have been discovered. Potential candidates include the purines inosine, hypoxanthine and methyl isoguanosine, nicotinamide, and individual hormonal agents, such as prostaglandin A and the diazepam binding inhibitor. All these substances exhibit, however, binding affinities several orders of magnitude lower than that of the benzodiazepines (K_i = 3–10 nM), so that it is now thought that benzodiazepines can be endogenously synthesized. The synthetic pathway and the involved enzyme systems nevertheless remain unknown.

The $GABA_A$ receptor-chloride channel complex occurs for the most part postsynaptically and is found on neuronal cell bodies, dendrites, and axons. However, research has identified also extrasynaptic $GABA_A$ receptor populations that enable neurons to sense the low ambient GABA concentrations present in the extracellular space in order to generate a form of tonic inhibition not previously considered in studies of neuronal excitability (Brickley and Mody 2012). The importance of this tonic inhibition in regulating states of consciousness is highlighted by the fact that extrasynaptic $GABA_A$ receptors are believed to be key targets for anesthetics, sleep-promoting drugs, neurosteroids, and alcohol.

The **regional distribution** of $GABA_A$ receptors in postmortem human brain has been primar-

ily investigated in binding studies with radioactive benzodiazepines: high binding densities have been identified in the CA1 and CA3 regions of the hippocampus, in the Purkinje and granulate cells of the cerebellums, in the striatum, and in the spinal cord.

The **$GABA_B$ receptor** is a **metabotropic receptor** that regulates the permeability of the cell membrane for K^+ and Ca^{2+} via G proteins (Table 1.14). $GABA_B$ receptors occur both pre- and postsynaptically. Activation leads to pre- and postsynaptic reduction of excitability by means of various effector systems (Table 1.14). Postsynaptic $GABA_B$ neuroreceptors open G protein-activated inwardly rectifying potassium channels (GIRKs; also known as inwardly rectifying K^+ Kir3 channels), which inhibit neuronal activity by local shunting and generate slow (100–500 ms) inhibitory postsynaptic potentials that hyperpolarize the membrane. The receptor has been characterized pharmacologically by its insensitivity to the $GABA_A$-antagonist bicuculline and certain $GABA_A$-specific agonists. The convulsant agent and GABA analog (–)baclofen (β-(4-chlorophenyl)-γ-aminobutyric acid) is a potent and selective agonist.

The $GABA_B$ receptor class belongs to group III of the G protein-coupled receptors and exhibits structural similarities to metabotropic glutamate receptors. Three principal subunits, $GABA_{B1a}$, $GABA_{B1b}$, and $GABA_{B2}$, have been cloned thus far; whereas the $GABA_{B1}$-isoform subunits contain the GABA binding site, $GABA_{B2}$ subunits couple to the G protein (Gassmann and Bettler 2012). $GABA_B$ neuroreceptors are now known to comprise principal and auxiliary subunits that influence receptor properties in distinct ways. The principal subunits regulate the surface expression and the axonal versus dendritic distribution of these receptors, whereas the auxiliary subunits determine agonist potency and the kinetics of the receptor response.

$GABA_B$ receptors are expressed by almost all neurons and glial cells in the CNS, and their activity influences many neural systems and behavioral states. It is therefore not too surprising that $GABA_B$ receptors have been implicated in a variety of neurological and psychiatric conditions, including epilepsy, anxiety, depression, schizophrenia, obsessive-compulsive disorder, addiction, and pain (Gassmann and Bettler 2012).

There have been only a few receptor binding investigations with respect to its distribution in the human brain; high binding densities appear to be present in Purkinje cell dendrites and the nerve terminals of cerebellar granulate cells.

1.4 Molecular Brain Structures as Targets for Psychopharmaceutical Agents

The effects of psychopharmaceuticals are achieved by modulation of neurotransmission. The agents most commonly employed in child and adolescent psychiatry have the following molecular sites of action:

- Enzymes involved in neurotransmitter metabolism
- Neuroreceptors
- Neuronal and glial transport proteins
- Voltage-gated ion channels

1.4.1 Modulation of Neurotransmitter-Catabolizing Enzymes

Inhibition of enzymes that catabolize neurotransmitters is a commonly encountered mode of action for psychopharmaceuticals. This leads both to an amplification of neurotransmitter action and to a temporal and spatial modulation of its effects. Table 1.15 lists examples of psychopharmaceuticals that utilize this mode of action.

The catabolism of monoaminergic neurotransmitters such as dopamine, noradrenaline, and 5-HT; of neuromodulators such as β-phenethylamine; as well as of other endogenous and exogenous monoamines such as tyramine by MAO was discussed in Sect. Biosynthesis and Inactivation Mechanisms. Inhibition of MAO-B with selective agents in human brain chiefly elevates synaptic concentrations of

Table 1.15 Examples of psychopharmaceutical agents that employ inhibition of neurotransmitter catabolism as their mode of action

Class	Mode of action	Major area of application
Antiepileptics		
Vigabatrin, valproic acid	Inhibition of GABA transaminase Elevation of presynaptic GABA concentration Amplification of GABA effect	Various forms of epilepsy
Antidepressants		
Tranylcypromine, moclobemide	Inhibition of MAO-A Elevation of presynaptic noradrenaline and serotonin concentrations	Depression Anxiety disorders

MAO-A isoform of monoamine oxidase

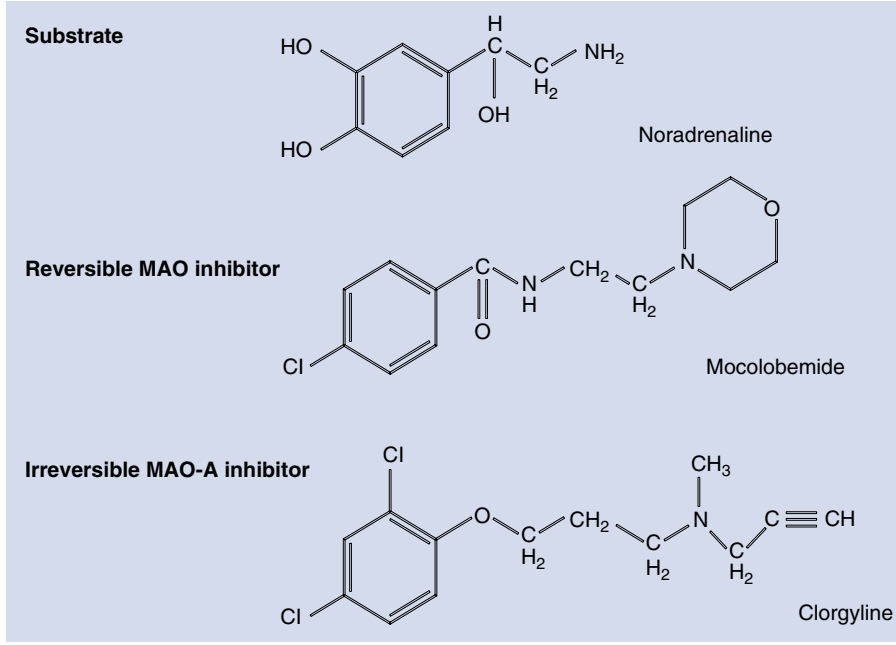

Fig. 1.22 Chemical formulae of noradrenaline and an example of reversible and irreversible monoamine oxidase type-A (MAO-A) inhibitors

β-phenethylamine and dopamine; selective MAO-A inhibition achieves increases in the concentrations of noradrenaline and 5-HT.

As with the interaction between pharmacological agents and receptors (see following section), that of MAO with an inhibitor initially involves the formation of an inhibitor-enzyme complex. The resulting enzyme inhibition can be competitive and reversible or noncompetitive and irreversible. Competitive inhibition ensues that the agent and the endogenous substrate compete reversibly at the binding site. Reversible MAO inhibitors are structurally very similar to the substrates of the enzyme (Fig. 1.22) but, unlike these substrates, are generally not metabolized by the enzyme. In noncompetitive inhibition, the agent reacts irreversibly with the active center; such inhibitors are also described as the so-called suicide inhibitors, as following their interaction with the active center of the enzyme, they are oxidized and covalently bound to the active center. In contrast to competitive, reversible inhibitors, typical irreversible MAO inhibitors, such as clorgyline, phenelzine, selegiline, and tranylcypromine

Table 1.16 Examples of typical monoamine oxidase (MAO) inhibitors

	Nonselective	MAO-A selective	MAO-B selective
Irreversible	Isocarboxazid Phenelzine Tranylcypromine	Clorgyline	Lazabemide Pargyline Rasagiline Selegiline
Reversible		Befloxatone Brofaromine Cimoxatone Moclobemide Toloxatone	

Classification is based upon their selectivity and reversibility of inhibition

(Table 1.16), are effective for extended periods, as the biological activity of the enzyme can be restored only by synthesis of new protein.

There are a number of inhibitors that selectively modulate one of the two forms of the enzyme (Table 1.16). Selective MAO-A inhibitors are currently employed as antidepressants (see Chap. 4); the major significance of selective MAO-B inhibitors is their application in the therapy of Parkinson's and Alzheimer's diseases. Selective MAO inhibitors have the advantage that they do not provoke the so-called **cheese effect** if consumed by patients who have also eaten tyramine-rich foodstuffs (such as cheese). The cheese effect leads to hypertensive crises with symptoms including severe cardiac palpitations, flushing of the face, sweating, nausea, and vomiting (Blackwell et al. 1967). This effect is caused by tyramine, a sympathomimetic that elevates blood pressure, and is metabolized by both MAO isoenzymes. If one isoform is selectively inhibited, the other is still available for the metabolism of tyramine. Therapy with the selective MAO-A inhibitor moclobemide, in contrast to tranylcypromine, a nonselective inhibitor, does not require a special diet.

1.4.2 Neuroreceptors

The binding characteristics of neuroreceptors determine the effect and specificity of a psychopharmacological agent that acts via these receptors. As the number of these receptors, like that of other endogenous functional body proteins, is limited, ligand binding is saturable. Furthermore, this binding is stereoselective and, in contrast to enzymatic reactions, is reversible without chemical alteration of the ligand occurring.

1.4.2.1 Occupation Theory as Explanation of the Action of Psychopharmaceutical Agents

There are numerous models of pharmacological receptors that can describe and predict the effect of pharmacological agents upon cells (Kenakin 2004). Long before the nature and molecular structure of receptors had been established, A. J. Clark (1937) systematically applied the mathematical methods of enzyme kinetic analysis to describe the effects of chemical substances upon biological tissue. He was thereby one of the founders of the occupation therapy, which was later extended by the operational model of receptor function (Kenakin 2004). The introduction of biochemical binding techniques enabled investigation of some of the molecules involved in the transmission of extracellular signals to the cell interior; this resulted in the development of the expanded ternary complex model, with which G protein-coupled receptor behavior could theoretically be described.

The occupation theory proposes that the effect of an agonist is proportional to the number of occupied receptors; further, it assumes that the agonist possesses the same affinity for all receptors of the one type. The occupation theory thus corresponds to the Michaelis-Menten model of the kinetic characteristics of many enzymes.

The simplest case – that of a reversible neurotransmitter-receptor interaction – is described

by Eq. (1.1), whereby [R] is the concentration of free receptor, [A] the concentration of free agonist, and [RA] the concentration of the receptor-agonist complex; the constants k_{+1} and k_{-1} are respectively the association and dissociation rates:

$$[R]+[A]\underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}}[RA]\rightarrow \text{Biological effect} \quad (1.1)$$

This produces a sigmoid dose-effect curve, from which the neurotransmitter concentration at which the half maximal effect is achieved can be calculated (**EC_{50}**, effector concentration 50 %). Michaelis-Menten equations can be used to calculate the dissociation constant (K_D) of the receptor-ligand complex (corresponding to the K_M value for enzymes). This is regarded as a measure of the affinity of the agonist for the receptor and is derived according to the law of mass action:

$$K_D = \frac{k_{-1}}{k_{+1}} = \frac{[A]\ [R]}{[RA]} \quad (1.2)$$

A low **K_D value** corresponds to a high affinity and is the result of a high association (k_{+1}) or low dissociation rate (k_{-1}).

The ratio of the effect achieved by a pharmacological agent A (E_A) to the maximum possible effect (E_{max}) is equal to the ratio of the concentration of occupied receptors [RA] to the total receptor concentration [B_{max}]:

$$\frac{E_A}{E_{max}} = \frac{[RA]}{[B_{max}]} \quad (1.3)$$

As the total receptor concentration $[B_{max}] = [R] + [RA]$, one can reexpress Eq. (1.3) in the form of Eq. (1.4). This is a Michaelis-Menten equation in which reaction velocities v and v_{max} are replaced by the biological effects E_A and E_{max}, and the substrate concentration by [A]:

$$E_A = \frac{E_{max}\ [A]}{K_D + [A]} \quad (1.4)$$

E_A can be obtained, for example, from the assay of cAMP in cells or brain homogenates that possess G protein-coupled neuroreceptors, by the double-reciprocal plot of $1/[E_A]$ versus $1/[A]$. Analogous to Lineweaver-Burk analysis in enzyme kinetics, one can graphically determine E_{max} and K_D in this manner.

As discussed above, the agent is designated an **agonist** if it both possesses affinity for a neuroreceptor and elicits an effect following formation of the agonist-receptor complex (intrinsic activity). The latter is a measure of the maximal effect that can be achieved by the pharmacological agent in a given biological system. This is usually expressed, however, as relative intrinsic activity α. This is proportional to the quotient of the effect elicited by the agonist (E_A) and the maximum achievable effect in the specified biological system (E_{max}). The maximum relative intrinsic activity can be derived from $E_A/E_{max} = 1$. Agonists with a relative intrinsic activity of 1 are termed full agonists; pharmacological agents with an intrinsic activity between 0 and 1 are called partial agonists.

It must, however, be noted that the occupation theory – like many theories – only applies under particular conditions. For instance, a biological system in which a receptor reserve is available, as is the case for G protein-coupled receptors, can be maximally stimulated when only a proportion of the receptors are occupied. Furthermore, the occupation theory does not predict which physicochemical changes occur as a result of the ligand-receptor interaction. These are specifically considered by the two-state model, according to which a receptor can exist in an inactive (resting) and an active (activated) state (conformation). The two states are in a dynamic equilibrium that, in the absence of an endogenous or exogenous ligand, is shifted almost completely towards the inactive state.

The occupation theory takes into account not only the fact that neuroreceptors are not static entities but also that both receptor number and their cellular reactions are altered by chronic stimulation or inhibition. **Desensitization** denotes the phenomenon whereby chronic agonist stimulation, as a result of the uncoupling of receptors from their effector mechanisms, reduces cellular response to further stimulation. The other extreme is **downregulation**, which is typically characterized by a slower time course and more extensive

molecular modifications, particularly receptor protein degradation. Chronic treatment with antagonists often results in an increased cellular response to receptor stimulation, the consequence of a compensatory elevation of receptor density and/or sensitivity. This phenomenon is termed **supersensitivity** or sensitization.

1.4.2.2 Psychopharmaceutical Agents That Act at Neuroreceptors

Many psychopharmaceuticals are exogenous ligands (agonists, antagonists) for neuroreceptors that, following interaction with receptor, either directly modulate ligand-gated ion channels (ion channel receptors) or elicit longer-term metabolic responses, functional changes via modulation of gene expression, or modification of neuronal excitability by indirect modulation of ion channels (G protein-coupled receptors). Table 1.17 lists examples of psychopharmaceuticals that exert their effects via neuroreceptors.

1.4.3 Neuronal and Glial Transport Proteins

A number of psychopharmaceuticals act by inhibiting reuptake of neurotransmitter. The antidepressants are an important example, selectively or nonselectively modulating noradrenergic and serotonergic neurotransmission through blockade of noradrenaline or 5-HT transporter. Further examples are summarized in Table 1.18.

1.4.4 Voltage-Gated Ion Channels

Voltage-gated ion channels, in contrast to ligand-gated ion channels, are opened and closed by changes in membrane potential. Na^+, Ca^{2+}, and Cl^- channels are generally closed in their resting state. When the membrane depolarizes at the beginning of an action potential, the channel opens as the result of a conformational change of

Table 1.17 Examples of psychopharmaceutical agents that act via neuroreceptors

Psychopharmaceutical class	Mode of action	Major area of application
Antiepileptics		
Clonazepam (benzodiazepine)	Agonists of a binding site on the $GABA_A$ receptor-chloride channel complex Amplification of GABA effect	Various forms of epilepsy
Felbamate	Probable agonist of glycine binding site of NMDA receptor	Various forms of epilepsy
Antipsychotics		
First-generation (haloperidol, benperidol)	Antagonists of the dopamine D2 receptor family Inhibition of dopamine effect	Schizophrenia, mania, organic psychosyndrome, agitation and anxiety conditions, alcohol withdrawal syndrome
Second and third-generation (aripiprazole, clozapine, olanzapine, quetiapine, risperidone)	Antagonists of the dopamine D2 receptor family Inhibition of dopamine effect Also antagonists of the serotonergic $5\text{-}HT_{2A/2C}$ receptors Inhibition of 5-HT effect	
Anxiolytics and hypnotics		
Benzodiazepines (zaleplon, zolpidem, zopiclone)	Agonists of the binding site on the $GABA_A$ receptor-chloride channel complex Amplification of GABA effect	Agitation, anxiety, stress conditions
H_1 antihistamines (diphenhydramine, doxylamine)	Antagonists of the H_1 histamine receptor	Psycho-vegetative disorders
Novel anxiolytics (buspirone, gepirone)	Agonists of the serotonergic $5\text{-}HT_{1A}$ receptor	Agitation, anxiety, stress conditions

NMDA N-methyl-D-aspartate

Table 1.18 Examples of psychopharmaceutical agents that inhibit neurotransmitter transport systems

Psychopharmaceutical class	Mode of action	Major area of application
Antidepressants		
Imipramine, desipramine	Nonselective inhibition of reuptake of catecholamines Amplification of effects of noradrenaline and 5-HT	Depression Anxiety disorders Enuresh
SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	Predominantly inhibition of 5-HT reuptake Amplification of 5-HT effect	Depression Anxiety disorders Obsessive-compulsive disorders
Antiepileptics		
Tiagabine	Selective GABA reuptake inhibitor Amplification of GABA effect	Various forms of epilepsy
Psychostimulants		
Methylphenidate	Inhibition of dopamine and noradrenaline reuptake Amplification of effects of dopamine and noradrenaline	ADHD Narcolepsy
Amphetamine	Release of dopamine and noradrenaline Inhibition of dopamine and noradrenaline reuptake Amplification of effects of dopamine and noradrenaline	ADHD Narcolepsy
Non-psychostimulants		
Atomoxetine	Selective inhibition of noradrenaline reuptake Amplification of noradrenaline effects	ADHD

ADHD attention deficit/hyperactivity disorder, *5-HT* serotonin, *SSRIs* selective serotonin reuptake inhibitors

the channel protein; after a certain time, the channel spontaneously closes again, and the ion channel enters a refractory state in which it cannot be activated. K^+ channels, on the other hand, are also open in their resting state and thus permeable to K^+ as well as during the entire action potential.

Apart from changes in membrane potential, central voltage-gated ion channels can also be modulated by psychopharmaceuticals. The antiepileptics carbamazepine, phenytoin, lamotrigine, topiramate, and valproic acid primarily block voltage-gated Na^+ channels, but also Ca^{2+} channels, and thereby suppress development of repeated neuronal firing. Characteristic for their effect is the dependence of the effect upon the opening probability of a channel (use dependence): the more frequently the channel is opened, the greater the inhibition by the antiepileptic agent. It is for this reason that normal reactive neurons are considerably less affected than neurons with higher discharge frequencies. Valproic acid, however, does not act by blocking Na^+ channels but by inhibition of GABA transaminase (Table 1.15) and is thus appropriate for the therapy of a number of epilepsy forms (broad-spectrum antiepileptic agent).

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2 Special Features of Psychopharmacological Therapy in Children and Adolescents

Manfred Gerlach, Laurence Greenhill, and Andreas Warnke

Contents

M. Gerlach, PhD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Laboratory for Clinical Neurobiology and Therapeutic Drug Monitoring, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: manfred.gerlach@uni-wuerzburg.de

L. Greenhill, MD
NYS Psychiatric Institute, New York Presbyterian Hospital, Riverside Drive 1051, New York, NY 10032, USA
e-mail: llg2@columbia.edu

A. Warnke, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: warnke@kjp.uni-wuerzburg.de

2.1 Special Prerequisites for Therapy with Psychopharmacological Agents in Children and Adolescents

2.1.1 Pharmacological Therapy as an Element of a Comprehensive Therapeutic Concept

Therapy with psychopharmacological agents of particular symptoms and psychiatric disorders in children and adolescents is part of a multifaceted therapeutic approach including complementary psycho- and socio-therapeutic measures (Fig. 2.1). This applies in particular to the treatment of children and adolescents with attention deficit/hyperactivity disorder (ADHD), tics and Tourette's syndrome, elimination disorders (enuresis, encopresis), psychoses, personality

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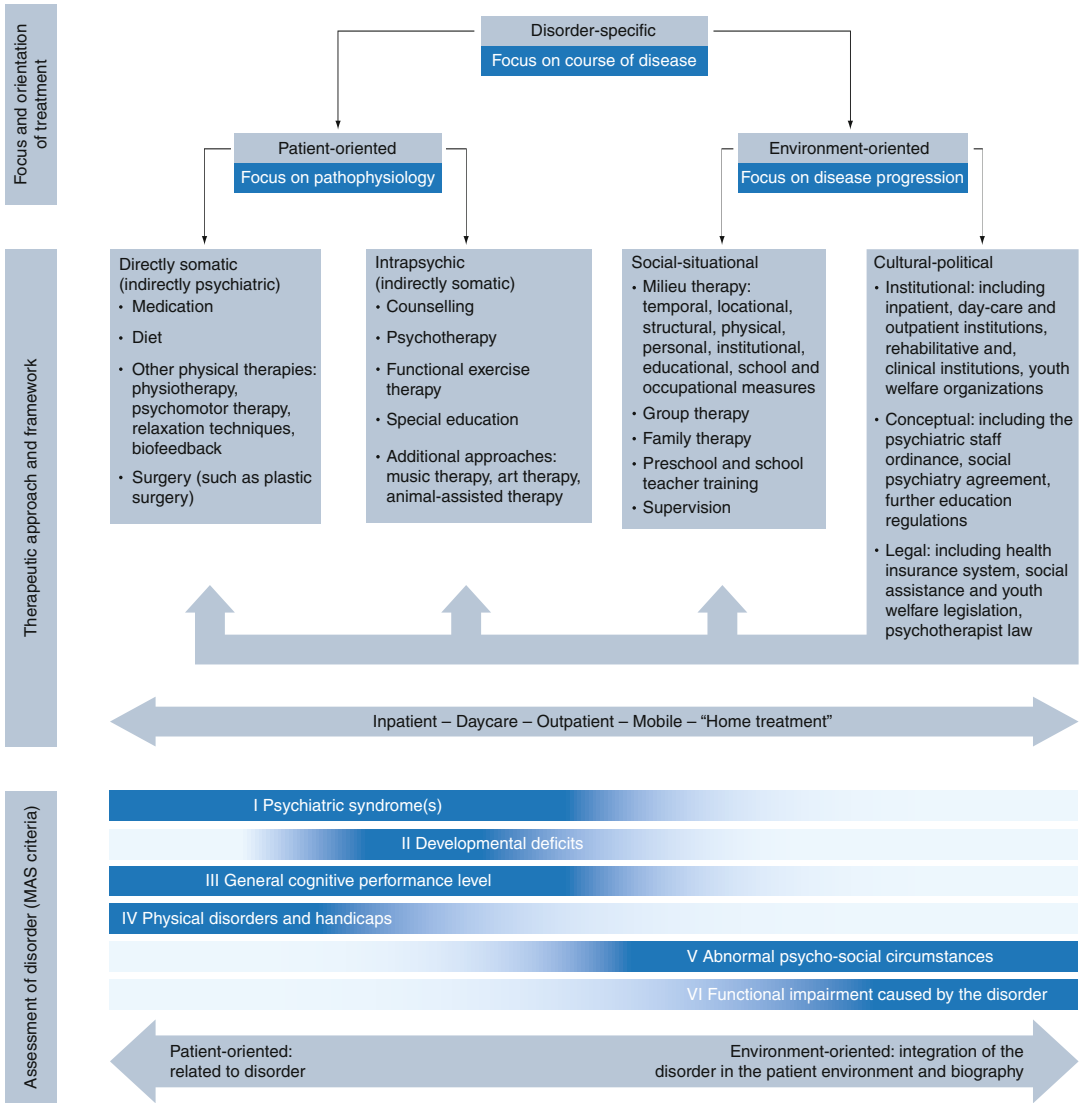

Fig. 2.1 The position of pharmacological treatment in the overall concept of child and adolescent psychiatric therapy (From (Gerlach et al. 2010), with friendly permission of Wissenschaftliche Verlagsgeschellschaft Stuttgart) MAS axes I to VI: refers to multiaxial schema of Remschmidt et al. (2001). This book is concerned only with the pharmacological therapy of psychiatric disorders. The goal of such therapy is disease-specific medication (e.g., antipsychotic treatment of schizophrenic psychosis, psychostimulant therapy of attention deficit/hyperactivity disorder). Medication is often directed at a particular symptom (e.g., antipsychotic treatment of impulsive-aggressive agitation or therapy of sleep disorders). Consideration of developmental stage recognizes the age-specific aspects of medication (e.g., the antidepressive effect of tricyclic antidepressants is uncertain in children but well established for adults; many psychopharmacological agents are only licensed for the therapy of psychiatric illness in adults and not in person under 18 years of age). Orientation with regard to disease course takes into account both the natural (un-medicated) and therapy-modified course of a disorder when making decisions concerning choice of medication and dose (e.g., the choice of medication or its dosage is different during an episode of acute agitation in a patient with schizophrenia than during the rehabilitation phase). Orientation with regard to progress encompasses the obligation to modify decisions regarding medication according to the most recent scientific findings (currently, e.g., the employment of slow release preparations in psychostimulant therapy)

disorders, obsessions and compulsions, panic attacks, and anxiety disorders as well as mood disorders (major depressive disorders and bipolar disorders).

Under certain conditions the diagnosis alone is a sufficient indicator to initiate emergency pharmacological therapy, including various forms of psychosis (such as schizophrenia, drug-induced psychosis, affective and schizoaffective psychoses) and conditions that pose a significant risk of harm to the patient or to others. However, this does not apply to the same degree to other childhood and adolescent psychiatric disorders. **Critical factors** have to be **considered** before deciding to initiate pharmacological therapy including the following aspects of the disorder or symptomatology and patient traits:

- Knowledge regarding the untreated course of the disorder in question (including the risk of chronicity and relapse, of associated comorbid disorders, or of early mortality).
- Symptom severity
- Impairments of the patient's general condition arising from the symptoms to be treated and the resulting limitations of their capacity for social adaptation and integration that might diminish their quality of life.
- The age of the patient (e.g., there are too few studies of the efficacy and safety of psychostimulants used to treat symptoms of ADHD in children under 3 years of age).
- An informed consent of the parent or guardian and the assent (if under age 18 years of age) of the patient to take the medication and that dispensing the medication will not enable abuse of the medication by other family members when abuse is suspected.

Psychopharmacological therapy for children and adolescents is only one element of a comprehensive therapeutic concept (Fig. 2.1). The other components of treatment include the involvement of the parents or other family members in the treatment plan and the school and should also include measure to support social integration.

2.1.2 Application of Medications Outside Their Area of Certification ("Off-Label Use")

Proprietary pharmaceuticals are meticulously examined in accordance with legal requirements regarding efficacy and safety, provided when the drugs are being employed as recommended. This is achieved by a series of clinical trial phases.

- Phase I: Initial administration of an agent to humans, usually healthy adults.
- Phase II: First, short-term investigations of efficacy and relative safety on a limited number of hospitalized patients.
- Phase III: Confirmatory studies with the aim of establishing efficacy and safety in a large number of patients.
- Phase IV: Post-licensing investigations of rare, unexpected, serious, or long-term adverse events that can affect the length and quality of life and the identification of novel indications.

Following completion of phase III studies, the results of the preclinical and clinical investigations are submitted to the appropriate health authorities (e.g., the European Medicines Agency [EMA] in the European Union, EU; the Food and Drug Administration [FDA] in the USA), who, following thorough review of the data, either grant or decline licensing approval and thereby the right to market the new drug.

There are two important aspects of the indications for a pharmacological therapy and thus of **areas of certification**, which can be distinguished: the age of the patient and the type of disorder or symptomatology of a disease. Further aspects of certification include gender-specific employment, dose, duration of therapy, mode of administration, and the pharmaceutical form of the product.

Most of the psychopharmacological agents employed in child and adolescent psychiatry are not officially licensed for these age groups, but only for patients over 18 years of age. The deficiencies of pediatric drug development procedures and reasons for a lack of labeled drugs are

well known and have been published elsewhere (Mehler-Wex et al. 2009). The pharmaceutical industry faces unique challenges in developing psychotropic medications for children and adolescents, such as:

- Longer-term effects on growth and the potential for psychomotor developmental disturbances that are not initially evident.
- Dose-effect relationships derived from investigations in adults often do not apply to children (see Sect. 2.2).
- The multiple medicolegal and ethical problems associated with clinical drug trials carried out with patients not legally capable of informed consent.
- Insufficient infrastructure for multicenter drug trials, including difficulties in patient recruitment.

As children and adolescents cannot be denied psychopharmacological therapy, medications are often employed in pediatric psychiatry outside the age group for which they are licensed and sometimes also for the treatment of conditions and symptoms outside the approved area of use stipulated by their certification (so-called off-label or unlicensed use). Under certain conditions, such use is legal (see Sect. 2.1.4) in the context of an individual therapeutic attempt – if, for example, the fundamental efficacy and a related application of the medication have been recognized (Kölch et al. 2008; Zito et al. 2008). The treating physician must, however, undertake a carefully balanced assessment of the benefits and risks of the medication and thus guarantee that the patient is adequately informed. Off-label applications of psychopharmacological agents, however, mean that the children and adolescents under treatment are exposed to greater risk than adults for ineffective pharmacological therapy and adverse drug reactions (ADRs).

A variety of national and international **efforts** have strived to end this discrimination against children and adolescents **regarding access to** adequate **pharmacological therapy** (Kölch et al. 2007; Stoyanova-Beninska et al. 2011). Under the aegis of the International Conference on Harmonization, guidelines for pharmaceutical development and testing have been developed, which have been reflected in the EU regulation on medicinal products for pediatric use ("Pediatric Regulation"). These guidelines deal with general considerations recognizing the need to develop medications specifically designated for pediatric psychiatry as well as the apposite time point for the involvement of children in pharmaceutical development, with appropriate study designs, and with the ethical and legal aspects of studies involving children. In order to facilitate medicinal testing for each indication in different age and developmental categories, five basic age groups or developmental stages have been internationally accepted, of which only the final two categories are relevant to child and adolescent psychiatry:

- Childhood (2–11 years)
- Adolescence (12–18 years) with the endocrinological transition during puberty

While in the USA publicly funded clinical trials, driven by some legislation, have been conducted with high impact on clinical practice in the last years (e.g., the MTA study, the TADS trial), clinical trials in Europe are predominantly industry-driven. Most data about second-generation antipsychotics in minors were collected by Research Units on Pediatric Psychopharmacology, driven by the "pediatric rule" (McCracken et al. 2002). A new EU regulation was implemented in summer of 2007 to increase drug safety also for minors. The collection of long-term safety data was one of the major aims of this directive since most safety investigations of randomized controlled trials refer to short follow-up durations only. The regulation stipulates that all pharmaceuticals for which approval is being sought in Europe must also have been clinically tested in children (exception: the pharmaceutical is unsuited for use in children and adolescents). The requirements for clinical testing are to be stipulated in a research and development program, the pediatric investigation plan; each plan must be submitted for approval to a committee consisting of scientists from EU countries and established by the EMA specifically for this purpose. As recompense for these new requirements, pharmaceutical manufacturers are granted incentives and benefits in the form of extended periods of commercial protection (the 20-year

patent protection is extended by 6 months). The same benefits can be granted for pharmaceuticals that have already been commercialized if their suitability for use in children and adolescents is subsequently ascertained on the basis of a pediatric investigation plan. Financial support by the EU for the promotion of the approval of generic agents (not subject to patent protection) for children and adolescents is planned. The packaging of medications specifically licensed for the use in children and adolescents shall in the future be marked by a special symbol.

2.1.3 Problems Associated with the Proof of Efficacy of Psychopharmacological Agents in Children and Adolescents

Establishing the efficacy of psychopharmacological agents in children and adolescents is rendered difficult by a variety of problems, including:

- **Symptoms** in children are to some extent quite **variable** and context dependent. The investigator is thus reliant on observations by parents, teachers, and other caretakers. The information gathered in this manner can be contradictory, less than objective, and unreliable. The effect of a medication is under different circumstances recognizable to varying degrees.
- Many clinical changes in children and adolescents are dependent upon their degree of **maturation**. Symptoms in children are bound up with their cognitive, affective, and psychosocial development. Children patients can often only inadequately register and describe disease characteristics; preschoolers do not have the same insight into their condition as adolescents. The prodromal signs of many clinical conditions are unspecific, as the complete clinical picture might require years of evolution in an individual case before a definitive diagnosis can be established. This applies, for instance, to autistic, schizophrenic, and manic-depressive disorders. Maturational processes and unrecognized psychosocial factors can play more significant roles for observed clinical changes during longer-term therapy or in longitudinal investigations than the effects of the medication.
- **Comorbidity** complicates the interpretation of the specific efficacy of a medication with respect to the target disorder, as, for example, in the case of the comorbidity of a depression disorder, ADHD, and/or tics.

Further problems relevant to the demonstration of efficacy were described above (Sect. 2.1.2).

2.1.4 Legal and Ethical Issues for the Daily Practice

Diagnosis is the prerequisite for therapy; only in acute emergencies (immediate danger to the patient or others) might be necessary to initiate symptomatic pharmacological therapy in some cases on the basis of the current psychopathological symptoms alone. Such emergency situations are, however, exceptions.

As a rule, diagnosis and, consequently, therapy of children and adolescents presuppose not only the consent of the patient but also that of his or her parents or caregivers. In children and adolescents the **principle of "vicarious consent"** applies, whereby decisions regarding consent to diagnosis and therapy are exercised for the most part by legal guardians.

Vicarious consent becomes problematic when the interests of the guardian are not in accordance with the welfare of the child; for example, if the parents are not able to care for the child (because the parents are themselves subject to severe mental handicaps or psychiatric disease, for instance) or when the parents act against the welfare of the child (e.g., in the Münchausen syndrome by proxy, a disturbance in which the caregiver intentionally does harm to the child in order to attract attention or sympathy).

Involvement of the child according to age or development should be actively sought. However, before the age of 14 or 16 years (the legal age for consent to treatment varies according to country), they cannot give legal permission to treatment,

which can be given only by parents of caregivers. The question remains unclear, however, as to the developmental stage from which the capacity to grant legal consent must be recognized. In practice this is the case for adolescents who have voluntarily established an independent existence away from their parents (legally capable minors). Parents and caregivers are also instrumental for implementing pharmacotherapy by ensuring appropriate administration of prescribed medication and for reporting ADRs.

Ethical principles for therapeutic measures (see, e.g., Kölch et al. 2008) assume that the procedure is efficacious, is appropriate for the treated disorder, and is initiated only following consent (informed consent) by the patient or his or her legal guardians (if the parents have separated, the custodial parent).

The **doctor-patient relationship** is determined by the following ethical principles (American Psychiatric Association 2002):

- The disorder to be treated must be defined.
- The patient or his or her parents must be informed regarding the goals of the therapy and the therapeutic procedure.
- Confidentiality provisions must be respected.
- The treatment plan must be based upon generally accepted clinical and scientific therapeutic standards.

As already discussed in Sect. 2.1.2, many pharmaceuticals employed in child and adolescent psychiatry are used outside their approved area of approval in the context of an "individual therapeutic attempt." This is in principle, however, only possible if the clinical efficacy and tolerance of the pharmaceutical has been firmly established and approved for adult use by a governing agency. In the case of the so-called **off-label use**, the following additional aspect must therefore be observed: The patient or his or her legal guardians must be informed that the prescribed medication has not been officially approved for this application in youth; the legal guardians or the patient must agree to the use of the medication; the guardians must also be informed about the effects of the medication, including potential ADRs, about approved therapeutic alternatives, and about the right to discontinue the therapeutic attempt at any time. The process of informing the patient and his or her legal guardians must be documented.

Regarding therapy with psychopharmacological agents, the following **key questions** must **be discussed** with the patient (modified from Fegert 1999):

- What is the name of the medication? Does this medication also have other names?
- What is known about the efficacy of this medication in other children who have problems similar to those of my child?
- How will the medication help my child? How long will I have to wait until I see an improvement? What are the criteria for determining if and when therapy has been successful?
- What ADRs can be expected?
- Which rare or serious ADRs are also possible?
- Can dependence upon this drug develop? Is there a risk of addiction?
- What is the recommended dose? How often must the medication be taken?
- Are there routine examinations, such as ECG and blood tests, that must be undertaken before the child can begin using the medication? Are laboratory tests required while the child is using the medication?
- Will a pediatric psychiatrist document my child's reaction to the drug, and will they adjust the dosage if this is necessary? How often will the progress of my child be evaluated and by whom?
- Are there any medications or foods that my child must avoid while using this medication?
- Are there any activities that my child must avoid while using this medication? Are there any that require special caution?
- How long does my child have to take this medication? Under which conditions could its use be ended?
- What should I do if problems arise (e.g., if my child becomes physically ill, if a dose is missed, or if ADRs develop)?
- How much does the treatment cost (are there differences between the brand name medication and the generic form)?

- Should I inform teachers, social workers, day-care workers, or others about this therapy?

The following **aspects** must **be considered**:

- The **medical briefing** must be conducted by a physician with the patient or his or her custodial parent (preferably with both parents)
- The **fundamentals** of the **therapy** must be explained, without necessarily discussing every detail
- The **risks and ADRs** should be explained to children and adolescents as soon as possible, insofar as they can understand the planned measures, but must, in any case, always be discussed with the child's guardians. This raises the issue of whether every conceivable risk needs to be explained. Even if legal decisions suggest that this should be the case, it does not usually occur in practice. The medication package leaflet lists all the ADRs ever reported, even where a causal connection between the "side effect" and the medication has not been established. An overly comprehensive discussion of less frequent but perhaps quite serious ADRs can also provoke a degree of anxiety that hinders effective therapy. In each case, the physician should discuss not only the possible adverse reaction but also its likelihood. Furthermore, it is recommended that the parents should be provided with printed informational material regarding the prescribed medication. A written confirmation that the briefing has taken place is generally not required, but it should nonetheless be documented. In the case of prescribing **clozapine**, a standardized documentation is required. The risk of dyskinesia in the course of therapy should certainly be discussed before prescribing first-generation antipsychotics for periods of longer than 4–6 weeks (Schatzberg et al. 2003).
- When prescribing **non-approved medications**, the aspects discussed above must be considered. The patient and his or her parents should know that they can withdraw their consent for an individual therapeutic attempt at any time. Should the patient have received a medication during a period of illness in which his or her condition reduced the capacity to consent, the medical briefing should be repeated once an improvement in his or her condition allows for a meaningful explanatory discussion, and the consent of his or her guardians can be supplemented by personal consent.

2.2 Dependence of Pharmacological Therapy in Children and Adolescents upon Age-Related and Developmental Organic, Psychiatric, and Psychosocial Factors

As children and adolescents are undergoing age-related developmental changes in their anatomy, tissue composition, endocrinological system, and liver and excretory functions and as they are also subject to changes and maturation of the central nervous system (CNS) at both the cellular and organizational levels, it must be expected that pharmacokinetics and pharmacodynamics in children and adolescents differ from those of adults. This explains the often, unforeseen ADRs during psychopharmacological therapy in younger patients as well as the difficulties encountered in predicting the dose-effect relationship on the basis of clinical trials in adults. For example, studies comparing rates of antipsychotic ADRs in children and adolescents with those in similar studies of adults indicated that children and adolescents were at higher risk for developing a number of antipsychotic-induced ADRs (Correll 2008). These included higher rates of sedation, extrapyramidal motor ADRs (except for akathisia), withdrawal dyskinesia, prolactin elevation, weight gain, and at least some metabolic abnormalities. By contrast, tardive dyskinesia and diabetes were less likely to occur in children and adolescents compared to adults.

Psychopharmacotherapy in child and adolescent psychiatry is an age- and development-related therapy that allows for these pharmacokinetic and pharmacodynamic variations and relates therapeutic efficacy to normal development. As each age level possesses its own specific physiology and psychopathology, it is evident that

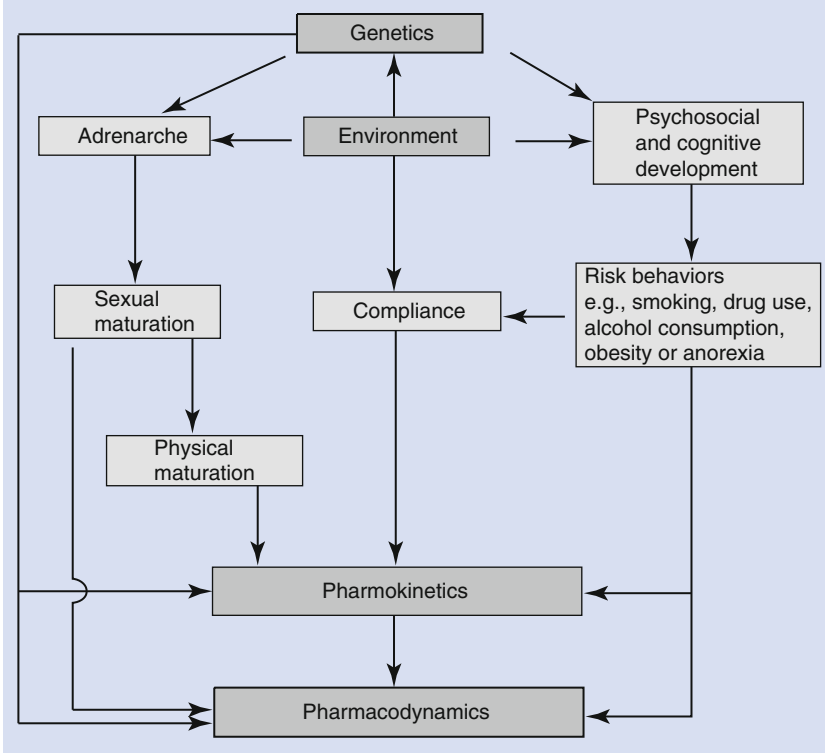

Fig. 2.2 Potential age and developmental factors and their influence upon psychopharmacology in children and adolescents (modified from Rogers 1994)

pharmacological therapy should be adjusted to the age of a child; the effect in an infant is not the same as in a 17-year-old adolescent.

Figure 2.2 illustrates the interactions between age- and development-related factors and their influence upon therapy with psychopharmacological agents. These factors have, however, not been adequately investigated with respect to puberty or the expected gender-related differences in the metabolism of pharmaceutical agents, nor with respect to the impact of gender-specific differences in physical maturation (fat distribution, muscle mass, hormone levels). Further developmental factors that potentially influence therapy with psychopharmacological agents include, in particular, behavioral features typical for adolescence, such as noncompliance, changes in eating behavior (e.g., anorectic and bulimic conditions), the consumption of alcohol and nicotine as well as comorbid substance abuse.

2.2.1 Ontogenetic Influences on Pharmacokinetics

As summarized in Table 2.1, developmental changes in physiology produce many of the age-associated changes in the absorption, distribution, metabolism, and excretion of psychotropic drugs following oral administration (most drugs are administered orally to children and adolescents) that result in altered pharmacokinetics and thus serve as the determinants of age-specific dose requirements.

Gastrointestinal resorption, for instance, is typically more effective in children and adolescents than in adults. Furthermore, the relative distribution of body fat varies widely according to the physical development in children and adolescents; storage of lipophilic psychopharmacological agents by slim, physically active school-age children is typically lower than in adults, so that, as an example, the plasma half-life (Table 2.2) of diazepam is

Table 2.1 Age-dependent factors that influence pharmacokinetics in children and adolescents

Pharmacokinetic parameter	Influencing factors
Absorption	Gastrointestinal function (e.g., gastric emptying and intestinal motility, hydrochloric acid production, bile acid secretion, intestinal and body length)
Distribution	Body composition (e.g., extracellular and total body water space, volume of distribution, changes in the composition, and amount of circulating plasma proteins, body fat) Regional blood flow Organ perfusion Permeability of cell membranes Acid-base balance Passive diffusion of drugs into the central nervous system
Metabolism	Metabolic capacity (e.g., liver size, activity of drug-metabolizing phase I and II enzymes such as P-450 cytochromes and glucuronosyltransferase)
Excretion	Renal function

From Mehler-Wex et al. (2009)

Table 2.2 Age-dependent pharmacokinetic parameters for diazepam

Age group	Half-life (h)	Distribution volume (l/kg)	Relative clearance (ml/h/kg)
Infants	10.6 ± 2	1.3 ± 0.2	98.5 ± 13.8
Children	17.3 ± 3	2.6 ± 0.5	102.1 ± 9.7
Adults	24.1 ± 5	2.3 ± 0.3	66.7 ± 5.4

From Morselli et al. (1978)

shorter. Reduced half-life could also be the result of a higher glomerular filtration rate and consequently accelerated renal elimination in children. More rapid elimination can also be related to more efficient metabolism of the pharmacological agent, as children have a proportionally larger liver (in relation to body mass) than adults.

However, to date no systematic studies have been carried out to show how these influencing factors of pharmacokinetics (Table 2.1) change over lifetime and whether there are gender-dependent changes. These developmental changes in physiology have – dependent on the psychotropic drug administered – different effects on pharmacokinetic parameters, on clinical efficacy, and on safety (Table 2.3). More rapid elimination of medications explains the observation that children and adolescents treated with psychopharmacological agents at the same dosage have a lower trough level (the lowest plasma concentration of the agent, assessed at least 12 h after the most recent dose and immediately before the next) than adults. Figure 2.3 illustrates this phenomenon for the antipsychotic chlorpromazine. Similar results have been reported for the tricyclic antidepressants nortriptyline and clomipramine (Morselli et al. 1978).

Table 2.3 Effects of developmental factors on the pharmacokinetics and the efficacy of psychotropic drugs

Developmental factor	Pharmacokinetic effect	Clinical effect
Liver size and activity of CYP450 enzymes ↑	Drug metabolism ↑	Drug efficacy ↓
Percentage of body fat ↓	Storage of lipophilic drugs ↓	
Glomerular filtration rate ↑	Urinary excretion ↑	
Protein binding ↓	Drug availability in the brain ↑	Risk of ADRs ↑
Gastrointestinal resorption ↑	Drug availability in both peripheral organs and the brain ↑	Risk of ADRs ↑

From Mehler-Wex et al. (2009)
ADRs adverse drug reactions, *CYP450* P-450 cytochrome, ↑ increase compared to adults, ↓ decrease compared to adults

Therefore, the approach to extrapolate age-specific dosing regimens from adult data has limited value, and the selection of doses in pediatric patients requires a consideration of pharmacokinetic parameters. It has been hypothesized that inaccurate dosing parameters are the reason for the negative outcome of the studies of antidepressants in pediatric patients with a major depressive disorder (Findling et al. 2006).

The **cytochrome P_{450} (CYP) system** is an important hepatic enzyme system, as the CYP enzymes are involved in the reactions of phase I metabolism, transferring an oxygen atom from

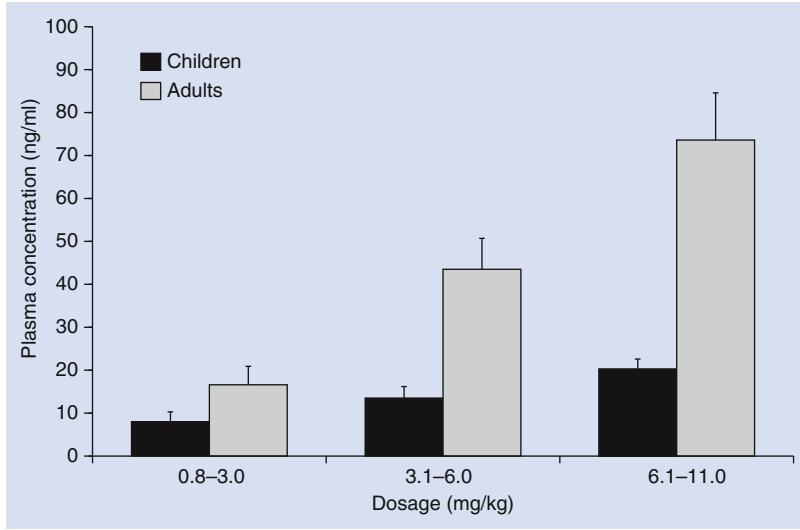

Fig. 2.3 Chlorpromazine plasma concentrations in children and adolescents (8–15 years) with psychiatric disorders, compared with those in adults. (From Rivera-Calimlin et al. 1979). The concentration was assessed 10 h following administration of the agent

molecular oxygen to the substrate drug (oxidation). The liver contains 90–95 % of total body CYP, whereby 60–65 % consists of enzymes that catalyze drug metabolism (Kirchheiner and Rodriguez-Antona 2009). The most important species, CYP3A4, constitutes approximately 30 % of total CYP protein; 60 % of all therapeutically employed pharmaceuticals are CYP3A4 substrates. The isoforms of the CYP2C family account for about 30 %; CYP1A2 ca. 10 %; CYP2A6, CYP2B6, and CYP2D6 together about 10–15 %; and CYP2E1 roughly 5 % of total CYP. The metabolism of many of the psychopharmacological agents employed in child and adolescent psychiatry (including tricyclic antidepressants, SSRIs, antipsychotics) is almost exclusively or at least partially catalyzed by CYP2D6.

Many enzymes involved in drug metabolism carry genetic variants (polymorphisms) that can decrease enzyme activity or even lead to complete deficiency (Kirchheiner and Rodriguez-Antona 2009). Genetic polymorphisms cause different phenotypes of drug metabolizers, which generally have been referred to as "**poor metabolizers**" (carrying two alleles predicting a low or no enzyme activity), "**intermediate metabolizers**" (being heterozygous carriers of one inactive allele or of two alleles with reduced activity), and "**extensive metabolizers**" (carrying two active alleles) and, for some enzymes, "**ultra-rapid metabolizers**" (showing a very high enzyme activity which is genetically caused by gene duplication, so far only found for CYP2D6 and CYP2A6; Kirchheiner and Rodriguez-Antona 2009; Mehler-Wex et al. 2009). The phenotypes reflecting the actual enzyme activity still show high interindividual variation, especially within the intermediate and extensive metabolizer groups. Thus, genetic prediction accuracy of enzyme activity is best for the poor and ultra-rapid genotypes, but poor or ultra-rapid metabolizing activity can also be the result of enzyme inhibitors or inducers.

The prevalence of the different types of metabolizers varies a lot between ethnic groups (Bertilsson 1995). For CYP2D6, 5–8 % poor metabolizers and 1–10 % ultra-rapid metabolizers have been found in Caucasians. As the elimination of psychopharmacological agents by deficient metabolizers is significantly impeded, accumulation of the agent can lead to higher plasma levels in such persons, resulting in concentration-dependent ADRs (e.g., cardiac ADRs of tricyclic antidepressants). In Ethiopia and some Arab countries, even up to 30 % are carriers of the CYP2D6 gene duplication (Akullu et al. 1996). CYP2C19 polymorphisms in Caucasian populations appear to be less important although several, mainly tricyclic

antidepressants are metabolized by this enzyme. In Asian populations, however, about 20 % of the population are CYP2C19 poor metabolizers (Wedlund 2000).

Although CYP enzyme gene expression is stable from the end of the first year of life, pharmacokinetic studies of drugs metabolized by specific CYP isoforms indicate that the development of activity of individual enzyme species occurs in a differential, age-dependent manner (Kearns et al. 2003); for example, the clearance of carbamazepine (an antiepileptic drug) from plasma, which is largely dependent on CYP3A4, is greater in children than in adults, thereby necessitating higher weight-adjusted doses of the drug to achieve therapeutic plasma levels. The maximal velocity of phenytoin (which reflects the extent of CYP2C9 activity) declines from an average value of 14 mg/kg/day in infants to 8 mg/kg/day in adolescents, producing a profound corresponding age-related difference in the daily therapeutic dose requirement.

In summary, the physiological parameters of the resorption of psychopharmacological agents by the gastrointestinal tract, of their distribution in the body, and of their storage, metabolism, and elimination differ in children and adolescents on the one hand and adults on the other and in the former vary according to the age and developmental stage of the child. For this reason, administration of the same dose can result in different plasma drug levels in children, adolescents, and adults, necessitating individual drug dose adjustment. The many different factors that influence the pharmacokinetics of a psychopharmacological agent mean, however, that a definitive prediction of the required individual dosage is not possible.

Individual dose adjustment is possible in a simple and inexpensive manner by means of **therapeutic drug monitoring** (**TDM**). TDM involves the assay of plasma or serum drug levels, with the goal of determining the pharmacokinetic parameters of the individual patient, enabling, where indicated, the more targeted adjustment of dosage. The strategy of TDM in the context of psychopharmacological therapy is based upon the view that blood concentrations of the active substances (the drug and its active metabolites) represent a better measure for their concentrations at their intended site action (the brain) than drug dose (Hiemke et al. 2011; Mehler-Wex et al. 2009). Further, it assumes that a definable relationship exists between the blood concentration of an active agent and its clinical effects (therapeutic effect, ADRs, toxic effects). This correlation has been demonstrated in adults for the tricyclic antidepressants nortriptyline, imipramine, and desipramine (Hiemke et al. 2011).

2.2.2 Ontogenetic Influences upon Pharmacodynamics

Although it is generally accepted that development can alter the action of and response to a drug, little information exists about the effect of human ontogenesis on interactions between psychoactive drugs and biological target structures (i.e., the pharmacodynamics) and the consequences of these interactions (i.e., efficacy and ADRs). Although cell birth, neuronal differentiation, and migration of neurons to target areas are almost complete within the first few years of life in humans, there is a lifelong change in the synaptogenesis (new nerve cell contacts are formed) and synapse elimination (or pruning) with changes in the density of neurotransmitter receptors, sensitivity of signal transduction pathways, activity of neurotransmitter metabolizing enzymes, and density of neurotransmitter reuptake transporters.

Both synapse building and elimination are lifelong processes and are critical factors for neuronal plasticity, regeneration, and the capacity to learn. At birth, which occurs during the middle of the most intensive neuronal growth period, only half of the several billion synaptic contacts of the adult brain are being established; in the womb and during infancy, two million new synapses are formed each minute. This is followed by a period of slower, smoother development that lasts until puberty, after which the pace slows down to the level maintained through adulthood. It is only during the senium that synaptogenesis abruptly declines. In phylogenetically more

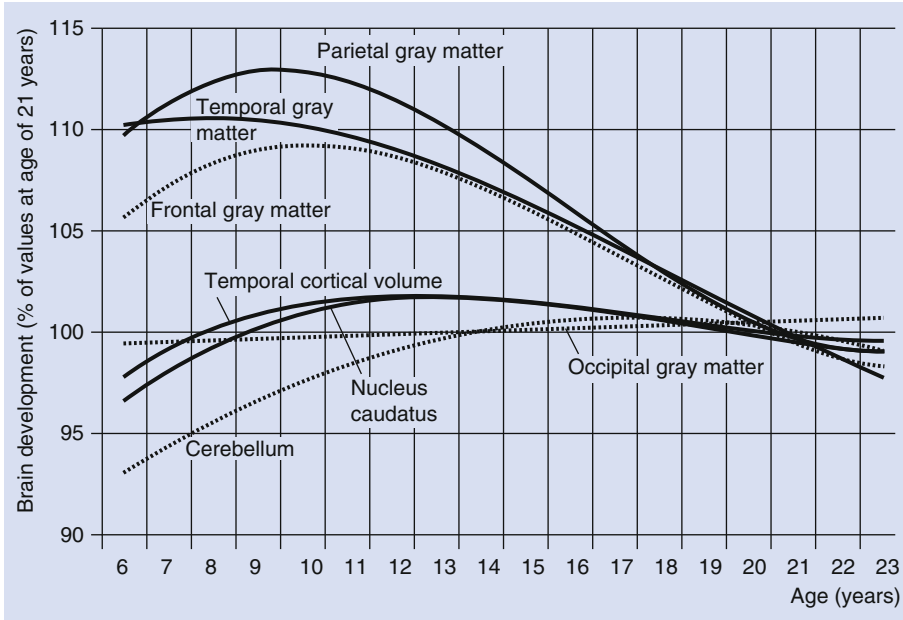

Fig. 2.4 Cortical and subcortical brain development in humans with respect to age. Changes in grey matter density, determined by longitudinal magnet resonance imaging (MRI) investigations, are illustrated (Giedd et al. 1996, 1999). (From Gerlach and Wewetzer (2008), with friendly permission of Schattauer)

ancient regions, such as the striatum and cortical areas associated with motor functions, synapse elimination commences earlier than in the more recently developed regions concerned with cognitive processes (Thompson et al. 2000).

Postmortem studies and high-resolution structural magnetic resonance imaging longitudinal studies demonstrated nonlinear region- and neurotransmitter-specific changes. Figure 2.4 depicts the relationship between age and grey matter density, "grey matter" denoting those parts of the CNS containing many nerve cell bodies but only few myelinated axons. In contrast, the "white matter" consists of innumerable axons, most enclosed by myelin, a glistening, lipidic substance that reflects light strongly and gives this component of the CNS its descriptive name.

In human postmortem studies it has been shown in the striatum that there is a transient elevation of both the dopamine D_1 and D_2 receptor density (the main therapeutic target of antipsychotics in the brain) in early childhood; after about 2–5 years, there is a rapid decline, and after 10 years the dopamine D_1 and D_2 receptor density decreases at about 3.2 and 2.2 % per decade, respectively (Seeman et al. 1987). In addition, it has been found that there is an age-dependent development of human neuromelanin (Federow et al. 2005). This dark-colored pigment is formed in the dopaminergic neurons of the human midbrain that projects to the striatum (see Sect. 1.3.2.1). Neuromelanin is not present at birth, and initiation of pigmentation begins at approximately 3 years of age, followed by a period of increasing pigment granule and coloration until the age of 20 (Federow et al. 2005). A different pattern of synaptogenesis and ontogenesis was demonstrated for the glutamatergic system (Fig. 2.5).

The ontogenesis of the CNS has an influence on the interaction of a psychotropic drug with biological structures in the brain (e.g., neurotransmitter metabolism, neurotransmitter receptors, neurotransmitter transporters, signal transduction) and the resulting therapeutic effect (efficacy, ADRs). These changes in the ontogenesis of pharmacodynamics indicate that there is a difference in the relationship between the blood concentration of a psychotropic drug and the therapeutic response to a psychotropic

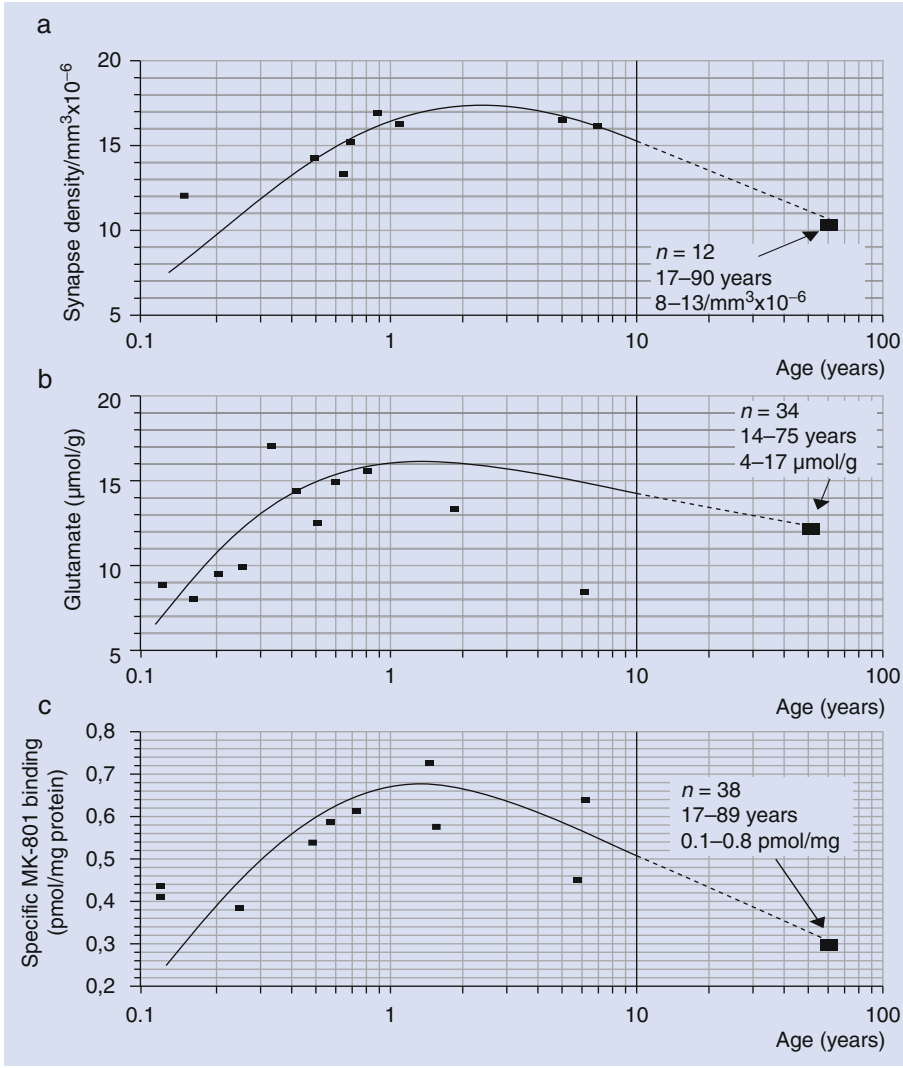

Fig. 2.5 Synaptogenesis and the development of the glutamatergic neurotransmission in the human brain. (**a**) Synapse density in frontal cortex; (**b**) Glutamate concentrations in the putamen; (**c**) MK-801 receptor binding site density, a measure of the density of the *N*-methyl-D-aspartate receptor, a glutamate receptor subtype. (Modified from Retz et al. (1996), Gerlach and Wewetzer (2008), with friendly permission of Schattauer)

drug in children, adolescents, and adults. Indeed, we have shown by performing TDM that more than 50 % of the quetiapine trough serum concentrations were not within the therapeutic range recommended for adults (Gerlach et al. 2007): 40.8 % of the determined values were below and 24.5 % above the therapeutic range (70–170 ng/ml) recommended for adults. Interestingly, none of the patients had severe ADRs.

2.3 TDM as a General Requirement in Child and Adolescent Psychiatry

Because of the special features of psychopharmacological therapy in children and adolescents discussed in this chapter, TDM can be recommended for child and adolescent psychiatry (Egberts et al. 2011; Hiemke et al. 2011; Mehler-Wex et al.

2009). TDM comprises the measurement of plasma or serum levels and the documentation of both the clinical efficacy and ADRs. It is a valid tool to optimize pharmacotherapy and enables the clinician to adjust the dosage of drugs according to the characteristics of the individual patient. The interdisciplinary TDM expert group of the Society of Neuropsychopharmacology and Pharmacopsychiatry (AGNP) analyzed published data on psychotropic drugs and defined therapeutic ranges of plasma levels in adults (Hiemke et al. 2011). Moreover, they constituted a recommendation system for the implementation of TDM of five levels, indicating TDM most urgently for the treatment with lithium, but also for amitriptyline, clomipramine, clozapine, fluphenazine, haloperidol, imipramine, nortriptyline, and olanzapine. For augmentation strategies or co-medication in general, TDM also provides support in dosage finding and prevention of toxic or ADRs. Other indications for TDM include the control of compliance, the lack of dosage-correlated medication efficacy, and the incidence of severe ADRs.

In order to detect potential age and developmental specific therapeutic ranges of blood concentrations in children and adolescents treated with psychotropic drugs, huge samples are needed for statistical analyses. Therefore, a "Competence Network on Therapeutic Drug Monitoring in Child and Adolescent Psychiatry" has been established in December 2007 (www.tdm-kjp.de), including 12 departments of child and adolescent psychiatry in Germany, Austria, and Switzerland. The Network uses a multicenter TDM system including both standardized measurements of blood concentrations of psychotropic drugs and the documentation of efficacy and ADRs of the medication. For practical reasons, the use of an Internet database was chosen in order to save and to systematically structure the huge data amounts that can be expected. Such a data-based documentation will simplify final evaluation procedures. Furthermore, individuals with abnormal blood levels and low drug efficacy or severe ADRs, respectively, despite of normal plasma levels, could be detected easily and transferred to further genetic analyses.

Correlations between blood levels and therapeutic efficacy and ADRs will enable the definition of specific therapeutic blood level ranges for psychopharmacological agents according to age and development. The primary objectives of the research network are thereby the promotion of patient safety by preventing over- and underdosing and ADRs, expediting dose optimization (shorter hospitalization), and providing a structure for quality assurance of treatment documentation.

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Pharmacotherapy in the Outpatient Practice

3

Andreas Warnke, Christoph Wewetzer, and Laurence Greenhill

Contents

Outpatient pharmacotherapy differs in several key areas from treatment in a hospital or other inpatient settings. These concern aspects of:

- The medical indication (diagnosis) that justifies psychopharmacological interventions
- Compliance
- Monitoring the intended effect and adverse drug reactions (ADRs)
- Monitoring the course of disease and therapy
- Financial aspects
- Collaboration with the clinic

3.1 Indication for Pharmacological Therapy

The indication for initiating psychopharmacological therapy in an outpatient setting, as for institutional therapy, is **determined primarily by the disorder or clinical symptoms**, although differences may arise as a result of the different settings. Mental disorder severity is generally not as great in the outpatient situation, so that treatment by means of psychoeducation, educational counseling, parent training, and psychotherapy is often adequate. This applies to almost all disorders apart from psychoses and epilepsy.

On the other hand, **acute emergencies** requiring pharmaceutical intervention are more likely to occur in outpatient settings, as the protective framework with intensive personal support provided by a hospital setting, which can eliminate the necessity for drug intervention in patients in a state of acute agitation or where there exists a risk

A. Warnke, MD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: warnke@kjp.uni-wuerzburg.de

C. Wewetzer, MD
Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Florentine-Eichler-Str. 1, 51067 Köln, Germany
e-mail: wewetzerC@kliniken-koeln.de

L. Greenhill, MD
NYS Psychiatric Institute, New York Presbyterian Hospital, Riverside Drive 1051, New York, NY 10032, USA
e-mail: llg2@columbia.edu

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of harm to themselves or to others, is not available in outpatient practice. The indication for pharmacological therapy is ultimately more dependent in outpatient practice than in inpatient settings, regarding the willingness and ability of the patient and his or her parents to implement the therapy, both at home and elsewhere, and upon monitoring therapeutic effects and possible ADRs. This aspect is not as critical for short-term pharmacological interventions in hospital, as drug administration and monitoring of its effectiveness can be undertaken by professional staff. Finally, ADRs of pharmaceutical interventions must be more closely monitored in an outpatient setting, particularly acute dyskinesias elicited by first-generation antipsychotics.

The employment of psychopharmacological agents requires that the **efficacy be monitored both at home and elsewhere** (e.g., day-care centers, schools) and the **availability at short notice of physician's advice** (e.g., the family doctor). For many medications there exists a period of latency before the intended effects are manifested. For example, the benefits of antidepressants are evident only after a delay, while ADRs (e.g., fatigue, impaired cognition) can be felt quickly after initiation of therapy. The dissociation of a therapeutic effect and ADRs can be managed in inpatient settings, where the special needs patients are known. This is generally more difficult to realize in the outpatient contexts, meaning that a supplementary medication (such as benzodiazepines for insomnia, more for a more serious acute anxious agitation of for suicidality) might be necessary. The **indication for a pharmaceutical intervention** for ambulant patients is thus **determined by the following issues**:

- Is a drug treatment alone sufficient or are other treatment approaches required (e.g., parent counseling, psychotherapy)?
- Can the monitoring of therapeutic effect and ADRs (in particular, life-threatening effects, such as agranulocytosis) be assured?
- Are life-threatening ADRs expected or will ADRs undermine medication compliance?
- Is there a temporal dissociation between the delayed onset of therapeutic effects and the early development of ADRs, and will this necessitate provisional prescription of a supplementary medication during the bridging period?
- Are the patient and his or her parents (and, where appropriate, non-family caregivers, non-clinical residential staff) capable of reliably implementing the therapy?
- Is the necessary psychopathological and medical supervision ensured in the outpatient context?

3.2 Aspects of Compliance

Issues of compliance are of great importance in outpatient pharmacotherapy. When treated in hospital, the patient and his or her parents have often considered issues related to the medication during prior ambulant treatment and are thus already familiar with it; this is rarely the case at the beginning of outpatient treatment. On admission to hospital, both the patient and his or her parents are more frequently informed about the disease and therapeutic options and thus know what to expect from a potential pharmacotherapy. During the primary outpatient session, in contrast, **initiation of therapy** must always be **preceded** (except in rare acute emergency situations) **by** a detailed **explanation** of the type and symptomatology of the disorder, its etiology, prognosis, and the therapeutic options, whereby pharmacotherapy is one component.

If pharmacotherapy is indicated, the second step includes the responsibility to comprehensively explain the therapy (see Chaps. 2, 4–8). **Information** must be **provided** regarding the precisely defined target symptoms of the medication, its active agent, its therapeutic effects and ADRs, the expected delay before its desired effects are manifested, the dosage schedule, the anticipated duration of treatment, and the required psychopathological and medical monitoring (that can be crucial to dose adjustment or change of medication), as well as concrete measures of the degree of improvement achieved. Fears, reservations, and misleading preconceptions (e.g., "psychopharmaceuticals are addictive"; "psychopharmaceuticals are dangerous"; "psychopharmaceuticals change a person's character"; "psychopharmaceuticals make you drowsy and

incapable of work") should be addressed and mitigated. It is advisable to actively raise potential reservations and preconceptions that hinder compliance.

Compliance in ambulant pharmacotherapy is not dependent upon the patient and his or her parents alone, but often also upon other family members and caregivers. With respect to the family, it is important to discuss the therapy with both parents, especially if they are separated and share custody or access rights. Similar information is required outside the family to ensure compliance if the target symptoms and ADRs attract significant attention away from home and if the medication will be administered somewhere else than at home. This applies, for example, to children with ADHD attending preschool or day-care centers or school or who are accommodated full-time in a residential facility. Compliance with regard to medication and its effects cannot be optimally assured without the cooperation of teachers and guardians.

Information brochures and standardized questionnaires regarding the effects and ADRs of the prescribed medication can be very helpful for assuring the necessary outpatient monitoring of medication and compliance. If the medication is not approved for use by children and adolescents ("off-label," see Chap. 2), the instruction given to that patient and his or her parents must be especially clear and supportive, and the ongoing monitoring must be planned out the family.

3.3 Monitoring of Drug Effects and Adverse Drug Reactions

The monitoring of the effectiveness and ADRs is especially difficult in outpatient therapy. Drug responses are not assessed by trained personnel, as in hospital-based therapy, but must be noted in daily life by laypersons, that is, the patient and those in closest contact. It is for this reason that the child or adolescent must be adequately informed, according to the cognitive development and capacity for insight; the same counts for the responsible caregivers in the family and in the daily life of the patient (preschool or day-care center, school, place of employment). In hospitalized patients cognitive limitations need not be decisive in the management of tasks in daily live, whereas the same restrictions can significantly incapacitate ambulant patients. For instance, antipsychotics can in certain patients reduce driving ability as well as school and occupational performance, and this can limit their usefulness and reduce compliance. It is generally advisable to gradually increase medication dosage in ambulant patients and to offer frequent follow-up appointments during this transitional phase.

Some ADRs only become apparent after a long period of treatment and thus may occur after discharge from hospital care. Examples include the weight gain associated with antipsychotic medication (especially second- and third-generation antipsychotics) and the risk of agranulocytosis connected with clozapine (see Chap. 5). Therapy with lithium salts, because of its narrow therapeutic range (see Chap. 7), requires stricter compliance by the patient. Particular features of other disorders with phasic or fluctuating courses, such as tic disorders, must also be borne in mind in order to avoid confusing spontaneous symptomatic variations with the effects of medication. On the other hand, complaints prior to the initiation of therapy are also frequently forgotten so that the slightest changes in mood or mental state may be interpreted as related to the medicine, not the patient's pretreatment condition. This, in turn, can raise doubts about the medication's effectiveness, and lead to premature withdrawal from treatment.

These features of the monitoring of the effectiveness and ADRs in ambulant patients, as well as blood drug levels, make it necessary to address the following questions when a medication is prescribed:

- Is monitoring of the effectiveness and ADRs in relevant everyday situations of the patient assured?
- Is long-term monitoring of the medication assured for the patient, so that late appearing therapeutic effects and ADRs can also be recognized and monitored?
- Has literature relevant to the treated disorder been provided for the patient and his family?
- Have information sheets for the prescribed medication been provided and, where appropriate, signed?

Part II

Special Psychopharmacology: Classes of Psychiatric Treatments

Antidepressants

4

Regina Taurines, Andreas Warnke,
Laurence Greenhill, and Manfred Gerlach

Contents

R. Taurines, MD (✉) • A. Warnke, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: taurines_r@ukw.de; warnke@kjp.uni-wuerzburg.de

L. Greenhill, MD
NYS Psychiatric Institute, New York Presbyterian Hospital, Riverside Drive 1051, New York, NY 10032, USA
e-mail: llg2@columbia.edu

M. Gerlach, PhD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Laboratory for Clinical Neurobiology and Therapeutic Drug Monitoring, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: manfred.gerlach@uni-wuerzburg.de

4.1 Definition

Antidepressants elevate pathologically depressed mood and can also provide relief for those suffering from depressive delusions. Some agents may increase activity or dampen psychomotor restlessness. Furthermore, antidepressants may diminish the somatic and vegetative symptoms associated with depression.

The term "antidepressants" (the older term "thymoleptica" is no longer used) encompasses a chemically (Figs. 4.1, 4.2, and 4.3) and pharmacologically (Table 4.1) **heterogeneous class** of psychopharmacological agents that were originally employed primarily in patients with

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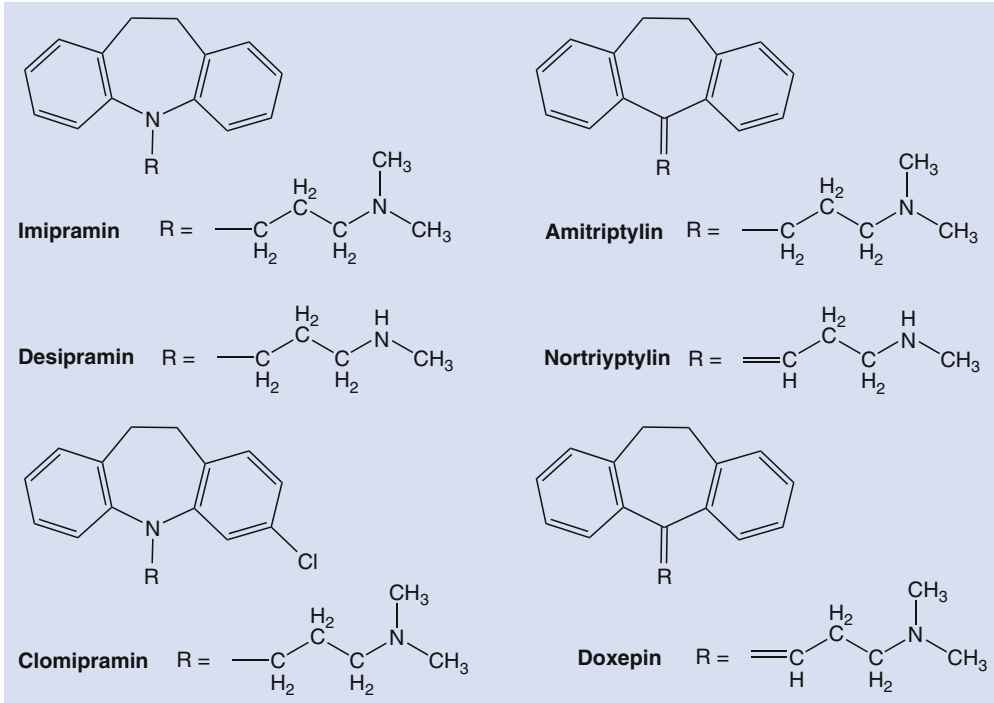
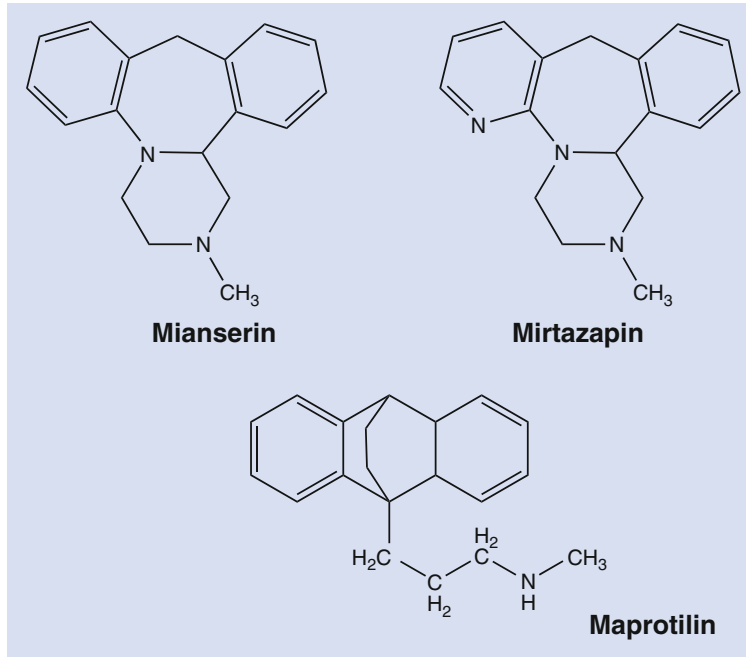


Fig. 4.1 Structural formulae of tricyclic antidepressants

Fig. 4.2 Structural formulae of tetracyclic antidepressants



depressive symptoms but which today find **widespread therapeutic application** in areas other than depressive disorders. These agents are thus also employed with clinical success in obsessive-compulsive disorder (OCD); in generalized anxiety; in panic, phobic, and eating disorders; as well as in the therapy of mutism and ADHD. The Na^+ channel blocking effect

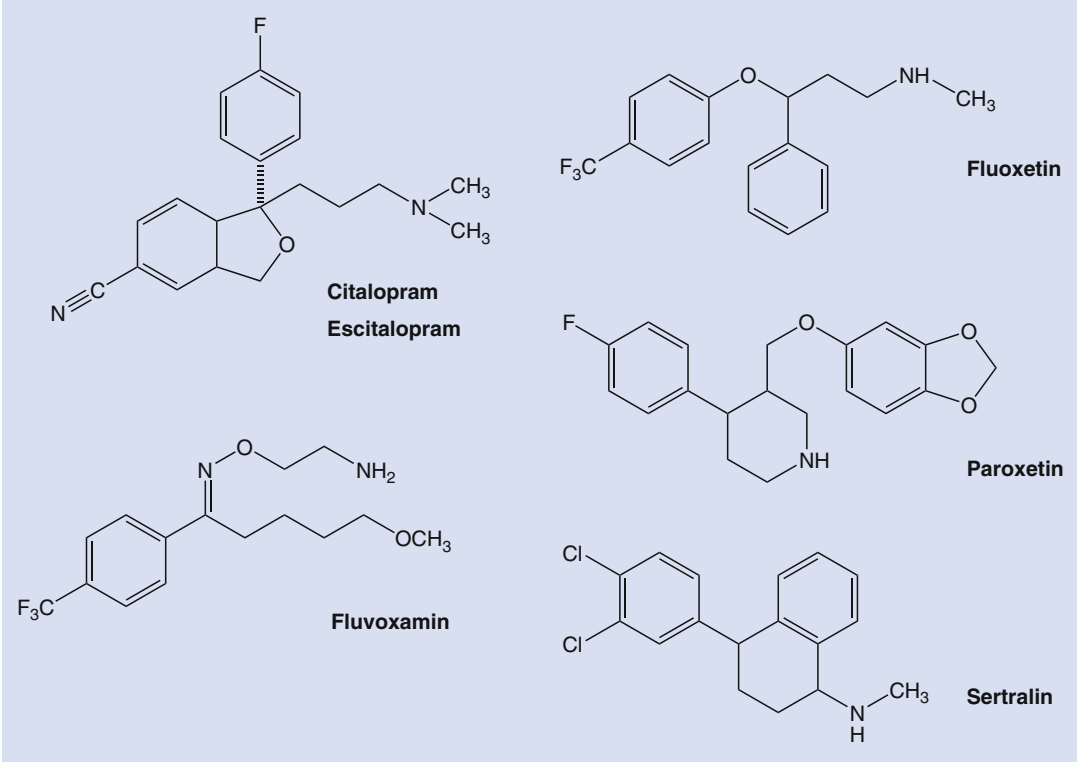


Fig. 4.3 Structural formulae of selective serotonin reuptake inhibitors (SSRIs)

Table 4.1 Classification of antidepressants according to their biological sites of action

Mechanism of action	Examples
Monoamine reuptake inhibitors	
Tricyclic antidepressants (also antagonists of various neurotransmitter receptors)	Amitriptyline, amitriptylinoxide, clomipramine, doxepin, desipramine, imipramine, nortriptyline, opipramol, trimipramine, dibenzepin
SSRIs (*s*elective *s*erotonin *r*euptake *i*nhibitors) (no affinity for neurotransmitter receptors)	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
(Selective) Noradrenaline uptake inhibitors (minimal or no affinity for neurotransmitter receptors)	Maprotiline, reboxetine
Serotonin and noradrenaline reuptake inhibitors	Duloxetine, venlafaxine
Selective monoamine oxidase type-A (MAO-A) inhibitors	Moclobemide
α_2-Adrenoceptor antagonists	Mianserin, mirtazapine
Miscellaneous antidepressants	Bupropion, St. John's wort

of the tricyclic antidepressants also renders these agents useful in the treatment of neuropathic pain. In a formal sense, the generic term "antidepressants" is therefore no longer entirely accurate.

4.2 Classification

Antidepressants were originally classified and grouped based on their **chemical structure**, such as the tricyclic or tetracyclic antidepressants

Table 4.2 Inhibition constants (K_i in nM; the smaller the value, the greater the effect) of antidepressants for noradrenaline and serotonin reuptake sites as well as for neurotransmitter receptors

Agent (group)	NA	5-HT	H_1	M	α_1	α_2	5-HT_2
Monoamine reuptake inhibitors							
Tricyclic antidepressants							
Amitriptyline	14	84	1	10	24	940	18
Clomipramine	28	5	31	37	38	>1,000	54
Desipramine	0.6	180	60	66	100	>1,000	350
Doxepin	18	220	0.2	23	24	>1,000	27
Imipramine	14	41	37	46	31	>1,000	150
Nortriptyline	2	154	6	37	55	>1,000	41
Trimipramine	510	>1,000	0.3	58	24	680	32
Selective serotonin reuptake inhibitors (SSRIs)							
Citalopram	>1,000	1	470	>1,000	>1,000	>1,000	>1,000
Fluoxetine	143	14	>1,000	590	>1,000	>1,000	280
Fluvoxamine	500	7	>1,000	>1,000	>1,000	>1,000	>1,000
Paroxetine	33	0.7	>1,000	110	>1,000	>1,000	>1,000
Sertraline	220	3	>1,000	630	380	>1,000	>1,000
(Selective) Noradrenaline reuptake inhibitors							
Maprotiline	7	>1,000	2	570	90	>1,000	120
Reboxetine	9	>1,000	>1,000	>1,000	>1,000	>1,000	>1,000
Serotonin and noradrenaline reuptake inhibitor							
Venlafaxine	210	39	>1,000	>1,000	>1,000	>1,000	>1,000
α_2-Adrenoceptor antagonists							
Mianserin	42	>1,000	0.4	820	34	73	7
Mirtazapine	–	–	0.5	500	500	10	5

Modified from Müller and Möller 2002b
The K_i values for the reuptake of noradrenaline (NA) and serotonin (5-HT) were determined in rat brain synaptosomes; the values for histaminergic H_1, muscarinic M receptors, α_1- and α_2-adrenoceptors, and serotoninergic 5-HT_2 receptors were determined in postmortem human brain tissue
– Not determined

(see Figs. 4.1 and 4.2). It was assumed that they constituted a pharmacologically homogenous group of agents that inhibited the neuronal reuptake of the neurotransmitters noradrenaline and serotonin (see Chaps. 1.3.2.2 and 1.3.2.3). They also were regarded as exercising antagonistic properties at a number of other neuroreceptors including α_1- and α_2-adrenergic, histamine H_1, muscarinic, and serotonergic 5-HT_{1A} and 5-HT_2 receptors. Antidepressants with completely different chemical structures and pharmacological characteristics (such as selective serotonin reuptake inhibitors or SSRIs) were later added to this pharmacological class (Fig. 4.3; Table 4.1).

In this chapter, antidepressants are divided into **four groups on the basis of** their putative **biological sites and mechanisms of action** (Table 4.1). Tricyclic antidepressants, in contrast to SSRIs and selective noradrenaline reuptake inhibitors, are nonselective monoamine reuptake inhibitors (Table 4.2). In this book, however, the internationally employed term "tricyclic antidepressant" will be retained. The term refers to the basic chemical structure rather than the biochemical action. This class of agents also differs in the pharmacological profile from the more recent serotonin and noradrenaline reuptake inhibitors (Table 4.2).

Antidepressants can also be divided with **clinical-therapeutic relevance** into those **with and without additional sedative-hypnotic effects** (Müller and Möller 2002a). This component of action is distinct from their antidepressive quality, so that some antidepressants can also be employed as primary sedative-hypnotics (see Chap. 6).

Antidepressants **without early sedative potential** include:

Table 4.3 Spectrum of clinical effects associated with antidepressants

	Action			
	Antidepressive	**Stimulant**	**Sedative**	**Anxiolytic**
Tricyclic antidepressants				
Amitriptyline	+++	–	++	++
Clomipramine	+++	+++	–	+
Doxepin	++	–	+++	++
Desipramine	++	+++	–	+
Imipramine	+++	++	+	++
Nortriptyline	+++	+++	–	++
Selective serotonin reuptake inhibitors (SSRIs)				
Citalopram	+++	++	–	++
Fluoxetine	+++	+	–	++
Fluvoxamine	+++	+	–	++
Paroxetine	+++	–	–	++
Sertraline	+++	–	–	++
Miscellaneous				
Moclobemide	+++	++	–	++
Venlafaxine	+++	+	–	++
Mirtazapine	+++	–	++	++
Trazodone	+++	–	++	++

Modified from Bezchlibnyk-Butler and Virani (2007)
– Very weak or no effect, + small effect, ++ moderate effect, +++ strong effect

- the monoamine oxidase (MAO) inhibitors moclobemide and tranylcypromine;
- tricyclic antidepressants, such as clomipramine, desipramine, imipramine, and dibenzepin;
- SSRIs, such as citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline;
- the selective noradrenaline reuptake inhibitor reboxetine;
- the serotonin and noradrenaline reuptake inhibitor venlafaxine.

Antidepressants **with primary sedative-hypnotic properties** include:

- tri- and tetracyclic antidepressants, such as maprotiline, amitriptyline, doxepin, mianserin, trimipramine, and trazodone;

The degree of blockade of the reuptake systems for the different monoamines (serotonin and noradrenaline, but also dopamine) and the antagonism of central and peripheral neurotransmitter receptors (Table 4.2) determine both the desired effects and the adverse drug reactions (ADRs; definition see Sect. 1.1) that occur during antidepressant therapy. For this reason, there are not only agent class-specific profiles with respect to desired clinical effects but also of ADRs. In Table 4.3, these are classified according to their pharmacodynamic profile.

4.3 Mechanisms of Action

The mechanism of action of antidepressants is only partially understood, as the etiology of depression itself has only been incompletely elucidated. Depression is a mental illness that is characterized by various symptoms including motor, vegetative, cognitive, and affective abnormalities, as they are subsumed under the concept of **major depressive disorder** (MDD). There is growing wealth of evidence that MDD is caused by an interaction between biological, genetic, and environmental factors inducing changes in several biological systems. These changes include the neuroendocrine and immune system, not only in the central nervous system (CNS) but also in the periphery (Hepgul et al. 2013; Northoff 2013). Depression in children usually arises from a combination of genetic vulnerability, suboptimal early developmental experiences, and exposure to stresses. However, depressive

syndromes sometimes occur as a sequel to physical illness such as viral infection and may overlap with fatigue syndromes (Garralda et al. 1999).

Neurochemically, serotonin and other neurotransmitters like GABA, glutamate, dopamine, adrenaline, and noradrenaline play an essential role in the pathogenesis of MDD. Among them serotonin is probably one of the most significant ones since (1) changes in serotoninergic function (i.e., receptors, metabolism, reactivity) have been observed in MDD (Northoff 2013) and (2) therapeutic efficacy of serotoninergic drugs in MDD is well documented.

As discussed in Chap. 1, there are numerous experimental and clinical findings indicating that antidepressants affect the metabolism of the neurotransmitters serotonin and noradrenaline, modulating their effects. Most antidepressants primarily inhibit the neuronal reuptake of the monoamines noradrenaline and/or serotonin from the synaptic cleft (see Sect. 1.4.3), amplifying noradrenergic and/or serotoninergic synaptic signal transmission. The degree of inhibition differs between the individual agents (Table 4.2). This primary effect, and the observation that reserpine-induced monoamine deficiency can elicit depressive symptoms, led to the proposition almost half a century ago that depression is based upon reduced noradrenergic and/or serotoninergic CNS neurotransmission (**monoamine deficit hypothesis** of depression).

The action of MAO-A inhibitors is also consistent with the monoamine deficit hypothesis of depression. As discussed in Sect. 1.4.1, the MAO-A isoform of the enzyme catabolizes noradrenaline and serotonin in human brain. The effect of this inhibition of noradrenaline and serotonin degradation at their respective nerve terminals is the short-term elevation of their synaptic levels, the result of which is amplification of noradrenergic and serotoninergic neurotransmission.

A further mechanism of action for antidepressants is their varying degree of neurotransmitter receptor antagonism, especially of α-adrenergic, histaminergic, and serotoninergic receptors (Table 4.2). Their activity profile is significantly influenced by this antagonism (Table 4.3), for example, sedative effects through inhibition of histamine H_1 receptors and anxiolytic effects through blockade of serotonergic 5-HT_2 receptors.

The primary action of many antidepressants, modulation of synaptic noradrenaline and/or serotonin concentrations, can, however, only partially account for their antidepressant effect. Although this effect presumably commences within a short time of drug administration, the antidepressive effect is apparent only after a latency of 2–4 weeks (e.g., Tao et al. 2010). One explanation of this phenomenon is that the primary effect of antidepressants also elicits longer-term regulatory **modulation of signal transduction cascades** and changes in gene expression (see Sect. 1.2.6). Animal experiments have shown that the administration of antidepressants affects an increase in the concentration of the second messenger cAMP, leading to increased phosphorylation of the cAMP response element-binding protein (CREB). CREB is a transcription factor that regulates the expression of numerous genes that have been associated with antidepressive mechanisms. For example, nerve growth factor brain-derived neurotrophic factor (BDNF), a protein regulated by CREB, critically influences neurogenesis and neuronal plasticity during embryogenesis and adulthood.

The purpose of this chapter is to review the key elements relevant to the therapeutic use of "antidepressants" in children and adolescents. The aim is to provide clinicians with a general framework for approaching the pharmacotherapy of depression in this age group.

4.4 Clinical Psychopharmacology

4.4.1 Monoamine Reuptake Inhibitors

4.4.1.1 Tricyclic Antidepressants

Indications

The areas of application are:

- Depressive symptomatology, regardless of nosological classification
- OCD (clomipramine)

Table 4.4 Comparison of the pharmacodynamic effects of antidepressants, their desired clinical effects, and agent-specific adverse drug reactions (ADRs)

Mechanism of action	Clinical effect	ADRs
Noradrenaline reuptake inhibition	Antidepressive	Tremor, tachycardia, restlessness, sweating, increased blood pressure, headache, sleep disturbances, erection and ejaculation disturbances
Serotonin reuptake inhibition	Antidepressive, positive in anxiety and obsessive-compulsive disorders	Gastrointestinal problems, nausea, emesis, reduced appetite, headache, sleep disturbances, sweating, mental restlessness, nervousness, akathisia, disturbances of sexual function
Dopamine reuptake inhibition	Antidepressive, positive in attention deficit/hyperactivity disorder (ADHD)	Excitement, restlessness, increased impulsivity
Blockade of muscarinic acetylcholine receptors	Possibly antidepressive	Obstipation, urinary retention, blurred vision, confusion, memory disturbances, sinus tachycardia, QRS changes
Blockade of serotonin 5-HT_1 receptors	Antidepressive, anxiolytic, anti-aggressive	None
Blockade of serotonin 5-HT_2 receptors	Antidepressive, anxiolytic, antipsychotic, positive in migraine and sleep disturbances	Hypotonia, ejaculation disturbances, sedation, weight gain
Blockade of dopamine D_2 receptors	Antipsychotic	Extrapyramidal motor ADRs, endocrine changes, disturbances of sexual function
Blockade of histamine H_1 receptors	None	Sedation, weight gain, orthostatic hypotonia
Blockade of adrenergic α_1-receptors	None	Orthostatic hypotonia, vertigo, reflexive tachycardia, sedation
Blockade of adrenergic α2-receptors	Antidepressive	Sexual dysfunction, priapism
Inhibition of monoamine oxidase type A	Antidepressive	Dry mouth (xerostomia), vertigo, headache, sedation, nausea, skin changes

Modified from Bezchlibnyk-Butler and Virani (2007)

- Phobias and panic disorders (clomipramine)
- Generalized anxiety disorder
- Long-term pain management
- Cataplexy, narcolepsy
- Mild withdrawal syndrome in alcohol and medication or drug dependence (doxepin)
- Sleep disorders (doxepin)
- Enuresis (imipramine, clomipramine)
- Pavor nocturnus (imipramine, clomipramine)

Tricyclic antidepressants are, however, also employed in the treatment of bulimia and anorexia and in children with ADHD (as medications of third choice).

Very few tricyclic antidepressants have a **pediatric indication** and defined posology. Only **clomipramine** has been US Food and Drug Administration (FDA)-approved for OCD from the age of 10 years and older; **imipramine** is FDA approved for use in children older than 6 years for nocturnal enuresis, and **doxepin** is FDA approved for anxiety and depression in adolescents older than 12 years.

Clinical Effects and Efficacy

In general, a range of symptoms of depression is ameliorated by antidepressants (Ambrosini 2000). Not only are mood and initiative improved but also concentration and attention. Complex psychological states, such as self-esteem and self-confidence, are positively influenced. The prominence of feelings of guilt and worthlessness as well as of negative thought patterns is reduced. Furthermore, antidepressants also improve appetite and sleep disorders. Table 4.4 summarizes the spectrum of clinical effects associated with different antidepressants.

Tricyclic antidepressants have proved to be effective in the treatment of depression in adults,

and clinical experience with this group of agents is the most extensive of all antidepressant types. Studies of adult depression indicate that they are effective and superior to placebo in around 50 % of patients (Storosum et al. 2001; Walsh et al. 2002). The mood-elevating effects of tricyclic antidepressants develop after 1–4 weeks of therapy; sedative effects are noted much earlier, and sleep disturbances are improved within a few days.

There have been only a **few placebo-controlled studies** of the efficacy of these agents in reducing depressive symptoms in children and adolescents. Papanikolaou and colleagues (2006) included 18 controlled and 23 open studies in their meta-analysis of the efficacy of tricyclic antidepressants and SSRIs in childhood and adolescent depression (see Sect. 4.4.1.2 for a detailed presentation of the study results). The authors detected **no difference in** the **efficacy** of tricyclic antidepressants and placebo, regardless of whether open studies were included in the analysis or not (see Cohen et al. 2004; Hazell et al. 1995, 2002; Maneeton and Srisurapanont 2000 for earlier meta-analyses of studies in children and adolescents).

In summary, it can be concluded that the following tricyclic antidepressants are not significantly superior to placebo in the treatment of childhood depression (level of evidence B: i.e., at least one randomized, placebo-controlled study has been reported): amitriptyline (Birmaher et al. 1998; Kashani et al. 1984; Kye et al. 1996), desipramine (Boulos et al. 1991; Klein et al. 1998; Kutcher et al. 1994), clomipramine (Sallee et al. 1997), imipramine (Petti and Law 1982; Preskorn et al. 1987; Puig-Antich et al. 1987), and nortriptyline (Geller et al. 1989, 1990, 1992).

The lack of evidence of efficacy in children and adolescents found by most studies and meta-analyses may be related to any of various methodological limitations, for example, the often small subject group sizes or the use of heterogeneous investigation instruments for the assessment of treatment success. There is a further **methodological weakness of studies** and meta-analyses, brought up by the position statement of the therapeutic drug monitoring (TDM) group of the Society of Neuropsychopharmacology and Pharmacopsychiatry (AGNP): "the ideal proof for the efficacy of a medication has long been a positive correlation of medication dose (or, to be more precise, the plasma concentration of the medication) and its effect." The AGNP TDM group further commented: "For newer antidepressants, data regarding the proof of a relationship between plasma levels and drug effect is … … deficient … If the usual placebo-controlled efficacy studies are accompanied by plasma drug level assessment, … sources of error can be avoided or minimized, such as the medication not being taken, and abnormal metabolism of the agent under investigation. The elucidation of dose- and plasma concentration-efficacy relationships for antidepressants will be directly translated into therapeutic improvements, such as improved dosing, and the detection of interactions and potential genetic peculiarities relevant to the metabolism of the test agent" (TDM-Gruppe der AGNP 2008). If considering the use of tricyclic antidepressants in the treatment of depression in children and adolescents, one should be aware of the methodological weaknesses of past studies of the efficacy of these medications.

In a placebo-controlled study of the treatment of **ADHD**, nortriptyline significantly reduced not only symptoms specific to ADHD but also oppositional symptoms (Prince et al. 2000). In a synopsis of other data from open studies, a limited efficacy of tricyclic antidepressants in ADHD, inferior to that of psychostimulants, was reported (Wood et al. 2007). A placebo-controlled, double-blind study of the treatment of chronic tic disorder and comorbid ADHD with desipramine found that significant improvement of both tic and ADHD symptoms was achieved, with good tolerance of the antidepressant (Spencer et al. 2002). Overall, however, this medication class plays no significant role in the clinical therapy of ADHD because of the concern over cardiotoxic ADRs that may occur.

Clomipramine exhibited significant efficacy in the treatment of **OCD** in children and adolescents in several randomized, controlled

studies (deVeaugh-Geiss et al. 1992; Flament et al. 1985; Leonard et al. 1989). In a meta-analysis of randomized, controlled studies of SSRIs and clomipramine, clomipramine was even more effective than the SSRIs but was also associated with a greater frequency of ADRs and withdrawals from the study (Geller et al. 2003). An open study that compared the effect of clomipramine in adults and adolescents suffering from obsessive-compulsive symptoms found that the drug was efficacious in both groups, but symptomatic relief was greater in adults (Ulloa et al. 2007).

In a meta-analysis of 54 randomized trials investigating the significance of tricyclic antidepressants for **enuresis nocturna**, it was found that the medication reduced the frequency of bedwetting. Without parallel behavioral-therapeutic interventions, however, most cases reverted to pretreatment levels following cessation of the medication (Glazener et al. 2003). For this reason, a comprehensive treatment concept including counseling and behavioral therapy is essential for lasting remission (see Chap. 19).

Recommended Dosages

The administered dose should be only slowly increased (**N.B.**: hasty increases in dose can lead to cerebral seizures). Starting with a low dose, it can be increased every 4–5 days, guided by the clinical response.

In Table 4.5, total daily dosages for selected (tricyclic) antidepressants are presented. This information is based on specific product informations of approved agents and – in case of off-license use – on peer-reviewed clinical studies or recommendations for the use in adult patients. Infusion of an agent possesses no clear advantages over oral administration and should be reserved for special circumstances only.

It is useful to implement therapeutic drug monitoring (TDM; see Sect. 2.3) during the steady-state phase. Indicative therapeutic blood level ranges for antidepressants in adults are found in Table 4.6.

The withdrawal of a medication or the change to a different antidepressant (see Sect. 4.5) must be undertaken gradually. **N.B.**: Hasty withdrawal can provoke a withdrawal syndrome, which often has a flu-like presentation: fever, increased sweating, headache and muscular pains, nausea, vomiting, vertigo, and anxiety. Abrupt withdrawal of a medication can also lead in the course of 1 or 2 days to a dramatic deterioration of mood.

> Overdosage and intoxication with tricyclic antidepressants can lead to fatal cardiac ADRs.

ADRs

This class of agents exhibits a narrow therapeutic range and, in comparison with other antidepressant types, an elevated risk of lethal intoxication (Henry et al. 1995; Shah et al. 2001). For this reason, prescriptions for maximal doses should not be provided, particularly in cases where there are suicidal tendencies and close monitoring should be undertaken (e.g., hospitalization).

In cases of overdose, the recognized undesirable anticholinergic effects are usually intensified. Furthermore, hyperarousal, myoclonus, hallucinations, respiratory depression, and even seizures can ensue. A common **cardiotoxic effect** is the widening of the PR interval; the anticholinergic effects suppress vagal tone and lead to tachycardia. Cardiac rhythm disturbances, requiring intensive medical treatment with continuous electronic monitoring, can occur. Widening of the QRS complex is possible.

A **central anticholinergic syndrome** can also develop, consisting of central fever, mydriasis, micturition disturbance (possibly even urinary retention), obstipation (as serious as paralytic ileus), and disturbed cardiac rhythm with tachycardia. With respect to psychopathology, the patient exhibits orientation disturbances, a high degree of excitement (ranging to delirium), sensory delusions, and optical and auditory hallucinations. With deterioration of the condition, seizures, somnolence, and coma can develop. Therapy consists of the immediate discontinuation of anticholinergic medications, and the

Table 4.5 Daily dosages of selected antidepressants used in children and adolescents, their clinical indication, approval status, and/or references for the listed dosages

Agents	Indication	Total daily dosages	Approval/references
Amitriptyline	Depression	25–150 mg/day in two or three dosages/day	US FDA approved ≥12 years In Europe approved ≥16 years
	Enuresis	10–50 mg/day as single bedtime dose	In Europe approved >5 years
Bupropion	Depression	100–150 mg/day Maximum 6 mg/kg/day or 300 mg/day (whichever is smaller) in two or three dosages/day	Off-label use in children and adolescents Barrickman et al. (1995), Daviss et al. (2001), Jafarinia et al. (2012), Lee et al. (2008)
Citalopram	Depression	20–40 mg/day as single morning dose	Off-label use in children and adolescents von Knorring et al. (2006), Wagner et al. (2004a)
Clomipramine	OCD	Maximum 3 mg/kg or 200 mg/day (whichever is smaller) as single evening dose	US FDA approved ≥10 years
	Nocturnal enuresis	10–50 mg/day as single bedtime dose	Not US FDA approved In some European countries approved >5 years
Doxepin	Depression	(25) 50–150 mg/day as single bedtime dose or in two dosages/day	US FDA approved and in Europe approved ≥12 years
Duloxetine	Depression	40–60 mg/day in one or two dosages/day Maximum: 120 mg/day	Off-label use in children and adolescents Prakash et al. (2012)
Escitalopram	Depression	10–20 mg/day as single morning dose	US FDA approved ≥12 years
Fluoxetine	Anxiety disorders	10–20 mg/day as single morning dose	Off-label use in children and adolescents Birmaher et al. (2003)
	Bulimia	20–60 mg/day as single morning dose	Off-label use in children and adolescents Hay and Claudino (2012)
	Depression	10–20 (–40) mg/day as single morning dose	US FDA approved and in Europe approved ≥8 years Emslie et al. (2008) and Gibbons et al. (2012b) reported higher doses than those approved
	OCD	20–60 mg/day as single morning dose	US FDA approved ≥7 years
Fluvoxamine	OCD	50–200 (–300) mg/day in two dosages/day (larger dose, if so, in the evening)	US FDA approved ≥8 years
Imipramine	Nocturnal enuresis	25–75 mg/day (depending on body weight) as single evening dose	US FDA approved and in Europe approved ≥6 years
Maprotiline	Depression	**Adults**: 75–225 mg/day in two or three dosages/day	Off-label use in children and adolescents Minuti and Gallo (1982), Simeon et al. (1981)
Mianserin	Depression	Average dose: 1 mg/kg body weight/day in one, two or three dosages/day; larger dose at bedtime	Off-label use in children and adolescents Dugas et al. 1985
Mirtazapine	Depression	15–45 mg/day in one, two or three dosages/day; larger dose at bedtime	Off-label use in children and adolescents Haapasalo-Pesu et al. (2004)

Table 4.5 (continued)

Agents	Indication	Total daily dosages	Approval/references
Moclobemide	Depression	150–300 mg/day in two or three dosages/day	Off-label use in children and adolescents Avci et al. (1999)
Paroxetine	Depression	20–40 mg/day as single morning dose	Off-label use in children and adolescents Keller et al. (2001)
	Anxiety disorders/ OCD	10–50 mg/day as single morning dose	Off-label use in children and adolescents Geller et al. (2004); Wagner et al. (2004b)
Reboxetine	Enuresis	4–8 mg/day as single bedtime dose	Off-label use Lundmark and Nevéus (2009)
	ADHD/ depression	3–8 mg/day in two dosages/day	Off-label use in children and adolescents Arabgol et al. (2009), Cohen-Yavin et al. (2009). Golubchik et al. (2013), Tehrani-Doost et al. (2008)
Sertraline	Anxiety disorders	25–50 mg/day as single morning dose	Off-label use in children and adolescents Rynn et al. (2001
	Depression	25–200 mg/day as single morning dose	Off-label use in children and adolescents Alderman et al. (2006), Wagner et al. (2003)
	OCD	25–200 mg/day as single morning dose	US FDA approved and in some European countries approved ≥6 years
St. John's wort	Depression	900 mg/day in three dosages/day	Approved in some European countries for adults and partly for adolescents Findling et al. (2003), Simeon et al. (2005)
Venlafaxine	Anxiety disorders Depression	37.5–225 mg/day in two or three dosages/day or as extended-release formula	Off-label use in children and adolescents Brent et al. (2008), Emslie et al. (2007a, b), March et al. (2007b), Rynn et al. (2007)

This information is based on specific product informations of approved agents and – in case of off-license use – on peer-reviewed clinical studies or recommendations for the use in adult patients

ADHD attention-deficit/hyperactivity disorder, *OCD* obsessive-compulsive disorder, *US FDA* US Food and Drug Administration

patient should be closely monitored. Where symptoms are particularly severe, 2–4 mg physostigmine can be administered intramuscularly (i.m.) or intravenously (i.v.). This measure always requires intensive medical care and continuous electronic monitoring.

ADRs during tricyclic antidepressant therapy **can be avoided** or at least mitigated by adopting the following measures:

- Conducting an ECG prior to treatment and upon achievement of the therapeutically effective dose.
- Use of slow-release preparations.
- Where possible, dose reduction in cases of marked tachycardia or administration of a β-adrenoceptor antagonist (β-blocker), such as metoprolol.
- Do not administer agents that significantly enhance impulsiveness (such as desipramine) in the evening.
- For dry mouth: increase fluid intake, chewing of gum, or sucking of sugar-free hard candy (boiled lollies); pilocarpine (10–15 mg/day) in some cases.

Table 4.6 Indicative therapeutic blood level ranges for antidepressants in adults

Agent	ng/ml	TDM as routine procedure
Amitriptyline plus nortriptyline	80–200[a]	Strongly recommended
Citalopram	50–110	Recommended
Clomipramine plus norclomipramine	230–450[a]	Strongly recommended
Desipramine	100–300	Recommended
Doxepin plus nordoxepin	50–150[a]	Recommended
Escitalopram	15–80	Recommended
Fluoxetine plus norfluoxetine	120–500	Recommended
Fluvoxamine	60–230	Recommended
Imipramine plus desipramine	175–300[a]	Strongly recommended
Maprotiline	75–130	Recommended
Mianserin	15–70	Useful
Mirtazapine	30–80	Recommended
Moclobemide	300–1,000	Useful
Nortriptyline	70–170	Strongly recommended
Paroxetine	30–120	Useful
Reboxetine	60–350	Useful
Sertraline	10–150	Recommended
Tranylcypromine	≤50	Potentially useful
Trazodone	700–1,000	Recommended
Trimipramine	150–300	Recommended
Venlafaxine plus *O*-desmethylvenlafaxine	100–400[a]	Recommended

From Hiemke et al. 2011
TDM therapeutic drug monitoring
[a]combined concentration of the parent substance and its active metabolite(s)

- For obstipation: increase fluid intake. One should further be mindful of the diet (e.g., increased consumption of yoghurt, sauerkraut, and plums). Caution is advised with respect to signs of paralytic ileus (intestinal paralysis), a possible countermeasure being administration of carbachol (1–4 mg/day p.o.).
- Administration of carbachol (1–4 mg/day) or acetylcholine esterase inhibitors (e.g., distigmine, 2.5–5 mg/day) for micturition disturbances; 0.25 mg carbachol i.m. or s.c. for acute urinary retention.

Drug Interactions

The most important interactions between antidepressants and other pharmaceutical agents occur at the level of biotransformation whereby the cytochrome P_{450} (CYP) system (see Sect. 2.2.1) plays a major role. All antidepressants, as far as effects are known, inhibit CYP enzymes (Table 4.7), while, for instance, antiepileptic agents can both inhibit them and induce their expression. Inhibition of an enzyme of the CYP system leads to slower elimination of medications metabolized by the enzyme, with the consequence that plasma drug levels can increase to toxic levels, increasing the frequency and severity of ADRs.

On the other hand, enzyme inducers lead to more rapid biotransformation of particular pharmaceutical agents. If the enzyme inducer is withdrawn without reducing the dosage of a concurrently employed pharmaceutical agent metabolized by the enzyme, there is a danger of overdosage because of the diminishing induction effect. TDM (see Sect. 2.3) can be employed to monitor the serum/plasma levels at the commencement of co-medication.

Table 4.8 summarizes potential interactions between tricyclic antidepressants and other pharmaceutical agents.

Table 4.7 Influence of antidepressants on cytochrome P450 (CYP) enzymes

Antidepressant	CYP1A2	CYP2C9/10/19	CYP2D6	CYP3A4
Amitriptyline				
Citalopram				
Clomipramine				
Duloxetine			↓	
Fluoxetine		↓	↓	
Fluvoxamine	↓	↓		↓
Imipramine				
Mianserin				
Mirtazapine				
Moclobemide		↓	↓	
Paroxetine			↓	
Reboxetine				
Trazodone				
Venlafaxine				

Modified from Hiemke et al. (2011)
↓ Enzyme inhibition, where not otherwise indicated, effect is unknown

Table 4.8 Interactions between tricyclic antidepressants and pharmaceutical agents, foodstuffs, stimulants, and recreational drugs relevant to therapy in children and adolescents

Interaction with	Consequences
Alcohol	Amplification, for example, of dampening effects, with sedation
Anticholinergics	Increased plasma levels, prolongation of transition period, amplification of anticholinergic effects
Anticonvulsive agents, such as carbamazepine, valproic acid	Carbamazepine: depression of antidepressant plasma concentration Valproic acid: elevation of antidepressants plasma concentration
Antipsychotics	Amplification of anticholinergic effects, rise in plasma concentration of antipsychotics, and QT prolongation possible
Cannabis	Particularly cardiac effects: ranging from tachycardia to instability of mood, confused, and deliriant states
Contraceptives	Elevated plasma concentration of tricyclic antidepressants
Hypnotic agents, such as benzodiazepines	Amplification of sedation and longer reaction times to respiratory depression
Insulin	Potentially reduced insulin sensitivity
Lithium salts	Potential amplification of antidepressive effect
Methylphenidate	Reduced elimination, with rise in plasma concentration of tricyclic antidepressants possible
Other antidepressants	Increased plasma levels of tricyclic antidepressants and consequently of their ADRs
	Amplification of antidepressive effect
Smoking	Induction of CYP1A2 with reduction of plasma level
Sympathomimetics (such as anesthetics)	Increase in blood pressure and pulse

Modified from Bandelow et al. (2011)
ADRs adverse drug reactions

Contraindications

Restrictions on use pertain in the following circumstances:

- Preexisting cardiac abnormalities: this particularly applies to all cardiac conduction disorders. According to FDA recommendations, the following ECG/blood pressure/pulse changes should be treated with concern where detected in children treated with tricyclic antidepressants: QRS interval >30 % of the normal range or >120 ms, PR interval >200 ms, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, and resting heart rate >130/min).
- Concurrent administration of a tricyclic antidepressant and an SSRI, which can lead to marked increases in plasma tricyclic antidepressant levels.

Caution is **advised** under these conditions:

- Combination therapy with other psychopharmacological agents, which can lead to marked amplification of their sedative effects.
- A history of cerebral seizures or myoclonus (reduction in seizure threshold by tricyclic antidepressants).
- Abrupt discontinuation of a tricyclic antidepressant; as with the SSRIs, a so-called discontinuation syndrome is also possible here (see below).
- Bipolar disorder, as tricyclic antidepressants can induce manic episodes.
- Suicidal tendency, as the impulsiveness of depressive patients can be increased significantly at the commencement of treatment with certain tricyclic antidepressants in the absence of an improvement in mood.

Tricyclic antidepressants should during pregnancy only be employed after careful consideration of their necessity, although a teratogenic effect has not yet been demonstrated. In particular, administration during the first trimester should be avoided. Similar caution should also be exercised with nursing mothers, as tricyclic antidepressants can be passed to the infant via breast milk.

Antidepressants including tricyclic antidepressants carry a **black box warning** from the US FDA that an increased risk of suicidal thinking and behavior in children and adolescents and young adults has occurred. Therefore, the worsening and emergence of suicidal thoughts and behaviors should be monitored.

4.4.1.2 SSRIs

Indications

Areas of application are:

- Depressive symptomatology, regardless of nosological classification
- OCD
- Bulimia nervosa
- Panic disorders and agoraphobia
- Social phobia
- Generalized anxiety disorder
- Post-traumatic stress disorder

SSRIs are also employed in cases of aggressive and impulsive behavior, in the treatment of autoaggression and of alcohol and drug withdrawal, as well as in children with mutism, Tourette syndrome, ADHD, trichotillomania, separation anxiety, profound developmental disorders (such as autism and Rett syndrome), obscure pain, and anorexia nervosa. The pediatric US FDA indications for SSRIs are summarized in Table 4.5.

Clinical Effects and Efficacy

Similar to tricyclic antidepressants, SSRIs ameliorate a range of symptoms of depression (Ambrosini 2000). Table 4.3 summarizes the spectrum of clinical effects associated with different antidepressants.

Efficacy and Safety in Depression

The **efficacy** of SSRIs in depressive illness in **adults** has been **confirmed** by numerous controlled studies. Williams et al. (2000) included 25 placebo-controlled studies in a meta-analysis of the efficacy of SSRIs (fluvoxamine, fluoxetine, paroxetine, and sertraline) in depression in adults. Of the included investigations, 90 % were short-term studies with an observation period of 6–8 weeks. This analysis also included comparisons of SSRIs with tricyclic and tetracyclic antidepressants. The meta-analysis indicated that each of these antidepressant classes was significantly more efficacious than placebo in the treatment of depressive symptoms and dysthymia in adults; the efficacy of SSRIs was not significantly different

from that of tricyclic or tetracyclic antidepressants, nor could any differences between the individual SSRIs be detected.

In recent years, the use of SSRIs in the clinical treatment of depressive symptoms in children and adolescents has become increasingly common (Chermá et al. 2011; Edwarts and Anderson 1999; Keller et al. 2001; Moreno et al. 2007). This is not only due to their good efficacy but also due to their effective use and good tolerability. Fortunately, SSRIs have minimal sedating treatment emergent adverse events on the psychomotor and cognitive functions needed for driving.

Several studies have indicated that SSRIs are **superior to placebo in children and adolescents** presenting depressive disorders (see Cohen et al. 2004; Hetrick et al. 2007; Usala et al. 2008 for overviews and meta-analyses). In the meta-analysis of Papanikolaou et al. (2006), which included 18 controlled and 23 open studies of the efficacy of various antidepressants, the odds ratios for SSRIs were 1.84 (95 % confidence interval [CI] 1.35–2.50) for controlled studies and 1.83 (95 % CI 1.40–2.40) for controlled and uncontrolled studies, also supporting a generally significant benefit from SSRIs when compared with placebo.

The best-studied SSRI with respect to children and adolescents is **fluoxetine**, found by several randomized, controlled studies to be superior to placebo in the treatment of depressive syndromes (Emslie et al. 1997, 2002, 2008; Gibbons et al. 2012b). Simeon and colleagues (1990) found a positive, but not a statistically significant, benefit from fluoxetine in a controlled study. In randomized, controlled comparisons of fluoxetine monotherapy, placebo, cognitive behavioral therapy (CBT), and fluoxetine plus CBT, the best results were achieved with the two options that included fluoxetine whereby the combination of fluoxetine and CBT was superior to pharmacological therapy alone (March et al. 2004, 2007a; Pathak et al. 2005). Similar results were reported by Brent and colleagues in the National Institute of Mental Health (NIMH)-sponsored TORDIA study (2008). The authors found that children and adolescents who did not respond to a particular SSRI benefited from the change to an alternative SSRI or venlafaxine to a greater degree if it was accompanied by CBT.

In a further randomized, controlled study of patients of this age group with depression, conduct disorder, or substance abuse, fluoxetine plus CBT more effectively reduced depressive symptoms (assessed with the Childhood Depression Rating Scale – Revised) than CBT alone or placebo. This beneficial effect could not, on the other hand, be detected by the Clinical Global Impression – Improvement scale (CGI-S; Riggs et al. 2007). In a randomized study of major depression in children and adolescents, Goodyer et al. (2008) failed to detect a significant difference between SSRI plus CBT and SSRI medication alone. In terms of potential moderators of the effect of fluoxetine in adolescents with comorbid depression and substance use disorder, a recent randomized, controlled study revealed that youths with chronic depression and no more than moderate alcohol consumption were likely to respond better to fluoxetine therapy compared with placebo than youths with transient depression and heavy alcohol use (Hirschtritt et al. 2012).

Sertraline was similarly found in controlled studies to be superior to placebo (Pössel and Hautzinger 2006; Wagner et al. 2003). In a study in which the first phase was placebo controlled and double-blind and the second phase was open, sertraline elicited more rapid, longer-term therapeutic successes than placebo (Donnelly et al. 2006; Rynn et al. 2006). Furthermore, an improvement of depressive symptoms combined with good tolerability could be observed in an open long-term study over 24 weeks (Alderman et al. 2006).

Significant superiority of **citalopram** over placebo was detected by Wagner et al. (2004a) in a randomized, controlled, double-blind study of the treatment of depression in children and adolescents; Pössel and Hautzinger (2006) drew a similar conclusion from their meta-analysis. In a further controlled, double-blind investigation, however, no significant remission rates between the citalopram and the placebo group were found (Von Knorring et al. 2006). However, post hoc analyses revealed that more than two-thirds of patients received psychotherapy during the study. For those patients not receiving psychotherapy,

there was a higher percentage of Kiddie-SADS-P (Schedule for Affective Disorders and Schizophrenia for school-aged children-Present episode version) responders with citalopram (41 %) versus placebo (25 %) and a significantly higher percentage of responders and remitters – assessed with the Montgomery-Asberg Depression Rating Scale – with citalopram (52 and 45 %, respectively) versus placebo (22 and 19 %, respectively).

Escitalopram, the enantiomer of citalopram, has shown superiority over placebo in the treatment of depressive children and adolescents aged 12–17 years (Emslie et al. 2009; Yang and Scott 2010). Data of another controlled study suggested that escitalopram may not be better than placebo in younger depressed children in the age 6–11 years but that it may have beneficial effects in adolescent patients in the age of 12–17 years (Wagner et al. 2006). Escitalopram appeared to be well tolerated in all these trials.

Studies of **paroxetine** have produced contradictory results. Paroxetine was superior to placebo in some randomized, controlled studies (Keller et al. 2001; Wagner et al. 2004b), but not in all (Emslie et al. 2006). Paroxetine and clomipramine were similarly efficacious in a randomized multicenter study in the treatment of childhood and adolescent depression (Braconnier et al. 2003).

Sertraline and fluoxetine improved depressive symptoms in the treatment of depression with **comorbid epilepsy** in an open study. Epileptic symptoms were exacerbated in 2 of 38 patients during medication with sertraline or fluoxetine, but all other patients tolerated SSRIs very well (Thomé-Souza et al. 2007).

As already mentioned in the discussion of tricyclic antidepressants, the dearth of evidence for efficacy from individual studies can be explained by a number of methodological limitations. **In clinical practice, it is quite clear that SSRIs improve depressive symptoms in children and adolescents**.

Efficacy and Safety in Anxiety Disorders

In the treatment of **generalized anxiety disorder**, social phobia, and separation anxiety, SSRIs reduced anxiety symptoms (see Masi et al. 2001; Segool and Carlson 2008 for overview). In a placebo-controlled study, **fluvoxamine** (at a maximum of 300 mg/day) was shown to be effective in the treatment for children and adolescents with social phobia, separation anxiety disorder, or generalized anxiety disorder, who had received psychological treatment for 3 weeks without improvement (Walkup et al. 2001). Children in the fluvoxamine group had a mean (± SD) decrease of 9.7 ± 6.9 points in symptoms of anxiety on the Pediatric Anxiety Rating Scale (range of possible scores, 0–25, with higher scores indicating greater anxiety), as compared with a decrease of 3.1 ± 4.8 points among children in the placebo group ($P<0.001$). On the CGI-S, 48 of 63 children in the fluvoxamine group (76 %) had a response to the treatment, as indicated by a score of less than four, as compared with 19 of 65 children in the placebo group (29 %, $P<0.001$). Five children in the fluvoxamine group (8 %) discontinued treatment because of adverse events, as compared with one child in the placebo group (2 %).

In a placebo-controlled, double-blind study of the treatment of generalized anxiety disorder in children and adolescents, Rynn and colleagues (2001) found that **sertraline** was significantly more effective than placebo. In a randomized, placebo-controlled study, **paroxetine** was similar superior to placebo in the treatment of social phobia in children and adolescents (Wagner et al. 2004b). In an open and a placebo-controlled study, **fluoxetine** improved the anxiety symptoms of children and adolescents with separation anxiety, generalized anxiety disorder, or social phobia (Birmaher et al. 1994; 2003).

SSRIs are clearly effective in the treatment of **OCD** in children and adolescents (Geller et al. 2003; Gentile 2011). In controlled studies, **fluoxetine** (Geller et al. 2001; Liebowitz et al. 2002; Riddle et al. 1992), **fluvoxamine** (Riddle et al. 2001), **sertraline** (March et al. 1998), and **paroxetine** (Geller et al. 2004) were superior to placebo. In an open study, sertraline exerted a positive effect on compulsion symptoms even after more than 24 weeks of treatment (Alderman

et al. 2006). In a randomized, controlled study, the effects of CBT alone, sertraline monotherapy, sertraline plus CBT, and placebo upon OCD were compared (Pediatric OCD Treatment Study Team 2004). All three active therapy forms were superior to placebo, but the best remission rate was achieved with combination treatment (sertraline plus CBT), although the difference from that with CBT alone was not statistically significant. A randomized but not placebo-controlled study that compared group CBT and sertraline monotherapy found that both therapy forms were associated with symptomatic improvement after 12 weeks, but there was no significant difference between the two groups. Nine months later, however, significantly less obsessive-compulsive symptoms were described in the CBT group than in the sertraline group (Asbahr et al. 2005).

In two randomized, placebo-controlled studies of the treatment of **post-traumatic stress disorder** (PTSD), sertraline could not demonstrate significant efficacy (Cohen et al. 2007; Robb et al. 2010). In a 24-week double-blind, placebo-controlled approach to prevent PTSD in a small group of burned children, sertraline showed a more favorable effect in preventing PTSD symptoms than placebo according to parent report, but not according to child report (Stoddard et al. 2011).

Efficacy and Safety in Other Indications

Fluoxetine, of all the SSRIs, proved particularly effective in open studies of the treatment of selective mutism (Carlson et al. 1999; Kaakeh and Stumpf 2008). In the treatment of **autism spectrum disorders** (ASD) in adults, a positive effect of SSRIs on associated symptoms, such as anxiety and repetitive behavioral patterns, was identified in a meta-analysis of three controlled and ten open studies (Kolevzon et al. 2006). Open studies have similarly found a positive effect in children and adolescents with ASD (e.g., Steingard et al. 1997).

A retrospective study of female adolescents with anorexia nervosa found at best a quite minor effect of SSRIs upon the eating syndrome or upon associated symptoms, such as depressive and obsessive-compulsive behaviors (Holtkamp et al. 2005). Further studies with larger patient groups are still required with respect to this disorder.

Recommended Dosages

The initial increase in dose proceeds **slowly** as **hasty dosage elevation** can lead to a **pharmacogenic delirium**. Dosage increases should be undertaken after achievement of steady-state equilibrium (around 8 weeks for fluoxetine, otherwise 1 week).

In Table 4.5 total daily dosages for selected SSRIs are presented.

As age effects on pharmacokinetic processes are suggested – on resorption, metabolization, and clearance of a drug – with possible impact on the bioavailability of SSRIs (Hiemke and Härtter 2000; van den Anker 2010), therapeutically effective dosages in children might differ from those recommended for adults. For fluoxetine, however, no major pharmacokinetic differences in minors compared to adults, for the labeled age range starting with the age of 8 years, are reported (Blazquez et al. 2012). **TDM** during steady state (see Sect. 2.3) is **recommended** for most SSRIs (Table 4.4).

A **single morning dose** is sufficient for most SSRIs. However, **fluvoxamine** is an **exception**: it has a plasma half-life between 10 and 22 h, so that, at higher dosages, two doses/day are recommended. The antidepressive effect of SSRIs is generally evident after 1–4 weeks (e.g., Tao et al. 2010). It is generally recommended that SSRI therapy be maintained for a further 6–9 months after remission, although the decision should be made on an individual basis.

Sertraline should be taken at meal times, but the patient should be advised not to drink grapefruit juice as it potentially increases plasma concentrations of the antidepressant (Ueda et al. 2009). **Fluvoxamine** tablets should be swallowed unchewed in order to maximize resorption; once again, the patient should be advised not to drink grapefruit juice at the same time (Hori et al. 2003).

Discontinuation and change of medication must be undertaken **gradually**. This applies in particular to SSRIs with short plasma half-lives (such as fluvoxamine). Abrupt discontinuation can lead to vertigo, gait disturbance, gastrointestinal complaints, disturbances of sensibility, and deterioration of mental state, for which reason SSRIs should be gradually reduced (by the slowest possible steps for each SSRI each week; Haddad 1998; Fava et al. 2007).

In the treatment of **OCD** and **bulimia**, higher daily doses (for fluoxetine, e.g., up to about 60 mg/day) than those employed in the treatment of depression are required (Geller et al. 2001; Hay and Claudino 2012; Jackson et al. 2010).

The toxicity of SSRIs in cases of overdosage and intoxication is generally quite low. Overdosage can be associated with nausea, emesis, increased impulsivity, excitement, tachycardia, and, very rarely, even seizures. At extremely high doses (e.g., 6,000 mg fluoxetine), there is a risk of death.

ADRs

SSRIs are well-tolerated drugs, which in clinical studies have been associated with less serious ADRs. These occur predominantly at the commencement of therapy and can spontaneously resolve. The most important ADRs are headache, loss of appetite, nausea, diarrhea, weight loss, dry mouth, sweating, disturbances of sexual function, allergic reactions, and, occasionally, extrapyramidal motor symptoms. SSRI-related sexual dysfunction is the most troubling ADR for adolescents and young adults. It occurs in over 30 % of cases. In contrast to tricyclic antidepressants, cardiac ADRs are rare. Paroxetine has occasionally been associated with disturbed hepatic function.

SSRIs do not cause sedation but rather exert an excitant effect, possibly resulting in agitation, restlessness, sleep disturbances, irritability, and loss of social inhibitions. For this reason, it is recommended that the agent be administered as a single morning dose. SSRIs can similarly trigger manic episodes in sufferers of bipolar affective disorder.

The **serotonin syndrome** is rare, but ominous ADRs or interaction can occur. This syndrome of central serotoninergic hyperactivity is a life-threatening complication if cardiac arrhythmias, seizures, or even comatose phenomena occur. Therapy consists of the immediate discontinuation of medication. Here, fluoxetine requires special attention because of its active metabolites and the long effective half-life. Marked fever requires that the patient be cooled; adequate fluid intake should be assured, including infusion of fluids if required. Some cases call for intensive medical treatment; increasing doses of methysergide can be administered as a pharmacological intervention.

A number of publications concerning the increase in impulsivity effected by SSRIs, and the consequently often expressed concerns that SSRIs might facilitate implementation of **suicidal ideas**, have in recent years provoked an intense debate concerning allegedly increased suicidality associated with SSRIs. The discussion was initiated by a meta-analysis published by the FDA, which included 24 placebo-controlled studies of the use of nine different antidepressants in children and adolescents, according to which SSRIs were associated with an almost twofold risk of suicide-related events. The corresponding UK agency, the Medicines and Healthcare Products Regulatory Agency (MHRA), responded by explicitly declaring that paroxetine was not approved for use in minors, while the FDA restricted itself to the recommendation that paroxetine should not be employed in depressive children and adolescents.

In the course of the SSRI debate, some subsequent studies and meta-analyses reported an increase in suicidal behavior, particularly with paroxetine and venlafaxine (e.g., Apter et al. 2006; Hetrick et al. 2007). In other studies, however, such a connection was not found, or there was a decrease in suicidal thoughts and self-harm during medication with SSRIs (e.g., Gibbons et al. 2006; Goodyer et al. 2008; Isacsson et al. 2005; March et al. 2006; Wong et al. 2004; Zuckerman et al. 2007). Gibbons et al. (2006) found a brief increase in the rate of completed suicides in adolescents and young adults after the US FDA black box warning appeared. The dropped prescription of antidepressants to young adults and adolescents can be associated with the warning. However, to jump to the conclusion that the rate of prescription was causally related to the increase in completed suicides cannot be proven from the data.

Repeated analysis of the SSRI data found a **favorable benefit/risk profile** for their use in the treatment of childhood and adolescent MDD, anxiety, and OCD (Bridge et al. 2007; Hammad et al. 2006; Henry et al. 2012; Whittington et al. 2004).

In these studies, there was no case of a completed suicide during treatment with SSRIs (e.g., Bridge et al. 2007; Mosholder and Willy 2006). Pooled risk differences in rates of primary study-defined measures of responder status significantly favored antidepressants for MDD (11.0 %), OCD (19.8 %), and non-OCD anxiety disorders (37.1 %), corresponding to a number needed to treat (NNT; definition see Chap. 1.1) of ten, six, and three, respectively. While there was an increased risk difference between suicidal ideation and suicide attempt across all trials and indications for drug versus placebo (0.7 %; number needed to harm 143), the pooled risk differences within each indication were not statistically significant: 0.9 % for MDD, 0.5 % for OCD, and 0.7 % for non-OCD anxiety disorders (Bridge et al. 2007). Based on the evidenced-based medicine calculation of NNT versus the number needed to harm, it can be concluded that benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications.

According to the SSRI meta-analysis by the FDA, fluoxetine, followed by sertraline and citalopram, had the lowest relative risk for an increase in suicidal thoughts and suicide-related acts. However, Bridge and colleagues (2007) showed **no increase in suicidal risk**, using the same analysis tool than the FDA but with a larger sample. In addition, the most recent (meta-)analyses showed that there is no elevated risk for suicidal thoughts or actions in the treatment with fluoxetine, citalopram, sertraline, or even paroxetine, which had previously met with particular criticism (Gibbons et al. 2012a). Finally, a large population-based cohort study showed no meaningful variation in the risk of suicidal acts according to antidepressant agents within the class of SSRIs or between antidepressant classes (Schneeweiss et al. 2010). The suicide risk associated with these antidepressants in the treatment of children and adolescents has been estimated as being less than 1 % (Bridge et al. 2007; Pössel and Hautzinger 2006).

Drug Interactions

Table 4.9 summarizes potential interactions between SSRIs and pharmaceutical agents, foodstuffs, psychostimulants, and recreational drugs, together with the resultant clinical consequences.

Contraindications

Restrictions apply in the following circumstances:

- Intoxication with medications that depress CNS function. This includes alcohol, as increased depression and the potentiation of alcohol effects are possible. The risk of serious complications, however, is low.
- During **pregnancy** (for citalopram, fluvoxamine, fluoxetine, and paroxetine; sertraline should only be employed with great caution). A teratogenic effect has thus far not yet been established. It is unclear whether SSRIs increase the risk for miscarriage. Withdrawal symptoms, including restlessness and tremor, have been described in newborn babies of mothers treated with SSRIs. Sertraline, paroxetine, fluvoxamine, fluoxetine, and citalopram have been detected in breast milk; it has been recommended that fluoxetine and fluvoxamine not be employed by nursing mothers, while the relative benefit and possible risks should be carefully considered for sertraline, citalopram, and paroxetine.

Caution is **advised** under these conditions:

- Epilepsy and other organic brain disorders
- Suicidal tendency (see above and below)
- High dosage or combination of an SSRI with other psychopharmacological agents, which can modulate serotoninergic neurotransmission, as a serotonin syndrome is possible, as is, in extreme cases, rhabdomyolysis (disintegration of striatal muscle).

Antidepressants including SSRIs carry a **black box warning from the US FDA** that an increased risk of suicidal thinking and behavior in children and adolescents and young adults has occurred. Therefore, the worsening and emergence of suicidal thoughts and behaviors should be monitored.

Table 4.9 Interactions between selective serotonin reuptake inhibitors (SSRIs) and pharmaceutical agents, foodstuffs, psychostimulants, and recreational drugs relevant to therapy in children and adolescents

Interaction with:	Consequences
Alcohol	Increased sedative ADRs
Anticonvulsives (carbamazepine, phenytoin, valproic acid)	Elevation of plasma concentrations of carbamazepine and phenytoin, lowering of plasma concentrations of SSRIs, frequent gastrointestinal problems with the combination of fluvoxamine and carbamazepine Elevation of valproic acid plasma concentrations, especially in combination with fluoxetine
Antipsychotics	Elevation of plasma antipsychotic concentrations, particularly for combination with clozapine or fluvoxamine and, to a lesser degree, for the combination with fluoxetine; further exacerbation of extrapyramidal motor ADRs possible. Improvement of possible negative symptoms of psychoses. Additive effect in the treatment of compulsive disorders possible
Benzodiazepines	Elevation of plasma benzodiazepine concentrations, especially in combination with fluvoxamine and fluoxetine; amplification of ADRs, such as sedation, elevated impulsivity, and memory disturbances
β-**Adrenoceptor antagonists** (β-blockers)	Increased effect, leading to more frequent ADRs, such as fainting spells, bradycardia, disturbances of drive
Caffeine	Excessive use, especially in combination with fluvoxamine, significantly increased plasma caffeine concentrations; potential ADRs including restlessness, shaking, sleep disturbance
Cannabis	Potential amplification of disturbances of drive
Grapefruit juice	Elevation of plasma concentrations of sertraline and fluvoxamine
Insulin	Increased insulin sensitivity (potential hypoglycemia)
Lithium salts	Elevation of plasma lithium concentration possible; potential amplification of ADRs for combination with fluoxetine and fluvoxamine, vertigo, headache, and seizures possible Combination with sertraline and paroxetine: increased tremor, shaking, and nausea Elevation of antidepressive effect possible
Other antidepressants	Elevation of plasma concentrations of SSRIs (particularly fluoxetine, fluvoxamine, paroxetine, and to higher dosages of sertraline) Amplification of antidepressive effect, but also of possible ADRs
Psychostimulants	Increased effect in the treatment of depression, dysthymia, compulsive disorders, and ADHD
Smoking	Lowered plasma concentrations, particularly of fluvoxamine

Modified from Bandelow et al. (2011)
ADHD attention deficit/hyperactivity disorder, *ADRs* adverse drug reactions

4.4.1.3 Selective Noradrenaline Reuptake Inhibitors

Indications

Maprotiline is most often employed in anxiety-agitated depression with sleep disturbances. Apart from this indication, it is also employed in the therapy of enuresis, pavor nocturnus, and refusal to attend school. Furthermore, **reboxetine** is employed as a component of ADHD therapy; in a few studies, it has also been used to treat enuresis.

Maprotiline is US FDA approved for the treatment of depressive illness in adult patients with depressive neurosis (dysthymic disorder) and manic-depressive illness, depressed type (major depressive disorder).

Reboxetine is approved in European countries for the acute treatment of depressive illness/major depression and for maintaining the clinical improvement of patients initially responding to treatment. Both antidepressants are not approved for use in children and adolescents.

Clinical Effects and Efficacy

There is little secure empirical data regarding the efficacy of **maprotiline** in children and adolescents, but for adults the efficacy of maprotiline

was similar to that of SSRIS, as shown in randomized, double-blind studies on the treatment of depression (de Jonghe et al. 1991; Szegedi et al. 1997).

In a case series (Quintero et al. 2010), several open short-term studies (Cohen-Yavin et al. 2009; Golubchik et al. 2013; Mozes et al. 2005; Ratner et al. 2005; Tehrani-Doost et al. 2008) and a similarly uncontrolled follow-up study of 18–36 months' duration (Toren et al. 2007), **reboxetine** exhibited positive effects upon the symptoms of **ADHD** and associated behaviors, such as aggression, anxiety, and depression. In a double-blind clinical trial of reboxetine versus methylphenidate in a small group of 30 children, in both groups, a significant improvement in ADHD symptoms was observed over 6 weeks of treatment with the Parent ADHD Rating Scale and Teacher ADHD Rating Scale (Arabgol et al. 2009).

Reboxetine was also effective in the treatment of **enuresis**. In a study of children with ADHD and comorbid enuresis, bed-wetting also improved with reboxetine treatment (Toren et al. 2005). In two non-placebo-controlled studies of children and adolescents with therapy-resistant enuresis, the symptoms were resolved in about half of the cases receiving reboxetine alone or in combination with desmopressin (Lundmark and Nevéus 2009; Nevéus 2006). A development of tolerance was reported after a few months of drug treatment and the need of regular medicine-free intervals to maintain the antienuretic effect (Nevéus 2006).

Recommended Dosages

As literature on dosage of **maprotiline** in children and adolescents is scarce (Minuti and Gallo 1982; Simeon et al. 1981), there are no dosage recommendations for this age group. In the treatment of adults, an initial dosage of 75–150 mg daily – depending on treatment setting and severity of depression – is suggested. Because of the long half-life of maprotiline, the initial dosage should be maintained for 2 weeks. Dosage may be gradually increased to a maximum of 225 mg in adults in case of severe depression. Dosage during prolonged maintenance therapy should be kept at the lowest effective level – e.g., at 75–150 mg daily – with subsequent adjustment depending on therapeutic response. To divide the daily dose into two is generally recommended, although administration as single dose is permitted by the long half-life of the agent.

According to the Summary of Product Characteristics (SPC)/Prescribing Information (PI) (issues concerning the preparation of SPCs and PI and their limitations were discussed in detail in Sect. 4.7), it is recommended that **reboxetine** treatment in adults should begin with an initial dose of 2–4 mg/day. The standard dosage of 4–8 mg for adults should be broken into two doses; a maximum dosage of 12 mg should not be exceeded.

In children and adolescents, initial dosages in the treatment of ADHD, depressive symptoms, or enuresis were 1–4 mg (Arabgol et al. 2009; Golubchik et al. 2013; Lundmark and Nevéus 2009). Enuresis was finally treated with a single nighttime dosage of 4–8 mg (Lundmark and Nevéus 2009); ADHD and depressive symptoms with final doses of 1.5–4 mg reboxetine twice a day (Arabgol et al. 2009; Cohen-Yavin et al. 2009; Golubchik et al. 2013; Tehrani-Doost et al. 2008).

ADRs

The initiation of **maprotiline** treatment is often associated with marked sedation; therefore, evening administration is recommended. ADRs associated with maprotiline include weight gain, dry mouth, and gastrointestinal complaints, such as nausea and diarrhea. Autonomic nervous system ADRs are only slightly less common than during therapy with tricyclic antidepressants; vertigo, disturbances of visual accommodation, micturition disturbances, and orthostatic hypotonia have been reported. With maprotiline, susceptibility to seizures is greater than with other antidepressants.

During medication with **reboxetine**, vertigo is possible, as are sleep disturbances, agitation, and nervousness. Patients often report dry mouth and micturition problems. Furthermore, cardiovascular (tachycardia, hypotonia, vertigo) and gastrointestinal ADRs (obstipation or diarrhea, nausea, emesis), disturbances of sexual function, and, occasionally, epileptic seizures can occur.

Table 4.10 Major potential interactions between selective noradrenaline reuptake inhibitors and psychotropic drugs

Interaction with	Consequences
Antipsychotics	Interactions with the CYP3A4 (and CYP2D6) systems and thus potential elevation of plasma concentrations (e.g., risperidone, clozapine)
CNS depressant agents such as sedatives, hypnotics, painkillers, alcohol	Orthostatic elevation of heart rate No indications for increased alcohol effect
Lithium salts	Close monitoring of therapy required, as there are no studies
Other antidepressants	Interactions with the CYP3A4 (and CYP2D6) systems and thus potential elevation of plasma concentrations

Modified from Bandelow et al. (2011)
CYP Cytochrome P_{450}

Drug Interactions

There is currently only limited data available regarding potential interactions of selective noradrenaline reuptake inhibitors in children and adolescents. Drug interactions typically associated with selective noradrenaline reuptake inhibitors and their potential consequences are summarized in Table 4.10.

The combination of maprotiline with psychotropic substances, such as alcohol and benzodiazepines, can significantly increase sedative effects. For the combination of reboxetine with SSRIs, tricyclic antidepressants, and α_2-adrenoceptor antagonists, no interactions are known so far, neither for second- and third-generation antipsychotics nor for lithium salts and psychostimulants.

Contraindications

Restrictions for maprotiline and reboxetine apply in the following circumstances:

- Acute overdose of a psychotropic agent
- Severe liver and kidney dysfunction
- Elevated seizure susceptibility
- Mania
- Cardiovascular disorders (hypotonia)

It is recommended, in the absence of extensive experience, that maprotiline and reboxetine be employed during **pregnancy** following very cautious assessment of the risk/benefit relationship. Since maprotiline accumulates in breast milk, it cannot be employed in nursing mothers according to SPC/PI (see Sect. 4.7.11). A careful risk/benefit assessment for the use of reboxetine during breast-feeding should be undertaken, as it passes into breast milk in small amounts.

Antidepressants including maprotiline and reboxetine carry a **black box warning** from the US FDA that an increased risk of suicidal thinking and behavior in children and adolescents and young adults has occurred. Therefore, the worsening and emergence of suicidal thoughts and behaviors should be monitored.

4.4.1.4 Selective Serotonin and Noradrenaline Reuptake Inhibitors

Indications

Areas of application for **duloxetine** and **venlafaxine** are:

- MDD
- Generalized anxiety disorder

Beyond these areas of application, duloxetine is also employed in the therapy of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain.

Venlafaxine is also employed in the prevention of recurrence of major depressive episodes and the therapy of social anxiety disorder and panic disorder, with or without agoraphobia. The agent finds additional applications in the treatment of children and adolescents with ADHD, ASD, and borderline personality disorder. Both antidepressants are not FDA approved for use in children and adolescents.

Clinical Effects and Efficacy

Duloxetine has been found to be efficacious in treating adult MDD and general anxiety disorder in a variety of double-blind, placebo-controlled, or active-comparator studies using dosages that varied between 40 und 80 mg/day (Cipriani et al. 2012; Müller et al. 2008). Efficacy was not demonstrated in two 10-week, placebo-controlled trials with 800 pediatric patients with MDD, aged 7–17 years (PI for duloxetine hydrochloride delayed-release capsules for oral use). In an

open-label 32-week study, it was shown that pediatric patients (aged 7–17 years) generally tolerated duloxetine doses of 30–120 mg once daily (Prakash et al. 2012). Of the 72 enrolled patients, 48 (66.7 %) completed acute treatment (18 weeks) and 42 (58.3 %) completed extended treatment. Most patients (55/72; 76 %) required doses ≥60 mg once daily to optimize efficacy based on investigator judgment and Clinical Global Impression – Severity score.

Venlafaxine has been employed clinically with great success in the treatment of depressive disorders in adults (Weller et al. 2000). In meta-analyses of randomized, controlled studies, significantly higher remission rates were achieved with venlafaxine than with SSRIs (e.g., Entsuah et al. 2001; Smith et al. 2002).

Venlafaxine also proved effective in adolescents with **depression** in an open study (Emslie et al. 2007b). On the other hand, the combination of venlafaxine plus psychotherapy was no more effective than treatment with placebo and psychotherapy in a placebo-controlled study of 40 children and adolescents (Mandoki et al. 1997). On the basis of two randomized, placebo-controlled multicenter studies, Emslie and colleagues (2007a) also concluded that extended-release (ER) venlafaxine was not superior to placebo. Post hoc analyses, however, indicated a clearly greater improvement with the agent than with placebo (according to the Children's Depression Rating Scale – Revised) in adolescents aged 12–17 years ($p<0.5$), but not in younger children. Those taking venlafaxine were more frequently troubled by suicidal and hostile thoughts, but in no case suicide was actually committed.

In the treatment of **social phobia** and **generalized anxiety disorder** in children and adolescents, venlafaxine proved to be significantly superior to placebo in randomized, controlled studies (March et al. 2007b; Rynn et al. 2007).

Recommended Dosages

In Table 4.5 total daily dosages for selected antidepressants (including selective serotonin and noradrenaline reuptake inhibitors) are presented. Pharmacokinetic results of an open-label safety study of **duloxetine** in pediatric patients with MDD suggested that the adjustment of the total daily dose, based on body weight or age, is not warranted for pediatric patients and different total daily doses may not be warranted for pediatric patients relative to adults (Prakash et al. 2012). Duloxetine should be administered at a total dose of 40 mg/day (20 mg twice daily) to 60 mg/day (maximum 120 mg/day in Prakash et al.'s study 2012; either once daily or 30/60 mg twice daily) for the treatment of MDD. For most patients, the recommended starting dose for the treatment of generalized anxiety disorder in adults should be 60 mg once daily. For a better adjustment to the medication, initially 30 mg can be chosen.

Starting with 37.5 mg/day, the dosage of **venlafaxine** should be slowly increased. In placebo-controlled studies for the treatment of anxiety disorders (March et al. 2007b; Rynn et al. 2007) and depression (Emslie et al. 2007a, b) in children and adolescents, final dosages of 37.5–225 mg/day as ER formulation were administered. Daily dosage depended on body weight with a maximum dose of 225 mg/day for participants weighing ≥50 kg.

Venlafaxine should not be discontinued suddenly or abruptly. Withdrawal phenomena can include vertigo, headache, and sleep disturbances as well as general weakness and nervousness. Therefore, it is recommended that it be gradually withdrawn over a period of 2–4 weeks.

ADRs

Most common ADRs associated with **duloxetine** are nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis (PI duloxetine hydrochloride delayed-release capsules for oral use). The most frequently reported ADRs in adults were similar to those observed in an open-label safety study of duloxetine in pediatric patients with MDD (Prakash et al. 2012); however, many (36/72, 50 %) pediatric patients experienced potentially clinically significant elevations in blood pressure, most cases (21/36, 58 %) being transient.

ADRs associated with **venlafaxine** include sedation, sleep disturbances, gastrointestinal complaints, increased blood pressure, vertigo, sexual dysfunction, and headache. Increased levels of agitation and nervousness have also been reported. Dry mouth, sweating, urinary retention,

Table 4.11 Major potential interactions between serotonin and noradrenaline reuptake inhibitors and psychotropic drugs

Interaction with	Consequences
Anticholinergics	Amplification of anticholinergic ADRs possible
Antipsychotics	Elevation of plasma levels possible
Lithium salts	Case reports of serotonin syndrome
Other antidepressants	Amplification of antidepressive effect, but possibly also exacerbation of ADRs (serotonin syndrome)
Psychostimulants	Case reports of serotonin syndrome (amphetamine)

Modified from Bandelow et al. (2011)
ADRs adverse drug reactions

and obstipation are less frequent. ADRs can be reduced by the administration of slow-release preparations, but the abrupt discontinuation can also lead to withdrawal phenomena.

Decreased appetite and weight loss have been observed in association with the use of SSRIs and selective noradrenaline reuptake inhibitors. Pediatric patients treated with duloxetine in MDD clinical trials experienced a 0.2 kg mean decrease in weight at 10 weeks, compared with a mean weight gain of approximately 0.6 kg in placebo treatment (PI duloxetine hydrochloride delayed-release capsules for oral use).

Drug Interactions

ADRs typically associated with serotonin and noradrenaline reuptake inhibitors are summarized in Table 4.11. For further information regarding drug interactions of duloxetine and venlafaxine, please refer to Sects. 4.7.6 and 4.7.18.

Contraindications

These are:

- Hypersensitivity to the active substance or to any of the excipients.
- Concomitant treatment with irreversible non-selective MAO inhibitors due to the risk of serotonin syndrome with symptoms such as agitation, tremor, and hyperthermia.

Antidepressants including duloxetine and venlafaxine carry a **black box warning** from the US FDA that an increased risk of suicidal thinking and behavior in children and adolescents and young adults has occurred. Therefore, the worsening and emergence of suicidal thoughts and behaviors should be monitored.

During **pregnancy**, duloxetine and venlafaxine should only be used if the potential benefits outweigh the potential risks to the fetus. A teratogenic effect of venlafaxine during pregnancy has not been reported, but there is evidence for an increased spontaneous abortion rate. It is recommended that venlafaxine be employed during pregnancy only when there is no alternative. Venlafaxine administration during pregnancy could be followed by withdrawal symptoms and complications in the newborn, so that respiratory assistance may be required.

Venlafaxine, its active metabolite O-desmethylvenlafaxine, and duloxetine pass into breast milk (Briggs et al. 2009), so that the advantages for the child must be carefully weighed against the necessity of venlafaxine therapy and, if necessary, the child should be weaned early. However, no evidence of developmental or any other type of toxicity was observed in infants exposed to duloxetine during the second half of gestation and during breast-feeding in the first 32 days after birth (Briggs et al. 2009).

4.4.2 MAO-A Inhibitor: Moclobemide

Indications

Areas of application are:

- Symptomatic relief of depressive illness
- Social anxiety

Beyond these areas of application, moclobemide is also employed in the therapy of ADHD. It is also used for panic disorder, bipolar disorder, and dysthymia. It is not US FDA approved for the use in children, adolescents, and adults.

Clinical Effects and Efficacy

Moclobemide is very effective in the treatment of depression and dysthymia in adults (Versiani et al. 1997; Woggon 1993). With only a few case reports and open studies, it has hardly been investigated for children and adolescents. In the treatment of ADHD, for example, an improvement of attention and behavior has been observed (Trott et al. 1992). In a small patient group of 20 children and adolescents, moclobemide was not significantly superior to placebo after a 5-week treatment of depressive symptoms (Avci et al. 1999).

Recommended Dosages

In Table 4.5, total daily dosages for selected antidepressants (including moclobemide) are presented. For moclobemide, an initial dosage of 150 mg was employed in a clinical study (Avci et al. 1999). In some children and adolescents with depressive symptoms, this dose is sufficient to achieve symptomatic improvement. Most patients with MDD, however, required a daily dosage of 300 mg (Avci et al. 1999), administered as two doses.

In contrast to treatment with the nonselective inhibitor tranylcypromine (see Sect. 1.4.1), antidepressive therapy with moclobemide does not require a special diet. In adults, a dosage of up to 600 mg/day does not elicit dramatic increases in blood pressure. With the consumption of food containing tyramine (such as certain types of cheeses, sauerkraut), patients may nevertheless experience transitory headache.

ADRs

ADRs associated with moclobemide include dry mouth, vertigo, hypotonia, headache, increased fatigue, and nausea. Itching, rashes, or sensations of heat are less frequent. Moclobemide can trigger manic symptoms in patients with bipolar affective disorder; it can also exacerbate the symptoms of patients with schizophrenic psychosis. Due to the increased impulsivity elicited by moclobemide, depressive patients with suicidal impulses should be closely monitored, especially at the beginning of therapy.

Table 4.12 Interactions between moclobemide and other pharmaceutical agents relevant to therapy in children and adolescents

Interaction with	Consequences
Other antidepressants	
Tricyclic antidepressants	Elevation of plasma concentrations of the antidepressants possible. Increase in ADRs such as weight gain, hypotonia, and anticholinergic effects (such as urinary retention)
SSRIs	Increase in ADRs such as sleep disturbances and headache In combination with fluoxetine and fluvoxamine, elimination of moclobemide can be slowed, so that amplification of serotonergic ADRs is possible
Antiphlogistics	Effect of ibuprofen, for example, can be significantly increased
Lithium salts	Increase of antidepressive effect possible
L-**Tryptophan**	Increase in serotonergic ADRs with risk of serotonin syndrome
Sympathomimetics	Increased blood pressure with risk of hypertensive crisis possible

Modified from Bandelow et al. (2011)

Drug Interactions

Table 4.12 summarizes interactions between moclobemide and other pharmaceutical agents relevant to therapy of children and adolescents.

Contraindications

Restrictions apply in the following circumstances:

- In combination with SSRIs, as there is a risk of inducing a serotonin syndrome.
- Acute psychotropic agent intoxication.

Few data are available regarding the employment of moclobemide during **pregnancy**, but animal investigations have identified transplacental movement of the agent. Only low levels have been detected in the breast milk of nursing mothers using moclobemide. It is therefore recommended that a careful risk/benefit assessment be

undertaken before employing the agent in pregnant or breast-feeding women.

4.4.3 α_2-Adrenoceptor Antagonists

Indications

Areas of application are depressive disorders. **Mianserin** and **mirtazapine** are especially employed in the therapy of anxious-agitated depressions with sleep disturbances. Apart from these areas of application, mianserin is also used in the therapy of enuresis and pavor nocturnus, school refusal, and mutism. Furthermore, mirtazapine is employed in the therapy of anxiety disorders (social phobia) and sleep disorders. Both antidepressants are not US FDA approved for use in children and adolescents.

Clinical Effects and Efficacy

The efficacy of **mianserin** has been found superior to that of placebo in depression therapy of adults and comparable with the effect of tricyclic antidepressants (e.g., McGrath et al. 1985; Wilcox et al. 1994). There is little data available for children and adolescents. In an open study of the efficacy of mianserin in depressive children and adolescents, positive effects and good tolerability were reported across an observation period of 60 days (Dugas et al. 1985).

Mirtazapine rapidly achieves an effect significantly greater than that of placebo in the treatment of depression in adults (Bech 2001). Only very few data exist on children and adolescents. The results of an open study (Haapasalo-Pesu et al. 2004) as well as personal clinical experience indicate that mirtazapine has positive effect on children and adolescents with MDD. In an open pilot study, significant reduction of anxiety and comorbid depressive symptoms in children and adolescents with social phobia was achieved with mirtazapine (Mrakotsky et al. 2008). With regard to its efficacy in ASD and other profound developmental disturbances, an open study concluded that mirtazapine had no significant impact upon associated symptoms, such as aggression, self-harming, and anxious and depressive behaviors (Posey et al. 2001).

Recommended Dosages

In Table 4.5 total daily dosages for selected antidepressants (including α_2-adrenoceptor antagonists) are presented. **Mianserin** dosage should be slowly increased from an initial dosage of 10–30 mg/day. The average daily dose of mianserin in the study by Dugas et al. (1985) on the treatment of depression in children and adolescents was 1 mg/kg/day. The total daily dose may be either given as a single nighttime dose or divided into three subdoses. Its sedative qualities make a larger evening dose desirable.

Beginning with 15 mg/day, the **mirtazapine** dose should be slowly increased to 30–45 mg/day, depending on therapeutic response (Haapasalo-Pesu et al. 2004). As mirtazapine has marked sedative properties, a single evening dose has proved convenient. Higher dosages can be divided into two once daily. Mirtazapine should be dosed very carefully and gradually, particularly in patients with preexisting hypertension.

ADRs

ADRs associated with mianserin and mirtazapine include weight gain, dry mouth, and gastrointestinal complaints such as nausea and diarrhea. Both drugs have a marked sedative effect; therefore, evening administration is recommended. Furthermore, orthostatic hypotension, tremor, dyskinesias, disturbance of hepatic function, blood count changes (leukopenia, agranulocytosis, thrombopenia), increased susceptibility to seizures, gynecomastia, exanthemata, edema, and joint pain and swelling were reported. Rare ADRs of mirtazapine include sleep disturbances, restlessness, and irritability. In contrast to tricyclic antidepressants and SSRIs, marked disturbances of sexual function have not been reported during therapy with mirtazapine or mianserin.

Drug Interactions

There is currently only limited data available regarding potential interactions in children and adolescents. The combination of mianserin and mirtazapine with psychotropic substances such as alcohol and benzodiazepines can significantly increase sedative effects.

Plasma **mianserin** concentrations can fall if inducers of the CYP3A4 system (such as phenytoin, carbamazepine, or phenobarbital) are used concomitantly. Inhibition of CYP3A4 (e.g., by erythromycin) can elevate plasma mianserin levels.

Therapy with mirtazapine in combination with an **SSRI** can lead to amplification of ADRs, yet an improvement of symptoms is possible as well; sleep disturbances can, for example, be mitigated, and antidepressive potency increased. Disturbances of sexual function associated with SSRIs can be reduced by combination treatment. The combination with **lithium salts** has been associated with an augmentation of effects, of both the antidepressant efficacy and the frequency and intensity of ADRs. Concomitant administration of mirtazapine and **psychostimulants** can lead to intensification of restlessness and impulsiveness. This must especially be considered in the treatment of bipolar disorder.

Contraindications

Restrictions on use apply in the following circumstances:

- Acute psychotropic agent intoxication
- Severe liver and kidney dysfunction
- Elevated seizure susceptibility
- (Hypo-)mania
- Cardiovascular disorders (e.g., previous heart attack, hypotonia, disturbances of conduction)
- Diabetes mellitus
- Suicidality

There are a few data as to the employment of mianserin and mirtazapine during **pregnancy**, but teratogenic effects have not been detected in animal investigations. It is therefore recommended that a careful risk/benefit assessment be undertaken before employing these agents in pregnant women. According to SPC/PI (see Sect. 4.7), although only very low levels pass into breast milk, breast-feeding should be stopped if therapy with mianserin is absolutely necessary. For the use of mirtazapine, during breast-feeding, a careful risk/benefit assessment should be undertaken.

Antidepressants including mianserin, venlafaxine, and mirtazapine carry a **black box warning** from the US FDA that an increased risk of suicidal thinking and behavior in children and adolescents and young adults has occurred. Therefore, the worsening and emergence of suicidal thoughts and behaviors should be monitored.

4.4.4 Miscellaneous Antidepressants

Bupropion is an antidepressant that is chemically and pharmacologically unrelated to tricyclic, tetracyclic, SSRIs, or other known antidepressant agents. Mechanistic studies have indicated that bupropion has both dopaminergic and noradrenergic activities, with no clinically significant serotonin uptake inhibition (Hudziak and Rettew 2004). In addition, it has been shown that it is not a sympathomimetic, cholinolytic, nor an inhibitor of MAO.

St. John's wort (*Hypericum perforatum* L.) preparations are popular herbal remedies used worldwide to treat a variety of medical illnesses including depression. These preparations exert a range of neurochemical effects in preclinical studies, including serotonin, noradrenaline, and dopamine reuptake inhibition and GABA and L-glutamate pathway modulation (Sarris et al. 2011). Like other herbal drugs, St. John's wort is a complex mixture containing a variety of constituents: the most abundant are hypericins, flavonoids and hyperforin (Sarris et al. 2011). There is still debate over which compounds form the active principle, variably attributed to hyperforins, hypericins and flavonoids. It is also hypothesized that additive or synergistic actions of various compounds may be responsible for the herb's therapeutic effects and that the total herbal drug preparation as a complex must be regarded as the active constituent or principle of St. John's wort (see Mueller et al. 2009).

Indications

Areas of applications for **bupropion** are the treatment of:

- MDD
- Smoking cessation
- ADHD
- Obesity

Bupropion is approved for the treatment of MDD in adults in the USA, Canada, and many countries in Europe. Bupropion was the first non-nicotine agent to get FDA approval for smoking cessation and is a first-line agent. Safety and effectiveness in the pediatric population have not been established.

Areas of applications of **St. John's wort** are the treatment of:

- Mild to moderate depression
- ADHD
- Anxiety disorder
- Somatization disorder
- Seasonal affective disorder

In certain areas of Europe, St. John's wort has been a commonly prescribed and approved treatment for depression in children, adolescents and adults, but, in the USA, various formulations (e.g., extracts, tablets, capsules, tinctures or teas) are available in different dosages either as over-the-counter drugs or as dietary supplements. The compositions of marketed St. John's wort products differ in the amount of pharmacologically active compounds, especially hyperforin. The hyperforin content of 33 different *Hypericum* products marketed in Germany ranges from <0.5 to 24.87 mg/unit (see Mueller et al. 2009). Clinical efficacy has been demonstrated in St. John's wort extracts with high hyperforin content but also in those with negligible hyperforin content.

Clinical Effects and Efficacy

Bupropion

In a variety of placebo-controlled, double-blind studies, it has been shown that immediate-release (three times daily), sustained-release (two times), and the extended-release formulations of bupropion (once-daily dose) are effective and well tolerated in the treatment of **MDD** in adults with response rates between 60 and 70 %, compared with approximately 30 % for placebo (e.g., see Hewett et al. 2009; Hudziak and Rettew 2004; Moreira 2011). Bupropion has consistently demonstrated comparable antidepressant efficacy and tolerability advantages (less sexual dysfunction and less sedation) in direct comparisons with SSRIs (e.g., see Hewett et al. 2009; Hudziak and Rettew 2004). Although bupropion is being used clinically for the treatment of children and adolescents with MDD, there is only one open study on children with MDD and ADHD disorder (Daviss et al. 2001).

Results of a meta-analysis of 49 trials showed bupropion to be more effective than placebo in promoting **continuous abstinence from smoking** (see Lingford-Hughes et al. 2012). This effect appears to be independent of its antidepressant action, and the effect is also independent of the patient's history of depression. As a partial explanation of its efficacy, it is thought that bupropion alters brain reward circuits by modulating dopaminergic and noradrenergic neurotransmission by inhibition of dopamine and noradrenaline transporters as well as by stimulation of nicotinic acetylcholine receptors (Cryan et al. 2003). A randomized, double-blind, prospective study supported the efficacy of treatment with bupropion on smoking cessation (150 mg p.o. for 90 days, beginning a week prior to the agreed date for quitting smoking) in 16–19-year-old subjects (Niederhofer and Huber 2004). However, a recent meta-analysis of randomized controlled trials found that pharmacological therapy for smoking cessation among adolescent smokers did not have a significant effect on abstinence rates at short-term and midterm follow-up times of <26 weeks (Kim et al. 2011).

Three studies compared the efficacy of bupropion with methylphenidate in the treatment of children and adolescents with **ADHD** showing discrepant results. One double-blind crossover study compared the effect of these two treatments (15 individuals) and found no difference in several measures between the two groups (Barrickman et al. 1995). In another unblinded study, 22 individuals were randomly assigned to methylphenidate or bupropion for 12 weeks (Lee et al. 2008). There were significant clinical improvements after 12 weeks in both treatment groups as measured by the Korean ADHD rating scale and the computerized ADHD diagnostic system. In the third 6-week randomized, double-blind study, 44 patients with a DSM-IV-TR diag-

nosis of ADHD (aged 6–17 years) were randomly assigned to receive bupropion 100–150 mg/day (100 mg/day for <30 kg and 150 mg/day for >30 kg) or methylphenidate 20–30 mg/day (Jafarinia et al. 2012). Symptoms were assessed using Teacher and Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) at baseline and weeks 3 and 6. No significant difference was found between the two groups on the parent and teacher ADHD-RS-IV. By week 6, 18 patients (90 %) in each group achieved response on the parent scale. With the Teacher ADHD-RS-IV used, eight (40 %) patients in the bupropion group and 12 (60 %) patients in the methylphenidate group achieved response by week 6. Headache was observed more frequently in the methylphenidate group. Frequency of other ADRs was not significantly different between the two groups.

Bupropion has shown some promise for treating **obesity** in adults in two placebo-controlled trials. Anderson et al. (2002) reported that both 300 and 400 mg/day bupropion dosing produced significantly greater weight loss than placebo when paired with a calorie deficit of 600 kcal/day. Jain and colleagues (2002), in a study with adult obese patients with subclinical levels of depression, found that 300 mg/day of bupropion resulted in significantly greater weight losses than placebo when added to a 500 kcal/day deficit diet. Since food cravings and negative mood are thought to contribute to binge eating and because both the noradrenaline and dopamine systems have been implicated in binge eating, bupropion has been investigated in a randomized, placebo-controlled trial to evaluate its short-term efficacy for the treatment of binge-eating disorder in overweight and obese women (White and Grilo 2013). Mixed-effects analyses revealed significant time effects for all outcomes but no significant differences between bupropion and placebo on any outcome measure except for weight loss. Participants taking bupropion lost significantly more weight (1.8 vs. 0.6 % BMI loss). Bupropion was well tolerated and produced significantly greater albeit quite modest short-term weight losses in overweight and obese women with binge-eating disorder. Bupropion did not improve binge-eating, food craving, or associated eating disorder features or depression relative to placebo.

St. John's Wort

Data regarding the efficacy in adults of St. John's wort in comparison to standard antidepressants and placebo are inconsistent (Werneke et al. 2004). Standardization and quality are issues with St. John's wort, as extracts show variability of efficacy according to different constituent profiles (Kasper et al. 2010). This is why results using high-quality pharmaceutical grade extracts for which efficacy in mild to moderate depression has been shown in randomized, placebo-controlled studies (Sarris et al. 2011) cannot be transferred to some inferior extracts. St. John's wort has not been studied in treatment-resistant depression, and it is unlikely to exert a sufficient thymoleptic effect (Sarris 2013).

There is **insufficient evidence** to support the use of St. John's wort in the treatment of depression in children and adolescents (Hazell 2009). No controlled studies of St. John's wort therapy of depression in children and adolescents have thus far been published. The efficacy and good tolerability of the preparation have been reported by open studies (Findling et al. 2003; Simeon et al. 2005).

A recent review on meta-analyses of randomized controlled trials and long-term studies involving St. John's wort for the treatment of psychiatric disorder in adults supported the use of high-grade, standardized extracts for the treatment of somatization disorder, with tentative support in seasonal affective disorder (Sarris 2013). This review does not show evidence for the efficacy of St. John's wort in the treatment of anxiety disorder, ADHD, or other psychiatric illnesses. In a placebo-controlled study of its efficacy in ADHD in children and adolescents, St. John's wort did not reduce major symptoms in comparison to placebo (Weber et al. 2008).

Recommended Dosages

In Table 4.5 total daily dosages for selected antidepressants (including bupropion and St. John's

wort) are presented. The usual adult dose of **bupropion** is 300 mg/day, given three times daily. Dosing should begin at 200 mg/day, given as 100 mg twice daily. Based on clinical response, this dose can be increased to 300 mg/day, given as 100 mg three times daily, no sooner than 3 days after beginning therapy (PI bupropion hydrochloride tablets). Dosing regimens for children and adolescents have not been firmly established, and many trials with bupropion in ADHD patients were conducted with the immediate-release formulation in varying doses that were smaller than those for adults (Hudziak and Rettew 2004). Mean total daily dosages in children and adolescents were about 100–150 mg/day with a maximum of 300 mg or 6 mg/kg body weight, whichever was smaller (Barrickman et al. 1995; Daviss et al. 2001; Jafarinia et al. 2012; Lee et al. 2008).

It is particularly important to administer bupropion in a manner most likely to **minimize the risk of seizure**. Increases in dosage should not exceed 100 mg/day in a 3-day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate- to long-acting sedative-hypnotic agent. Insomnia can be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

Well-defined **St. John's wort** products that have been studied include LI-160 (Lichtwer), Ze117 (Zeller), and WS-5570 (Schwabe). Some of these may be purchased online; however, a regular prescription is still more advisable. The common daily dosage of concentrated St. John's wort is 900 mg, often given in divided doses two to three times daily in tablet form, amounting to about 1.0 μg of hypericin (the active component) and/or 0.5–5 % of hyperforin (depending on whether the extract is standardized to reduce hyperforin). However, more severely depressed adult patients may need up to 1,800 mg/day (Sarris 2013).

ADRs

Bupropion is generally well tolerated in all age groups. It has a minimal effect on sexual function and comparable or lower rates of somnolence than placebo and is associated with lower rates of weight gain and sedation than other antidepressants. In the larger trials of the bupropion sustained-release preparation in outpatients with depression, the common ADRs were headache, nausea, dry mouth, and insomnia (Hudziak and Rettew 2004). Sweating and constipation were also reported to be common at higher (300 mg/day) dosages.

St. John's wort has a sound safety profile, based on a review of 16 postmarketing surveillance studies ($N = 34{,}834$) that found it to be tenfold safer than synthetic antidepressants (Sarris 2013). Furthermore, a meta-analysis noted a significant difference in favor of St. John's wort extracts over conventional antidepressants for discontinuation due to ADRs. Aside from rare idiosyncratic reactions, most ADRs involve reversible dermatologic and gastrointestinal symptoms (Sarris 2013). Photosensitization, particularly in light-skinned persons exposed to strong sunlight, can lead to sunburn-like skin reactions. Several case reports have reported possible St. John's wort-induced mania, psychosis, and serotonin syndrome (Sarris 2013).

Drug Interactions

Bupropion is extensively metabolized by the liver through CYP enzymes. The principal enzyme that metabolizes bupropion to hydroxybupropion is the CYP2B6 enzyme. Therefore, there is a potential drug interaction between bupropion and drugs that are substrates of or inhibitors/inducers of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, cyclophosphamide, ticlopidine, and clopidogrel). In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as

nelfinavir inhibit the hydroxylation of bupropion (PI bupropion hydrochloride tablets). However, there are no clinical studies to evaluate this finding. While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin).

Bupropion and hydroxybupropion are inhibitors of the CYP2D6 isoenzyme in vitro. Therefore, there is a potential drug interaction between bupropion and drugs that are metabolized by this enzyme. Many drugs, including most antidepressants (SSRIs, many tricyclic antidepressants), β-blockers, antiarrhythmics, and antipsychotics, are metabolized by the CYP2D6 isoenzyme. In a study of 15 male subjects (aged 19–35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion (150 mg twice daily followed by a single dose of 50 mg **desipramine**) increased the maximal plasma concentration, the area under the curve, and the elimination half-life of desipramine by an average of approximately two-, five-, and twofold, respectively (PI bupropion hydrochloride tablets). The effect was present for at least 7 days after the last dose of bupropion.

Although there are concerns about interactions between **St. John's wort** and other drugs, this issue is focused on extracts containing higher amounts of hyperforin, which is responsible for inducing CYP pathways (in particular CYP3A) and P-glycoprotein drug efflux pumps, thereby reducing drug serum levels (Mueller et al. 2009; Sarris 2013). For this reason, clinicians are advised to prescribe low-hyperforin St. John's wort products if the patient is taking other medications. If employed together with other photosensitizing drugs, the phototoxic effect of St. John's wort can be increased. Women taking oral hormonal contraceptives can experience breakthrough bleeding maximal plasma concentration. Additional methods of contraception have to be recommended.

Contraindications

Restrictions on the use of **bupropion** apply in the following circumstances (PI bupropion hydrochloride tablets):

- Patients with seizure disorder.
- Patients treated with other medications containing bupropion because the incidence of seizure is dose dependent.
- Patients with a current or prior diagnosis of bulimia or anorexia nervosa because in such patients treated with bupropion there is a higher incidence of seizures noted.
- Patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).
- Concomitant use of nonselective MAO inhibitors because this can increase the risk of hypertensive reactions.

Antidepressants including bupropion carry a **black box warning** from the US FDA that an increased risk of suicidal thinking and behavior in children and adolescents and young adults has occurred. Therefore, the worsening and emergence of suicidal thoughts and behaviors should be monitored.

Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious ADRs in **nursing** infants from bupropion, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. A recent study that analyzed the impact of exposure to antidepressants during pregnancy on the risk of ADHD in the offspring demonstrated that children of mothers treated with bupropion have an increased risk of ADHD; however, a possible causal effect needs to be further studied (Figueroa 2010).

Restrictions on the use of **St. John's wort** apply in the following circumstances:

- Known sensitivity to the extract
- Known light hypersensitivity
- Severe depressive symptoms
- Therapy with cross-reacting agents

St. John's wort should not be co-prescribed with synthetic antidepressants, because several case reports of **serotonin syndrome** have been documented by drug surveillance agencies and this is likely due to the use of high-dose St. John's wort and/or concomitant use with synthetic antidepressants (Sarris 2013). It is recommended that St. John's wort extract only be employed during pregnancy or nursing if absolutely necessary, as few data regarding teratogenic effects are available.

4.5 Duration of Therapy

Antidepressant therapy should be continued for approximately 6 months after the depressive symptoms have subsided (National Institute for Health and Care Excellence 2005). During this period, the dosage should be maintained within the range with which optimal therapeutic benefit was achieved. The medication can subsequently be gradually withdrawn over a period of weeks if symptoms do not reappear.

If the patient has experienced three clear episodes of unipolar depression, a longer-term (even lifelong) prophylactic approach is appropriate for the prevention of the recurrence of depressive symptoms. In adults, antidepressants have proved effective for this purpose, as well as mood stabilizers (see Chap. 7) such as lithium salts, carbamazepine, and valproic acid.

Successes in the **treatment of OCD** can generally be judged only after a period of about 10 weeks. The advisability of a change in medication can only be determined after this period (unless ADRs have necessitated a switch before this time). Longer-term pharmacotherapy of OCD must be expected, and discontinuation can generally be considered only after 6 months of treatment. The majority of patients require medicinal therapy for a period of 12–18 months (Cook et al. 2001; Leonard et al. 1989).

The duration of **therapy** for **anxiety disorders** should take existing comorbid symptoms into consideration. Medication can be gradually reduced after 4–6 months, according to disease course and symptomatic relief.

4.6 Therapeutic Monitoring

On the basis of recommendations derived from therapeutic experience in adults, before starting treatment with an antidepressant, the assessment of blood count, electrolytes, liver and kidney parameters, heart rate and pulse as well as an ECG is recommended. These parameters should be controlled in the treatment course. Prior to antidepressant pharmacotherapy, also an EEG is recommended. In case of the prescription of a **tricyclic antidepressant**, the patient and family history on cardiovascular diseases has to be very carefully assessed. ECG controls are essential in patients with (risk for) a cardiovascular disease (see also Chap. 14).

TDM during the steady-state period is advisable where ADRs occur, or where the medication is changed, the dose elevated, or supplemented by other medications (see Sect. 2.3). Reference therapeutic blood antidepressant level ranges in adults are listed in Table 4.6.

4.7 Clinical Pharmacology of Selected Antidepressants: Overview

The following summaries are based upon information included in the SPC and the PI, respectively, depending on whether the drug is approved in the EU and the USA. They form the basis of information for clinicians in order to learn how to use these specific products safely and effectively. The detailed SPCs and PIs that represent comprehensive clinical-pharmacological monographs can be found on regulatory authority websites (e.g., EMA, FDA).

However, there is significant disparity between relevant national guidance and SPCs as well as between SPCs and PIs; these differences extend to licensed indications, contraindications, warnings and precautions, and monitoring schedules.

The **SPC** is a documentation that must be prepared by the manufacturer as part of the pharmaceutical approval and licensing process in the EU. This documentation is the description of the product in terms of both its chemical, pharmacological, and pharmaceutical properties and the results of studies conducted by the manufacturer for the process of licensing and marketing of the agent as well as spontaneous reports of ADRs and drug interactions as part of a pharmacovigilance system. The SPC must be completed and submitted as an application to the or one of the national competent authorities of the member states before marketing is authorized. The document is thus an intrinsic part of the authorization process and can only be changed after approval by means of an approved variation. It forms the basis of information for health-care professional how to use the product safely and effectively. The package leaflet supplied (patient information leaflet) contains information, which are in line with guidelines set out for this purpose.

In the USA, the FDA regulates the content and format of **PI** for human drug and biological products. The rule is commonly referred to as "Physician Labeling Rule" (PLR) because it addresses prescription drug labeling, which is used by prescribers and other health-care providers. The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug. The goal of the PLR content and format requirements is to enhance the safe and effective use of prescription drug products by providing health-care providers with clear and concise PI, which is easy to access, read, and use. The PLR format also makes PI more accessible for the use of electronic prescribing tools and other electronic information resources.

SPCs and PIs **differ from scientific publications** and monographs primarily in the fact that they are less transparent: the content can often be uncomprehensible for the reader, methods are not detailed, and no sources are cited (Ulrich et al. 2007). The basis for the presented information is ultimately difficult to check. Criteria that must be fulfilled in the production of a scientific text are thus not satisfied by SPCs and PIs. Furthermore, **legal aspects** are also considered during the preparation of SPC and IP texts in order to protect manufacturers with respect to liability law, e.g., a drug combination could be contraindicated in an SPC and IP although neither the mechanism of action nor spontaneous reports or clinical studies might justify this contraindication. A further example that legal aspects are considered in SPCs and IPs to protect the pharmaceutical company against liability claims is that many drugs used in child and adolescent psychiatry carry black box warning from the US FDA, when their safety and effectiveness in the pediatric population has not been established.

Abbreviations used in the following tables: ADR, adverse drug reactions, AUC, area under the curve; b.i.d., 2× day; c_{max}, maximal plasma concentration after oral dosing; CNS, central nervous system; CYP, cytochrome P_{450}; $D_{1–5}$, molecular dopamine receptor subtype of the D_2 receptor family; EMA, European Medicine Agency; FDA, Food and Drug Administration; i.m., intramuscular; MAO, monoamine oxidase; MDD, major depressive disorder; NSAIDs nonsteroidal anti-inflammatory drugs OCD, obsessive-compulsive disorder; q.i.d., 4× day; SSRIs, selective serotonin reuptake inhibitors; SNRIs, selective serotonin and noradrenaline reuptake inhibitors; TCAs, tricyclic antidepressants; t.i.d., 3× day; t_{max}, time required to reach peak plasma concentration (c_{max}); $t_{1/2}$, elimination half-life; TDM, therapeutic drug monitoring; 5-HT, 5-hydroxytryptamine = serotonin

4.7.1 Amitriptyline

Pharmacodynamic properties	TCA with anticholinergic and sedative properties; inhibition of 5-HT and noradrenaline reuptake and amplification of central effects of 5-HT and noradrenaline; high-affinity antagonist of serotonin 5-HT_{2A} and adrenergic α_1-receptors and moderate-affinity antagonist of muscarinic ACh and histamine H_1 receptors
Pharmacokinetic properties	t_{max} 2–6 h, $t_{1/2}$ 9–25 h (parent compound), ca. 30 h (active metabolite nortriptyline); protein binding ca. 94 %, bioavailability 43–45 %; metabolism by CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4
Indications	**US FDA approved for**: Treatment of depression in adults In view of the lack of experience with the use of this drug in children, it is not recommended at the present time for patients under 12 years of age **Europe** Symptoms of depression (especially where sedation is required) Treatment of nocturnal enuresis where organic pathology is excluded Due to the lack of clinical experience, amitriptyline is not recommended for the treatment of depression in children under 16 years of age
Dosage	**Depression** Adults – initial dosage: usually 75 mg a day in divided doses (or a single dose at night). If necessary, this may be increased to a total of 150 mg a day, the additional doses being given in the late afternoon and/or at bedtime. The sedative effect is usually rapidly apparent. The antidepressant activity may be seen within 3 or 4 days or may take up to 30 days to develop adequately Adults – maintenance dosage: usually 50–100 mg a day. The total dosage may be given in a single dose preferably in the evening or at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. Maintenance therapy should be continued for 3 months or longer to lessen the chances of relapse **Enuresis** Children aged 6–10 years may receive 10–20 mg a day, while those aged 11–16 years may need 25–50 mg a day. Treatment should not exceed 3 months
ADRs	Fatigue, vertigo, dry mouth, weight gain, accommodation disturbances, micturition disturbances as well as orthostatic hypotonia Amitriptyline may also produce sexual difficulties, including impotence and ejaculatory difficulty in men and decreased sexual drive in both men and women. If this is a problem, the physician may switch the patient's medication to another antidepressant, such as bupropion that does not interfere with sexual functioning
Drug interactions	The concurrent use of antidepressants having varying modes of action should be made only with due recognition of their possible potentiation and with a thorough knowledge of their respective pharmacologies. MAO inhibitors can potentiate the effects of TCAs such as amitriptyline, and hyperpyretic crises, severe convulsions and fatalities have occurred. Amitriptyline may block the antihypertensive action of guanethidine, debrisoquine, bethanidine, and possibly clonidine. It would be advisable to **review all antihypertensive therapy** during treatment with TCA Amitriptyline should not be given with **sympathomimetic agents** such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine Amitriptyline may enhance the response to alcohol, barbiturates, and other CNS depressants. In turn, barbiturates may decrease, and methylphenidate may increase the antidepressant action of amitriptyline. Delirium has been reported in patients taking amitriptyline with disulfiram Paralytic ileus may occur in patients taking TCAs in combination with drugs having an anticholinergic action Based on the known metabolism of amitriptyline, the protease inhibitor, ritonavir, may increase the serum levels of amitriptyline. Therefore, careful monitoring of therapeutic effects and ADRs is recommended when these drugs are administered concomitantly Cimetidine is reported to reduce hepatic metabolism of certain TCAs. Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients treated with 1 g ethchlorvynol and 75 to 150 mg amitriptyline St. John's wort may decrease plasma levels of amitriptyline Amitriptyline may increase levels of thioridazine leading to cardiac ADRs

Contraindications	Coadministration with MAO inhibitors, prior sensitization to amitriptyline, during the recovery phase after myocardial infarction, arrhythmias particularly heart block of any degree, mania, severe liver disease, porphyria, lactation, and children under 6 years of age Amitriptyline is detectable in breast milk. Because of the potential for serious ADRs in infants, a decision should be made whether to discontinue breast-feeding or discontinue the drug

4.7.2 Bupropion

Pharmacodynamic properties	An antidepressant that is chemically and pharmacologically unrelated to TCAs, tetracyclic antidepressants, SSRIs, or other known antidepressant agents. The mechanism of action of bupropion as an antidepressant is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms. Bupropion is a selective inhibitor of the neuronal reuptake of noradrenaline and dopamine with minimal effect on the reuptake of 5-HT and does not inhibit either MAO
Pharmacokinetic properties	t_{max} 2 h (immediate release), t_{max} 5 h (modified release), mean $t_{1/2}$ after chronic dosing 21 h; protein binding 84 %, bioavailability not known Bupropion is extensively metabolized in humans. Three pharmacologically active metabolites have been identified in plasma: hydroxybupropion and the amino-alcohol isomers, threohydrobupropion, and erythrohydrobupropion. These may have clinical importance, as their plasma concentrations are as high or higher than those of bupropion. The active metabolites are further metabolized to inactive metabolites (some of which have not been fully characterized but may include conjugates) and excreted in the urine In vitro studies indicate that bupropion is metabolized to its major active metabolite hydroxybupropion primarily by the CYP2B6, while CYP1A2, CYP2A6, CYP2C9, CYP3A4, and CYP2E1 are less involved. In contrast, formation of threohydrobupropion involves carbonyl reduction but does not involve cytochrome P450 isoenzymes Bupropion and hydroxybupropion are both inhibitors of the CYP2D6 isoenzyme with K_i values of 21 and 13.3 μM, respectively. Bupropion has been shown to induce its own metabolism in animals following subchronic administration. In humans, there is no evidence of enzyme induction of bupropion or hydroxybupropion in volunteers or patients receiving recommended doses of bupropion hydrochloride for 10–45 days
Indications	Immediate- and sustained-release formulations are **FDA approved** for the treatment of MDD and smoking cessation in adults **Approved** in some **European countries** for treatment of major depressive episodes
	Not indicated for use in children or adolescents aged less than 18 years. The safety and efficacy in patients under 18 years of age have not been established
Dosage	The usual **adult dose** of bupropion is 300 mg/day. Dosing should begin at 200 mg/day, given as 100 mg twice daily. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg 3 times daily, no sooner than 3 days after beginning therapy
	Dosing regimens for children and adolescents have not been firmly established, and many trials with bupropion in ADHD patients were conducted with the immediate-release formulation in doses that varied and that were generally less than those used in adults
ADRs	Bupropion is generally well tolerated in all age groups. In particular, it has a minimal effect on sexual function and comparable or lower rates of somnolence than placebo and is associated with lower rates of weight gain and sedation than some other commonly used antidepressants. In the larger trials of the bupropion sustained-release preparation in outpatients with depression, the common ADRs were headache, nausea, dry mouth, and insomnia. Sweating and constipation were also reported to be more common at higher (300 mg/day) dosages

Drug interactions	Bupropion is extensively metabolized by the liver through CYP enzymes. The principal enzyme that metabolizes bupropion to hydroxybupropion is the CYP2B6 enzyme. Therefore, the potential exists for a drug interaction between bupropion and drugs that are substrates of or inhibitors/inducers of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, cyclophosphamide, ticlopidine, and clopidogrel). In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir inhibit the hydroxylation of bupropion. However, no clinical studies have been performed to evaluate this finding. While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin). Multiple oral doses of bupropion had no statistically significant effects on the single-dose pharmacokinetics of lamotrigine in 12 healthy volunteers Bupropion and hydroxybupropion are **inhibitors of the CYP2D6 isoenzyme** in vitro. Therefore, the potential exists for a drug interaction between bupropion and drugs that are metabolized by this enzyme. Many drugs, including most antidepressants (SSRIs, many TCAs), β-blockers, antiarrhythmics, and antipsychotics, are metabolized by the CYP2D6 isoenzyme. In a study of 15 male subjects (ages 19–35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the c_{max}, AUC, and $t_{1/2}$ of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion
Contraindications	Seizure disorder; treatment with other medications containing bupropion because the incidence of seizure is dose dependent; current or prior diagnosis of bulimia or anorexia nervosa, because a higher incidence of seizures noted is in such patients treated with bupropion; abrupt discontinuation of alcohol or sedatives (including benzodiazepines); concomitant use of MAO inhibitors because this can increase the risk of hypertensive reactions; previous allergic response to bupropion or other ingredients Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious ADRs in nursing infants from bupropion, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

4.7.3 Citalopram

Pharmacodynamic properties	SSRI; selective inhibition of 5-HT reuptake with minimal effect on noradrenaline and dopamine reuptake: amplification of central 5-HT effects; no or very low affinity for 5-HT_{1A}, 5-HT_{2A}, dopamine D_1 and D_2, α_1, α_2, and β-adrenergic, histamine H_1, GABA, muscarinic cholinergic, and benzodiazepine receptors. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects of other psychotropic drugs
Pharmacokinetic properties	t_{max} 3–4 h, $t_{1/2}$ 33–36 h: protein binding ca. 80 %, bioavailability 80 % Citalopram is metabolized to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-*N*-oxide, and a deaminated propionic acid derivative. In humans, unchanged citalopram is the predominant compound in plasma. At steady state, the concentrations of citalopram's metabolites, DCT and DDCT, in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. In vitro studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of 5-HT reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isoenzymes involved in the N-demethylation of citalopram
Indications	FDA approved (USA) but also in various European countries for the treatment of MDD in adults Safety and effectiveness in the pediatric population have not been established. Two placebo-controlled trials in 407 pediatric patients with MDD have been conducted, and the data were not sufficient to support a claim for the use in pediatric patients. Anyone considering the use in children or adolescents must balance the potential risks with the clinical need
Dosage	Adults: It should be administered as a single oral dose of 20 mg daily. Dependent on individual patient response, the dose may be increased to a maximum of 40 mg daily

ADRs	ADRs observed with citalopram are in general mild and transient. They are most prominent during the first weeks of treatment and usually attenuate as the depressive state improves. ADRs include nausea, restlessness, sweating, and diarrhea; less common: loss of appetite, emesis, sleep disturbances, headache, sexual dysfunction, dry mouth, and bleeding The only commonly observed ADR that occurred with an incidence of 5 % or greater and at least twice the incidence in placebo patients was **ejaculation disorder** (primarily ejaculatory delay) in male patients. Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be the result of pharmacological treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences During marketing of citalopram and other SSRIs and SNRIs, there have been spontaneous reports of ADRs occurring upon discontinuation of these drugs, particularly when abrupt, including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious **discontinuation symptoms**. Patients should be monitored for these symptoms when discontinuing treatment with citalopram. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate
Drug interactions	**Serotonergic drugs**: Based on the mechanism of action of SNRIs and SSRIs including citalopram, and the potential for **5-HT syndrome**, caution is advised when citalopram is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible nonselective MAO inhibitor), lithium salts, tramadol, or St. John's wort. The concomitant use of citalopram with other SSRIs, SNRIs, or tryptophan is not recommended **CNS drugs**: Given the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs **Alcohol**: Although citalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, consumption of alcohol by depressed patients taking citalopram is not recommended **Drugs that interfere with hemostasis** (NSAIDs, aspirin, warfarin, etc.): 5-HT release by platelets plays an important role in hemostasis. Epidemiological studies of the case–control and cohort design that have demonstrated an association between the use of psychotropic drugs that interfere with 5-HT reuptake and the occurrence of upper gastrointestinal bleeding have also shown that the concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored Biotransformation of citalopram to DCT is mediated by CYP2C19 (approximately 38 %), CYP3A4 (approximately 31 %), and CYP2D6 (approximately 31 %) isoenzymes of the CYP system. The fact that citalopram is metabolized by more than one CYP means that inhibition of its biotransformation is less likely because the inhibition of one enzyme may be compensated by another. Therefore, coadministration of citalopram with other medicinal products in clinical practice has very low likelihood of producing pharmacokinetic medicinal product interactions Escitalopram (the active enantiomer of citalopram) is an inhibitor of the enzyme CYP2D6. Caution is recommended when citalopram is coadministered with medicinal products that are mainly metabolized by this enzyme and that have a narrow therapeutic index, e.g., flecainide, propafenone, and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolized by CYP2D6, e.g., **antidepressants** such as desipramine, clomipramine, and nortriptyline or **antipsychotics** like risperidone, thioridazine, and haloperidol. Dosage adjustment may be warranted

Contraindications	Concomitant use in patients taking MAO inhibitors, use in patients taking pimozide, and hypersensitivity to citalopram or any of the inactive ingredients
	There are no adequate and well-controlled studies in **pregnant women**; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risks to the fetus. In animal reproduction studies, citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including **teratogenic effects**, when administered at doses greater than human therapeutic doses
	As with many other drugs, citalopram is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with **breast-feeding** from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram, and in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or citalopram therapy should take into account the risks of citalopram exposure for the infant and the benefits for the mother

4.7.4 Clomipramine

Pharmacodynamic properties	TCA; inhibition primarily of 5-HT and noradrenaline reuptake, to a lesser extent of dopamine reuptake; amplification of central 5-HT and noradrenaline effects; moderate-affinity antagonist of adrenergic α_1, muscarinic acetylcholine, serotonergic, and histamine H_1-receptors
Pharmacokinetic properties	t_{max} 2–6 h, $t_{1/2}$ 21–25 h (parent compound), around 35 h (active metabolite desmethylclomipramine); protein binding 97 % (albumin), bioavailability 45 %
	The major route of transformation of clomipramine is demethylation to desmethylclomipramine. In addition, clomipramine and desmethylclomipramine are hydroxylated to 8-hydroxyclomipramine and 8-hydroxydesmethylclomipramine, but little is known about their activity in vivo. The hydroxylation of clomipramine and desmethylclomipramine is under genetic control similar to that of debrisoquine. In poor metabolizers of debrisoquine, this may lead to high concentrations of desmethylclomipramine; concentrations of clomipramine are less significantly influenced
Indications	**FDA approved** (USA) for the treatment of OCD in children above the age of 10
	Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established. Anyone considering the use of clomipramine in children or adolescents must balance the potential risks with clinical needs. The safety and effectiveness in pediatric patients below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of clomipramine in pediatric patients under the age of 10
	Approved in Europe (sustained-release tablets) for the treatment of:
	Symptoms of depressive illness especially where sedation is required in adults
	Obsessional and phobic states in adults
	Adjunctive treatment of cataplexy associated with narcolepsy in adults
	In children and adolescents, there is no sufficient evidence of safety and efficacy in the treatment of depressive states of varying etiology and symptomatology, phobias and panic attacks, cataplexy accompanying narcolepsy, and chronic painful conditions. The use in children and adolescents in these indications is therefore not recommended
Dosage	Before initiating treatment, hypokalemia should be treated
	During initial titration, clomipramine should be given in divided doses with meals to reduce gastrointestinal ADRs
	Because both clomipramine and its active metabolite, desmethylclomipramine, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2–3 weeks after dosage change. Therefore, after initial titration, it may be appropriate to wait 2–3 weeks before further dosage adjustments
	As with adults, the starting dose in children and adolescents is 25 mg daily and should be gradually increased during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller. As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation

ADRs	The most commonly observed ADRs associated with the use of clomipramine and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes
Drug interactions	The risks of using clomipramine in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of clomipramine, caution is advised in using it concomitantly with other CNS-active drugs **Close supervision** and careful adjustment of dosage are required when clomipramine is administered with **anticholinergic** or **sympathomimetic drugs** Several TCAs have been reported to block the pharmacological effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with clomipramine because of its structural similarity to other TCAs The plasma concentration of clomipramine has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related TCAs have been reported to be increased by the concomitant administration of methylphenidate or hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin), and such an effect may be anticipated with clomipramine as well. Administration of clomipramine has been reported to increase the plasma levels of phenobarbital, if given concomitantly **Drugs metabolized by the CYP2D6 isoenzyme** The biochemical activity of the drug-metabolizing isozyme CYP2D6 (debrisoquine hydroxylase) is reduced in a subset of the Caucasian population (about 7–10 % of Caucasians are so-called **poor metabolizers**); reliable estimates of the prevalence of reduced CYP2D6 isoenzyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of TCAs when given usual doses. Depending on the fraction of the drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual being stable on a given dose of TCA may be intoxicated when given one of these **inhibiting drugs** as concomitant therapy. The drugs that inhibit CYP2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many others that are substrates for CYP2D6 (many other antidepressants, phenothiazines, and the type 1C antiarrhythmics propafenone and flecainide). While all the **SSRIs**, e.g., fluoxetine, sertraline, paroxetine, and fluvoxamine, inhibit CYP2D6, they may vary in the extent of inhibition. Fluvoxamine has also been shown to inhibit CYP1A2, an isoform involved in TCA metabolism. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other It is of **particular importance** that sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from **fluoxetine**, given the long $t_{1/2}$ of the parent and active metabolite (at least 5 weeks may be necessary). Concomitant use of agents in the TCA class (which includes clomipramine) with drugs that can inhibit cytochrome CYP2D6 may require lower doses than usually prescribed for either the TCA agent or the other drug. Furthermore, whenever one of these drugs is withdrawn from co-therapy, an increased dose of TCA agent may be required. It is desirable to monitor TCA plasma levels whenever an agent of the TCA class (including clomipramine) is going to be coadministered with another drug known to be an inhibitor of CYP2D6 (and/or CYP1A2) Because clomipramine is highly bound to serum protein, the administration of clomipramine to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause increased plasma concentrations of these drugs, potentially resulting in ADRs. Conversely, ADRs may result from displacement of protein-bound clomipramine by other highly bound drugs

Contraindications	Patients with a history of hypersensitivity to clomipramine or other TCAs, concomitant use with MAO inhibitors, and during the acute recovery period after a myocardial infarction
	Clomipramine should be used during **pregnancy** only if the potential benefits justify the potential risk to the fetus. **No teratogenic effects** were observed in studies performed in rats and mice at doses up to 100 mg/kg, which is 24 times the maximum recommended human daily dose (MRHD) on a mg/kg basis and 4 times (rats) and 2 times (mice) the MRHD on a mg/kg basis. Slight nonspecific embryo/fetotoxic effects were seen in the offspring of treated rats given 50 and 100 mg/kg and of treated mice given 100 mg/kg. There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken clomipramine hydrochloride until delivery
	Clomipramine has been found in human milk. Because of the potential for ADRs, a decision should be made whether to discontinue **nursing** or to discontinue the drug, taking into account the importance of the drug to the mother

4.7.5 Doxepin

Pharmacodynamic properties	TCA; the mechanism of action is not definitely known. It is neither a CNS system stimulant nor a MAO inhibitor. The current hypothesis is that the clinical effects are due, at least in part, to influences on the adrenergic activity at the synapses so that deactivation of noradrenaline by reuptake into the nerve terminals is prevented. In animal studies, anticholinergic, antiserotonergic, and antihistaminergic effects on smooth muscle have been demonstrated. At higher than usual clinical doses, adrenaline response was potentiated in animals. This effect has not been demonstrated in humans
Pharmacokinetic properties	t_{max} 2–4 h, $t_{1/2}$ 8–24 h (parent compound); t_{max} 2–10 h, $t_{1/2}$ 33–80 h (active metabolite desmethyldoxepin); protein binding ca. 76 %, bioavailability 25 %; metabolism by CYP1A2, CYP3A4, CYP2C19, CYP2D6, and CYP2C9
	Approximately 55–87 % of orally administered doxepin undergoes first-pass metabolism primarily by CYP2D6 (with CYP1A2 and CYP3A4 as minor pathways) in the liver, forming the primary active metabolite desmethyldoxepin. Paths of metabolism of doxepin include demethylation, N-oxidation, hydroxylation, and glucuronide formation. Doxepin is excreted primarily in the urine, mainly as its metabolites, either in free or in conjugate form
Indications	**FDA approved** (USA) for the treatment of:
	Psychoneurotic patients with depression and/or anxiety
	Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol)
	Depression and/or anxiety associated with organic disease (the possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly)
	Psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders
	Owing to the lack of clinical experience in the pediatric population, doxepin is not approved for use in children younger than 12 years of age
	Approved in Europe for the treatment of:
	Symptoms of depressive illness, especially where sedation is required
	The use of doxepin in children under 12 years is not recommended because safe conditions for its use have not been established

Dosage	For most patients with illnesses of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75–150 mg/day
	In more severely ill patients, higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effects are rarely obtained by higher doses than 300 mg/day
	In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25–50 mg/day
	The total daily dosage of doxepin may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. Antianxiety effects are apparent before antidepressant effects. Optimal antidepressant effects may not show before 2–3 weeks
ADRs	Doxepin is well tolerated. Most ADRs are mild and generally disappear with continued treatment or with a dose reduction. The most common ADRs to doxepin (≥5 % and at least twice the incidence of placebo patients) are drowsiness, dry mouth, and constipation. Infrequently reported CNS ADRs are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor
	Withdrawal symptoms may occur on abrupt cessation of TCA therapy and include insomnia, irritability, and excessive perspiration. Withdrawal symptoms in neonates whose mothers received TCAs during the third trimester have also been reported and include respiratory depression, convulsions, and "jitteriness" (hyperreflexia)
Drug interactions	Doxepin, like other TCAs, is metabolized by CYP2D6. Inhibitors or substrates of CYP2D6 (e.g., quinidine, **SSRIs**) may increase the plasma concentration of TCAs when administered concomitantly. The extent of interaction depends on the variability of effect on CYP2D6 and the therapeutic index of the TCA. The clinical significance of this interaction with doxepin has not been systematically evaluated
	Combined use with other antidepressants, alcohol, or antianxiety agents should be undertaken with due recognition of the possibility of potentiation. It is known, for example, that MAO inhibitors may potentiate other drug effects; therefore, doxepin should not be given concurrently, or within 2 weeks of cessation of therapy, with MAO inhibitors
	Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of doxepin
	Doxepin should not be given with **sympathomimetic agents** such as ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine
	General anesthetics and local anesthetics (containing sympathomimetics) given during TCA or tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension or hypertension. If surgery is necessary, the anesthetist should be informed that the patient is under treatment
	Doxepin may decrease the antihypertensive effect of agents such as debrisoquine, bethanidine, guanethidine, and possibly clonidine. It usually requires daily doses of doxepin higher than 150 mg before any effect on the action of guanethidine can be seen. It would be advisable to **review** all **antihypertensive therapy** during treatment with TCAs
	Barbiturates may increase the rate of metabolism of doxepin
Contraindications	In individuals who have shown hypersensitivity to TCAs, doxepin, or any of the inactive ingredients. Doxepin is also contraindicated in patients with mania, severe liver disease, lactation, glaucoma, and tendency to urinary retention
	The use of doxepin is contraindicated during **lactation**. Doxepin and its active metabolite desmethyldoxepin are excreted in breast milk. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking doxepin
	Doxepin crosses the placenta. Reproduction studies have been performed in rats, rabbits, and monkeys, and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is insufficient experience in **pregnant women** who have received this drug, its safety in pregnancy has not been established

4.7.6 Duloxetine

Pharmacodynamic properties	Although the exact mechanisms of the antidepressant, central pain inhibitory, and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal 5-HT and noradrenaline reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors in vitro. Duloxetine does not inhibit MAO
Pharmacokinetic properties	t_{max} 6 h; food does not affect the c_{max} of duloxetine but delays the t_{max} from 6 to 10 h; $t_{1/2}$ 12 h, protein binding ca. 90 %, bioavailability not known Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacological activity of duloxetine. Elimination of duloxetine is mainly through hepatic metabolism involving CYP1A2 and CYP2D6
Indications	**FDA approved** (USA) for the treatment of adults with: MDD Generalized anxiety disorder Diabetic peripheral neuropathic pain Fibromyalgia Chronic musculoskeletal pain Efficacy was not demonstrated in two 10-week, placebo-controlled trials with 800 pediatric patients with MDD, aged 7–17 years. Neither duloxetine nor the active control (indicated for the treatment of pediatric depression) statistically separated from placebo. Duloxetine steady-state plasma concentration was comparable in children (7–12 years of age), adolescents (13–17 years of age), and adults Duloxetine has not been studied in patients under the age of 7. Thus, safety and effectiveness in the pediatric population have not been established **Approved in Europe** for the treatment of adults with: MDD Diabetic peripheral neuropathic pain Generalized anxiety disorder Duloxetine is not recommended for use in children and adolescents due to insufficient data on safety and efficacy
Dosage	**MDD** Duloxetine should be administered at a total dose of 40 mg/day (given as 20 mg twice daily) to 60 mg/day (given either once daily or 30 mg twice daily). For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day bring any additional benefits It is generally agreed that acute episodes of MDD require several months or longer of sustained pharmacological therapy. Duloxetine should be administered at a total dose of 60 mg once daily **Generalized anxiety disorder** For most patients, the recommended starting dose is 60 mg administered once daily. For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg one-time daily dose was shown to be effective, there is no evidence that doses greater than 60 mg/day bring additional benefits It is generally agreed that episodes of generalized anxiety disorder require several months or longer of sustained pharmacological therapy. Duloxetine should be administered in a dose range of 60–120 mg once daily

ADRs	Most common ADRs (≥5 % and at least twice the incidence of placebo patients): nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Pediatric patients treated with duloxetine in MDD clinical trials experienced a 0.2 kg mean decrease in weight at 10 weeks, compared with a mean weight gain of approximately 0.6 kg in placebo-treated patients. The proportion of patients who experienced a clinically significant decrease in weight (>3.5 %) was greater in the duloxetine group than in the placebo group (11 and 6 %, respectively). Subsequently, over a 6-month uncontrolled extension period, most duloxetine-treated patients regained baseline weight percentile based on population data from age- and gender-matched peers
Drug interactions	Because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. **Fluvoxamine** (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77 % and increased AUC sixfold. Therefore, duloxetine should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine The risk of using duloxetine in combination with other **CNS-active medicinal products** has not been systematically evaluated, except in the cases described in this section. Consequently, caution is advised when duloxetine is taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (e.g., benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines) In rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g., paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if duloxetine is used concomitantly with **serotonergic antidepressants** like SSRIs, TCAs like clomipramine or amitriptyline, St. John's wort (*H. perforatum*), venlafaxine or triptans, tramadol, pethidine, and tryptophan Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased threefold. Caution is advised if duloxetine is coadministered with **medicinal products** that are predominantly **metabolized by CYP2D6** (risperidone, TCAs such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone, and metoprolol) Caution should be exercised when duloxetine is combined with **oral anticoagulants** or antiplatelet agents due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction
Contraindications	The concomitant use of nonselective MAO inhibitors, use in patients with uncontrolled narrow-angle glaucoma, and hypersensitivity to the active substance or to any excipients It should be used in **pregnancy** only if the potential benefits justify the potential risks to the fetus. There are no adequate data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels of duloxetine lower than the maximum clinical exposure. Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with duloxetine taking into account the related mechanism of action (inhibition of the reuptake of serotonin) Duloxetine is very weakly excreted into human milk based on a study of six lactating patients, who did not breast-feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14 % of the maternal dose. As the safety of duloxetine in infants is not known, the use of duloxetine while **breast-feeding** is not recommended

4.7.7 Escitalopram

Pharmacodynamic properties	S-Enantiomer of citalopram. SSRI; selective inhibition of 5-HT reuptake, amplification of central 5-HT effects Escitalopram is at least 100 times more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Escitalopram has no or very low affinity for serotonergic (5-HT_{1-7}) or other receptors including α- and β-adrenergic, dopamine (D_{1-5}), histamine (H_{1-3}), muscarinic acetylcholine (M_{1-5}), and benzodiazepine receptors. Escitalopram also does not bind to, or has low affinity for, various ion channels including Na^+, K^+, Cl^-, and Ca^{2+} channels. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular ADRs of other psychotropic drugs
Pharmacokinetic properties	t_{max} 5 h, $t_{1/2}$ 27–32 h; protein binding ca. 56 %, bioavailability 80 % In vitro studies show that escitalopram is at least 7–27 times more potent than its main metabolites in the inhibition of 5-HT reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isoenzymes involved in the N-demethylation of escitalopram
Indications	**FDA approved** (USA) for the: Acute and maintenance treatment of MDD in adults and adolescents aged 12–17 years Acute treatment of generalized anxiety disorder in adults Safety and effectiveness have not been established in pediatric patients (younger than 12 years of age) with MDD. Safety and effectiveness have been established in adolescents (12–17 years of age) for the treatment of MDD. Although maintenance efficacy in adolescent patients with MDD has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients Safety and effectiveness have not been established in pediatric patients younger than 18 years of age with generalized anxiety disorder **Approved in Europe** for the treatment of: MDD in adults Generalized anxiety disorder in adults OCD in adults Panic disorder with or without agoraphobia in adults Social anxiety disorder (social phobia) Escitalopram should not be used in the treatment of children and adolescents under the age of 18 years

Dosage	**MDD** Adults: usual dosage is 10 mg once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily. Usually 2–4 weeks are necessary to obtain an antidepressant response. After symptoms resolved, a treatment of at least 6 months is required to consolidate the response Adolescents: the recommended dose is 10 mg once daily. If the dose is increased to 20 mg, this should only be done after a minimum of 3 weeks **Generalized anxiety disorder** Initial dosage is 10 mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20 mg daily. Long-term treatment of responders has been studied for at least 6 months in patients receiving 20 mg/day **OCD** Initial dosage is 10 mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20 mg daily. As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom-free **Panic disorder with or without agoraphobia** An initial dose of 5 mg is recommended for the first week before increasing the dose to 10 mg daily. The dose may be further increased, up to a maximum of 20 mg daily, depending on individual patient response. Maximum effectiveness is reached after about 3 months. The treatment lasts several months **Social anxiety disorder** Usual dosage is 10 mg once daily. Usually 2–4 weeks are necessary to obtain symptom relief. The dose may subsequently, depending on individual patient response, be decreased to 5 mg or increased to a maximum of 20 mg daily. Social anxiety disorder is a disease with a chronic course, and treatment for 12 weeks is recommended to consolidate response. Long-term treatment of responders has been studied for 6 months and can be considered on an individual basis to prevent relapse
ADRs	Most commonly observed ADRs (incidence ≥5 % and at least twice the incidence of placebo patients) are insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, increased sweating, fatigue and somnolence, decreased libido, and anorgasmia Decreased appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI such as escitalopram
Drug interactions	See Sect. 4.7.3
Contraindications	See Sect. 4.7.3

4.7.8 Fluoxetine

Pharmacodynamic properties	SSRI. This probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as α_1, α_2, and β-adrenergic, serotonergic, dopaminergic, histaminergic H_1, muscarinic acetylcholine, and GABA receptors
Pharmacokinetic properties	t_{max} 6–8 h, $t_{1/2}$ 4–6 days (parent compound), 4–16 days (active metabolite norfluoxetine); these long $t_{1/2}$ are responsible for persistence of the drug for 5–6 weeks after discontinuation. Protein binding 95 %, bioavailability 70–85 % The mean fluoxetine concentration in children is approximately 2 times higher than that observed in adolescents, and the mean norfluoxetine concentration 1.5 times higher Fluoxetine is extensively metabolized by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolized by the liver to the active metabolite norfluoxetine (desmethylfluoxetine) by desmethylation
Indications	**FDA approved** (USA) for: Acute and maintenance treatment of MDD in adults and pediatric patients aged 8–18 years Acute and maintenance treatment of OCD in adults and pediatric patients aged 7–17 years Acute and maintenance treatment of bulimia nervosa in adult patients Acute treatment of panic disorder, with or without agoraphobia, in adult patients The safety and effectiveness in pediatric patients <8 years of age in MDD and <7 years of age in OCD have not been established **Approved in Europe** for the treatment of: MDD in adults OCD in adults Complement of psychotherapy for the reduction of binge-eating and purging activity in adults. Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4–6 sessions in children and adolescents aged 8 years and above. Antidepressant medication should be offered to children or young persons with moderate to severe depression only in combination with a concurrent psychological therapy
Dosage	**MDD in children and adolescents** Short-term (8–9 weeks) controlled clinical trials of fluoxetine support its effectiveness in the treatment of MDD; patients were administered fluoxetine doses of 10–20 mg/day. Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day However, due to higher plasma levels in children of lower weight, the starting and target dose in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if there is no sufficient clinical improvement **OCD in children and adolescents** A controlled clinical trial of fluoxetine supports its effectiveness in the treatment of OCD; patients were administered fluoxetine doses in the range of 10–60 mg/day In adolescents and children of higher weight, treatment should be initiated with a dose of 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases may be considered after several more weeks if there is no sufficient clinical improvement. A dose range of 20–60 mg/day is recommended In children of lower weight, treatment should be initiated with a dose of 10 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20–30 mg/day is recommended. Experience with daily doses greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg

ADRs	Most common ADRs (≥5 % and at least twice that for placebo) associated with MDD, OCD, bulimia, and panic disorder: abnormal dreams, abnormal ejaculation, anorexia, anxiety, asthenia, diarrhea, dry mouth, dyspepsia, flu syndrome, impotence, insomnia, decreased libido, nausea, nervousness, pharyngitis, rash, sinusitis, somnolence, sweating, tremor, vasodilatation, and yawn
Drug interactions	**Phenytoin** Changes in blood levels have been observed when combined with fluoxetine. In some cases, manifestations of toxicity have occurred. Consideration should be given to using conservative titration schedules of the concomitant drug and to monitoring clinical status **Serotonergic drugs** Coadministration with serotonergic drugs (e.g., tramadol, triptans) may increase the risk of 5-HT syndrome. Use with triptans carries the additional risk of coronary vasoconstriction and hypertension **Lithium salts and tryptophan** There have been reports of 5-HT syndrome when SSRIs have been given with lithium or tryptophan, and, therefore, the concomitant use of fluoxetine with these drugs should be undertaken with caution. When fluoxetine is used in combination with lithium, closer and more frequent clinical monitoring is required **Drugs metabolized by the CYP2D6 isoenzyme** Because fluoxetine's metabolism (like TCAs and other SSRIs) involves the hepatic cytochrome CYP2D6 isoenzyme system, concomitant therapy with medicinal products also metabolized by this enzyme system may lead to medicinal product interactions. Concomitant therapy with medicinal products predominantly metabolized by this isoenzyme, which have a narrow therapeutic index (such as flecainide, encainide, vinblastine, carbamazepine, and TCAs), should be initiated at or adjusted to the low end of their dose range. This will also apply if fluoxetine has been taken in the previous 5 weeks **Oral anticoagulants** Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms) with no consistent pattern, but including increased bleeding, have been reported uncommonly when fluoxetine is coadministered with oral anticoagulants. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped **Alcohol** In formal testing, fluoxetine did not raise blood alcohol levels or enhance the effects of alcohol. However, the combination of SSRI treatment and alcohol is not advisable **St. John's wort** Pharmacodynamic interactions between fluoxetine and the herbal remedy St. John's wort (*H. perforatum*) may occur, resulting in an increase of undesired effects
Contraindications	Hypersensitivity to fluoxetine or any of the excipients, concomitant use of nonselective MAO inhibitors, concomitant use of pimozide due to the risk of drug interaction or QTc prolongation, and use with thioridazine due to QTc interval prolongation or potential for elevated thioridazine plasma levels Fluoxetine should be used during pregnancy only if the potential benefits justify potential risks to the fetus. Breast-feeding in nursing mothers is not recommended

4.7.9 Fluvoxamine

Pharmacodynamic properties	The mechanism of action in OCD and depression is linked to its specific 5-HT reuptake inhibition in brain neurons. Fluvoxamine has been shown to be a potent inhibitor of the 5-HT reuptake transporter in preclinical studies, both in vitro and in vivo. In in vitro studies, it had no significant affinity for histaminergic, α- or β-adrenergic, muscarinic, or dopaminergic receptors. Antagonism of some of these receptors is thought to be associated with various sedative, cardiovascular, anticholinergic, and extrapyramidal effects of some psychotropic drugs

Pharmacokinetic properties	t_{max} 3–8 h, $t_{1/2}$ 15.6 h; protein binding 80 %, bioavailability 53 % The multiple-dose pharmacokinetics of fluvoxamine have been determined in male and female children (aged 6–11 years) and adolescents (aged 12–17 years). Steady-state plasma fluvoxamine concentrations were 2–3 times higher in children than in adolescents. AUC and c_{max} in children were 1.5–2.7 times higher than that in adolescents. As in adults, both children and adolescents exhibited nonlinear multiple-dose pharmacokinetics Fluvoxamine is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified, constituting approximately 85 % of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60 % of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10 %. Fluvoxamine acid and fluvoxethanol were tested in an in vitro assay of 5-HT and noradrenaline reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of 5-HT uptake (one to two orders of magnitude less potent than the parent compound)
Indications	**FDA approved** (USA) for: Acute and maintenance treatment of OCD in adults and pediatric patients aged 8–17 years The safety and effectiveness in pediatric patients <8 years of age in MDD and <7 years of age in OCD have not been established **Approved in Europe** for the treatment of: Major depressive episode in adults OCD in adults
Dosage	**OCD** The recommended starting dose in pediatric populations (age 8–17 years) is 25 mg, administered as a single daily dose at bedtime. In a controlled clinical trial establishing the effectiveness of fluvoxamine in OCD, pediatric patients (aged 8–17 years) were titrated within a dose range of 50–200 mg/day Physicians should consider age and gender differences when dosing pediatric patients. The maximum dose in children up to the age of 11 should not exceed 200 mg/day. Therapeutic effects in female children may be achieved with lower doses. Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefits. The dose should be increased in 25 mg increments every 4–7 days, as tolerated, until maximum therapeutic benefit is achieved. It is advisable that a total daily dose of more than 50 mg should be given in two divided doses. If the two divided doses are not equal, the larger dose should be given at bedtime **Major depressive episodes** The recommended starting dose for adults is 50 or 100 mg, given as a single dose in the evening. It is recommended to increase the dose gradually until an effective dose is reached. Doses up to 300 mg/day have been given. Dosages above 150 mg should be given in divided doses In agreement with the consensus statement of the WHO, antidepressant medication should be continued for at least 6 months after recovery from a depressive episode. A dose of 100 mg daily may be sufficient
ADRs	The majority of ADRs associated with fluvoxamine are common to the class of SSRIs (headache, nausea, insomnia, somnolence, dry mouth, and others) and are often not serious in nature. More serious ADRs, although not frequently reported, should be kept under **close monitoring**, e.g., hypertension, syncope, dyspnea, flatulence, vertigo, minor increase in creatinine, and decreased thrombocyte count In the 10-week placebo-controlled trial in children and adolescents with OCD, frequently reported ADRs with a higher incidence than placebo were insomnia, asthenia, agitation, hyperkinesia, somnolence, and dyspepsia. Serious ADRs in this study included agitation and hypomania. Convulsions in children and adolescents have been reported during outside clinical trials Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term

Drug interactions	Fluvoxamine is a potent inhibitor of CYP1A2 and to a lesser extent of CYP2C and CYP3A4. Drugs which are largely metabolized (TCAs such as clomipramine, imipramine, and amitriptyline and antipsychotics such as clozapine and olanzapine) via these isoenzymes are eliminated slower and may have higher plasma concentrations when coadministered with fluvoxamine. This is particularly relevant for drugs with a narrow therapeutic index. Patients should be carefully monitored, and, if necessary, dose adjustment of these drugs is recommended
	Antipsychotic drugs Rare instances of neuroleptic malignant syndrome (NMS) or NMS-like events have been reported in association with fluvoxamine treatment when coadministered with antipsychotics
	Benzodiazepines Benzodiazepines metabolized by hepatic oxidation (e.g., alprazolam, midazolam, and triazolam) should be used with caution because the clearance of these drugs is likely to be reduced by fluvoxamine
	Alprazolam When fluvoxamine (100 mg every day) and alprazolam (1 mg q.i.d.) were coadministered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, c_{max}, $t_{1/2}$) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50 %. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is coadministered, particularly since fluvoxamine exhibits nonlinear pharmacokinetics over a dosage range of 100–300 mg. If alprazolam is coadministered with fluvoxamine, the initial alprazolam dosage should be divided in two, and titration to the lowest effective dose is recommended. No dosage adjustment is required for fluvoxamine
	Diazepam The coadministration of fluvoxamine and diazepam is generally **not advisable**. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite, *N*-desmethyldiazepam; there is a strong likelihood of substantial accumulation of both species during chronic coadministration
	Clozapine Elevated serum levels of clozapine have been reported in patients taking fluvoxamine maleate and clozapine. Since clozapine-related seizures and orthostatic hypotension appear to be related to the dose, the risk of these adverse events may be higher when fluvoxamine and clozapine are coadministered. Patients should be **closely monitored** when fluvoxamine maleate and clozapine are used concurrently
	Methadone Significantly increased methadone (plasma level/dose) ratios have been reported when fluvoxamine maleate was administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in one patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient
	Ramelteon When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose coadministration of ramelteon 16 mg and fluvoxamine, the AUC for ramelteon increased approximately 190-fold and the c_{max} increased approximately 70 times compared to ramelteon administered alone. Ramelteon should **not be used** in combination with fluvoxamine
	Theophylline The effect of steady-state fluvoxamine (50 mg b.i.d.) on the pharmacokinetics of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy nonsmoking, male volunteers. The clearance of theophylline was decreased approximately 3 times. Therefore, if theophylline is coadministered with fluvoxamine, its dose should be reduced to one-third of the usual daily maintenance dose, and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for fluvoxamine
	Serotonergic drugs The development of a potentially life-threatening **5-HT syndrome** may occur with fluvoxamine treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs that impair metabolism of 5-HT (including nonselective MAO inhibitors). 5-HT symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea)
	Warfarin and other drugs that interfere with hemostasis (NSAIDs, aspirin, etc.) 5-HT release by platelets plays an important role in hemostasis. Epidemiological studies of the case–control and cohort design have demonstrated an association between the use of psychotropic drugs that interfere with 5-HT reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Thus, **patients** should be **cautioned** about the use of such drugs concurrently with fluvoxamine

Contra-indications	Coadministration of tizanidine, thioridazine, alosetron, and pimozide and the use of nonselective MAO inhibitors concomitantly with or within 14 days of treatment with fluvoxamine Consider both potential risks and benefits when treating a **pregnant woman**. Infants exposed to SSRIs late in pregnancy have developed various complications and may be at risk for persistent pulmonary hypertension of the newborn. Consider tapering during the third trimester. **Nursing mothers**: fluvoxamine is secreted in human breast milk

4.7.10 Imipramine

Pharma-codynamic properties	TCA; the mechanism of action is not definitely known. However, it does not act primarily by stimulation of the CNS. The mode of action of the drug in controlling childhood enuresis is thought to be a part of its antidepressant effect Imipramine has several pharmacological actions including α-adrenergic, antihistamine, anticholinergic, and 5-HT receptor blocking properties. However, the main therapeutic activity is believed to be inhibition of the neuronal reuptake of noradrenaline and 5-HT. It is a so-called "mixed" reuptake blocker, i.e., it inhibits the reuptake of noradrenaline and 5-HT to about the same extent
Pharmacokinetic properties	t_{max} 1–4 h, mean $t_{1/2}$ 19 h; protein binding 86 %, bioavailability 30–75 % Imipramine is extensively metabolized in the liver by CYP1A2, CYP3A4, CYP2B6, CYP2C19, CYP2D6, and CYP2C9. It is cleared mainly by demethylation and to a lesser extent by hydroxylation. Both metabolic pathways are under genetic control The biochemical activity of the drug-metabolizing isoenzyme CPY2D6 (debrisoquine hydroxylase) is reduced in a subset of the Caucasian population (about 7–10 % of Caucasians are so-called **poor metabolizers**); reliable estimates of the prevalence of reduced CYP2D6 activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of TCAs when given at usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8 times increase in plasma AUC of the TCA)
Indications	**FDA approved** (USA) for the treatment of: Depression in adults Childhood enuresis in children aged 6 years and older **Approved in Europe** for the treatment of: Symptoms of depressive illness in adults Relief of nocturnal enuresis in children aged 6 years and older Safety and effectiveness in the pediatric population other than pediatric patients with nocturnal enuresis have not been established. Anyone considering the use of imipramine in a child or adolescent must balance the potential risks with the clinical need. The safety and effectiveness of the drug as temporary adjunctive therapy for nocturnal enuresis in pediatric patients less than 6 years of age have not been established
Dosage	**Depression** 1 × 25 mg up to 3 times daily, increasing stepwise to 150–200 mg in adults. This should be reached by the end of the first week and maintained until definite improvement has occurred. The subsequent maintenance dose should be individually determined by gradually reducing the dosage, usually to about 50–100 mg daily In patients in hospital, i.e., severe cases, the dose may be increased to 100 mg 3 times daily until a distinct improvement is seen **Childhood enuresis in children aged 6 years and older** The tablets should be administered just before bedtime: Over 11 years (weight 35–54 kg): 50–75 mg daily 8–11 years (weight 25–35 kg): 25–50 mg daily 6–7 years (weight 20–25 kg): 25 mg daily The dose should not exceed 75 mg daily. The maximum period of treatment should not exceed 3 months, and withdrawal should be gradual. If relapse should occur, treatment should not be re-instituted until a full physical examination has been carried out

ADRs	Common ADRs include dry mouth, blurred vision, obstipation, micturition disturbances, tachycardia, mania/hypomania, headache, photosensitivity, sleep disturbances, restlessness, tremor, cerebral seizures, cardiac conduction disorders, allergic reactions, weight gain, vertigo, trembling, hypotonia, and disturbances of sexual function In **enuretic children** treated with imipramine, the most common ADRs have been nervousness, sleep disorders, tiredness, and mild gastrointestinal disturbances. These usually disappear during continued drug administration or when the dosage is decreased. Other reactions which have been reported include constipation, convulsions, anxiety, emotional instability, syncope, and collapse. All of the ADRs reported with adult use should be considered The signs and symptoms of overdose with imipramine are similar to those reported with other TCAs. Cardiac abnormalities and neurological disturbances are the main complications. Deaths may occur from **overdose** with this class of drugs. Multiple-drug ingestion (including alcohol) is common in deliberate TCA overdose. As the management is complex and changing, it is recommended that the physician contacts a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after TCA overdose. Therefore, hospital monitoring is required as soon as possible. Children have been reported to be more sensitive than adults to an acute overdosage. An acute overdose of any amount in infants or young children, especially, must be considered serious and potentially fatal
Drug interactions	**Drugs that inhibit the activity of CYP2D6** make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCAs may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit CYP2D6 include some that are not metabolized by the enzyme (quinidine, cimetidine) and many that are substrates for CYP2D6 (many other **antidepressants**, phenothiazines, and the type 1C antiarrhythmics propafenone and flecainide). While all **SSRIs**, e.g., fluoxetine, sertraline, and paroxetine, inhibit CYP2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interaction may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long $t_{1/2}$ of the parent and active metabolite (at least 5 weeks may be necessary) Concomitant use of TCAs with drugs that can inhibit CYP2D6 may require **lower doses** than usually prescribed for either the TCA or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of TCA may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of CYP2D6 The plasma concentration of imipramine may increase when the drug is given concomitantly with **hepatic enzyme inhibitors** (e.g., cimetidine, fluoxetine) and decrease by concomitant administration with hepatic enzyme inducers (e.g., barbiturates, phenytoin), and adjustment of the dosage of imipramine may therefore be necessary Avoid the use of preparations, such as decongestants and local anesthetics containing any **sympathomimetic amine** (e.g., adrenaline, noradrenaline), since it has been reported that TCAs can potentiate the effects of catecholamines Caution should be exercised when imipramine is used with agents that lower blood pressure. Imipramine hydrochloride may potentiate the effects of CNS depressant drugs Patients should be warned that imipramine hydrochloride can enhance the CNS depressant effects of **alcohol**
Contra-indications	Concomitant use of nonselective MAO inhibitors, during the acute recovery period after a myocardial infarction, patients with a known hypersensitivity to this compound should not be given the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind There have been no well-controlled studies conducted with **pregnant women** to determine the effect of imipramine on the fetus. However, there have been clinical reports of congenital malformations associated with the use of the drug. Although a causal relationship between these effects and the drug could not be established, the possibility of fetal risk from the maternal ingestion of imipramine cannot be excluded. Therefore, it should be used in women who are or might become pregnant only if the clinical condition clearly justifies potential risks to the fetus Limited data suggest that imipramine is likely to be excreted in human breast milk. As a general rule, a woman taking a drug should **not nurse** since the possibility exists that the drug may be excreted in breast milk and be harmful to the child

4.7.11 Maprotiline

Pharmacodynamic properties	Tetracyclic antidepressant; the mechanism of action is not precisely known. It does not act primarily by stimulation of the CNS and is no MAO inhibitor. The postulated mechanism is that it acts primarily by potentiation of central adrenergic synapses by blocking reuptake of noradrenaline at nerve endings. This pharmacological action is thought to be responsible for the drug's antidepressant and anxiolytic effects
Pharmacokinetic properties	Mean t_{max} 12 h, mean $t_{1/2}$ 51 h; protein binding ca. 88 %, bioavailability 60–90 %; metabolism primarily by CYP2D6
Indications	Approval by the FDA (USA) and in European countries for the treatment of: MDD Depressive illness in patients with depressive neurosis (dysthymic disorder) and manic-depressive illness It is not approved for use in children and adolescents
Dosage	A single daily dose is an alternative to divided daily doses. Therapeutic effects are sometimes seen within 3–7 days, although 2–3 weeks are usually necessary **Initial adult dosage** A dosage of 75 mg daily is suggested for outpatients with mild to moderate depression. Because of the long $t_{1/2}$ of maprotiline, the initial dosage should be maintained for 2 weeks. The dosage may then be increased gradually in 25 mg increments as required and tolerated. In most outpatients, a maximum dose of 150 mg daily will result in therapeutic efficacy. It is recommended that this dose not be exceeded except in the most severely depressed patients. In such patients, dosage may then be gradually increased to a maximum of 225 mg. More severely depressed, hospitalized patients should be given an initial daily dose of 100–150 mg which may be gradually increased as required and tolerated. Most hospitalized patients with moderate to severe depression respond to a daily dose of 150 mg although dosages as high as 225 mg may be required in some cases. Daily dosage of 225 mg should not be exceeded **Maintenance** Dosage during prolonged maintenance therapy should be kept at the lowest effective level. Dosage may be reduced to levels of 75 to 150 mg daily during such periods, with subsequent adjustment depending on therapeutic response
ADRs	The following ADRs have been noted and are generally similar to those observed with TCAs: tiredness, vertigo, dry mouth, weight gain, accommodation disturbances, micturition disturbances, allergic reactions, tremor, headache, restlessness, obstipation, cardiac conduction disorders as well as orthostatic hypotonia, and increased susceptibility to seizures, more marked than with other antidepressants **Deaths** may occur from **overdosage** with this class of drugs. Multiple-drug ingestion (including alcohol) is common in deliberate overdose. As the management is complex and changing, it is recommended that the physician contacts a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after overdose. Therefore, hospital monitoring is required as soon as possible
Drug interactions	Close supervision and careful adjustment of dosage are required when administering maprotiline concomitantly with **anticholinergic or sympathomimetic drugs** because of the possibility of additive atropine-like effects Caution should be exercised when administering maprotiline to hyperthyroid patients or those on **thyroid medication** because of the possibility of enhanced potential for cardiovascular toxicity of maprotiline The risk of seizures may be increased when maprotiline is taken concomitantly with phenothiazines or when the dosage of **benzodiazepines** is rapidly tapered in patients receiving maprotiline Because of the pharmacological similarity of maprotiline to TCAs, the plasma concentration of maprotiline may be increased when the drug is given concomitantly with hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decreased by concomitant administration with hepatic enzyme inducers (e.g., barbiturates, phenytoin), as has occurred with TCAs. Adjustment of the dosage of maprotiline may therefore be necessary in such cases

Contraindications	In patients hypersensitive to maprotiline and in patients with known or suspected seizure disorders. It should not be given concomitantly with nonselective MAO inhibitors Reproduction studies have been performed in female laboratory rabbits, mice, and rats at doses up to 1.3, 7, and 9 times the maximum daily human dose, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to maprotiline. There are, however, no adequate and well-controlled studies in **pregnant women**. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed Maprotiline is excreted in breast milk. At steady state, the concentrations in milk correspond closely to the concentrations in whole blood. Caution should be exercised when maprotiline is administered to a **nursing woman**

4.7.12 Mianserin

Pharmacodynamic properties	Tetracyclic antidepressant; it does not appear to have significant anticholinergic properties but has a marked sedative action. Unlike amitriptyline, it does not prevent the peripheral reuptake of noradrenaline; it blocks presynaptic α-adrenoceptors and increases the turnover of brain noradrenaline. It has little effect on central 5-HT uptake but has been shown to increase peripheral 5-HT uptake in depressed subjects. It has antihistamine properties. Although many of the effects differ from those of amitriptyline, its activity in depression is similar. Like amitriptyline, its mode of action in depression is not fully understood
Pharmacokinetic properties	t_{max} 3–5 h, $t_{1/2}$ 6–29 h; protein binding around 90 %, bioavailability 30 %; metabolism by CYP2D6
Indications	Approved in some **European countries** for the treatment of: Primary depressive illness (e.g., endogenous depression, reactive depression, involutional melancholia depression in association with physical complaints) In those cases where marked anxiety or insomnia is a predominant feature of depressive illness, mianserin may be effective without concomitant tranquillizing treatment Mianserin should not be used in the treatment of children and adolescents under the age of 18 years
Dosage	Clinical treatment in **adults** should be started with 30 mg daily and the dosage adjusted according to the clinical reaction. The daily effective dose in adults usually lies between 30 and 90 mg. The total daily dose may be either given as a single nighttime dose or divided into three sub-doses
ADRs	Cases of **suicidal ideation** and suicidal behaviors have been reported during mianserin therapy or early after treatment discontinuation. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening suicidal behavior or thoughts and unusual changes in behavior and seek medical advice immediately if these symptoms are present The frequency and severity of **depression-related symptoms** such as blurred vision, dry mouth, and constipation do not usually increase during treatment with mianserin; in fact an actual decrease has been observed in many cases The most commonly occurring ADR is drowsiness. Additional ADRs that may occur include breast disorders (gynecomastia, nipple tenderness, and non-puerperal lactation), disturbances of liver function, arthralgia, dizziness, postural hypotension, edema, polyarthropathy, skin rash, sweating, and tremor **Bone marrow depression**, usually presenting a granulocytopenia or agranulocytosis, has been reported during treatment with mianserin. These reactions have occurred most commonly after 4–6 weeks and were generally reversible on stopping treatment. A **full blood count** is **recommended** every 4 weeks during the first 3 months of treatment. In addition, monitoring of the patient's clinical condition should continue, and if a patient develops fever, sore throat, stomatitis, or other signs of infection, treatment should be stopped and a full blood count obtained. These adverse reactions have been observed in all age groups but appear to be more common in elderly patients

Drug interactions	The drug should not be administered concomitantly with or within 2 weeks of cessation of therapy with **nonselective MAO inhibitors** **Great caution** should be exercised if mianserin is used in patients receiving barbiturates, anticonvulsant therapy, or narcotic analgesics. Adjustment of dosage will likely be required Additional monitoring procedures are recommended for patients receiving concurrent **anticoagulant therapy** of the coumarin type (e.g., warfarin) Mianserin may potentiate the CNS depressant action of alcohol, and patients should be advised to avoid consuming alcohol during treatment
Contraindications	Mania, use during pregnancy and lactation, use in children, and severe liver disease

4.7.13 Mirtazapine

Pharmacodynamic properties	Tetracyclic antidepressant; the mechanism of action, as with other drugs effective in the treatment of MDD, is unknown Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2-adrenergic inhibitory autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity. Mirtazapine is a potent antagonist of 5-HT_2 and 5-HT_3 receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors Mirtazapine is a potent antagonist of histamine H_1 receptors, a property that may explain its prominent sedative effects Mirtazapine is a moderate peripheral α_1-adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anticholinergic side effects associated with its use
Pharmacokinetic properties	t_{max} 2 h, $t_{1/2}$ 20–40 h; protein binding ca. 85 %, bioavailability 50 %
	Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. In vitro data from human liver microsomes indicate that CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A is considered to be responsible for the formation of the *N*-desmethyl and *N*-oxide metabolite. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels
Indications	**FDA approved** (USA) for the treatment of MDD in adults Approved in several **European countries** for the treatment of episodes of major depression Mirtazapine should not be used in children and adolescents under the age of 18 years as efficacy was not demonstrated in two short-term clinical trials and because of safety concerns
Dosage	The effective daily dose is usually between 15 and 45 mg; the starting dose is 15 or 30 mg In general, mirtazapine begins to take effect after 1–2 weeks of treatment. Treatment with adequate doses should result in a positive response within 2–4 weeks. With an insufficient response, the dose can be increased
ADRs	The most commonly reported ADRs, occurring in more than 5 % of patients treated with mirtazapine in randomized, placebo-controlled trials, are somnolence, sedation, dry mouth, increased weight, increase in appetite, dizziness, and fatigue **Bone marrow depression**, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment. Reversible agranulocytosis has been reported as a rare occurrence in clinical studies. In the postmarketing period of mirtazapine, very rare cases of agranulocytosis have been reported, mostly reversible, but in some cases fatal. Fatal cases mostly concerned patients with an age above 65. The physician should be **alert for symptoms** like fever, sore throat, stomatitis, or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken

Drug interactions	**Pharmacodynamic interactions** Mirtazapine may increase the sedating properties of **benzodiazepines** and other sedatives (notably most antipsychotics, antihistamine H_1 antagonists, opioids). Caution should be exercised when these medicinal products are prescribed together with mirtazapine Mirtazapine may increase the CNS depressant effect of **alcohol**. Patients should therefore be advised to avoid alcoholic beverages while taking mirtazapine Mirtazapine dosed at 30 mg once daily caused a small but significant increase in the international normalized ratio (INR) in subjects treated with **warfarin**. As at a higher dose of mirtazapine a more pronounced effect cannot be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine **Pharmacokinetic interactions** **Carbamazepine and phenytoin**, CYP3A4 inducers, increased mirtazapine clearance about twofold, resulting in a decrease in average plasma mirtazapine concentration of 60 and 45 %, respectively. When carbamazepine or any other inducer of hepatic metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the mirtazapine dose Coadministration of the potent CYP3A4 inhibitor **ketoconazole** increased the c_{max} and the AUC of mirtazapine by approximately 40 and 50 %, respectively When **cimetidine** (weak inhibitor of CYP1A2, CYP2D6, and CYP3A4) is administered with mirtazapine, the mean plasma concentration of mirtazapine may increase more than 50 %. Caution should be exercised, and the dose may have to be decreased when coadministering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine, or nefazodone Interaction studies did not indicate any relevant pharmacokinetic effects on concurrent treatment of mirtazapine with paroxetine, amitriptyline, risperidone, or lithium preparations
Contraindications	Hypersensitivity to the active substance or to any of the excipients and concomitant use of mirtazapine with nonselective MAO inhibitors Limited data of the use in **pregnant women** do not indicate an increased risk for congenital malformations. Studies in animals have not shown any teratogenic effects of clinical relevance; however, developmental toxicity has been observed. Caution should be exercised when prescribing to pregnant women. If mirtazapine is used until, or shortly before, birth, postnatal monitoring of the newborn is recommended to account for possible discontinuation effects Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the **risk of persistent pulmonary hypertension** in the newborn (PPHN). Although no studies have investigated the association of PPHN to mirtazapine treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in 5-HT concentrations) Animal studies and limited human data have shown excretion of mirtazapine in breast milk only in very small amounts. A decision on whether to continue/discontinue **breast-feeding** or to continue/discontinue therapy with mirtazapine should be made taking into account the benefit of breast-feeding to the child and the benefit of mirtazapine therapy to the woman

4.7.14 Moclobemide

Pharmacodynamic properties	Short-acting selective, reversible MAO-A inhibitor that blocks the metabolism of noradrenaline and 5-HT; amplification of central effects of 5-HT and noradrenaline; no affinity for neurotransmitter receptors and reuptake sites
Pharmacokinetic properties	t_{max} 1 h, $t_{1/2}$ 0.5–3.5 h; protein binding around 50 %, bioavailability 55 % (after single dose), 90 % (after multiple doses) Extensive metabolism, largely via oxidative reaction on the morpholine moiety of the molecule. Active metabolites recovered in vitro or in animal experiments are present only at very low concentrations in the systemic circulation Because it is partly metabolized by CYP2C19 and CYP2D6, blood levels of the drug can be affected in patients with genetically or drug-induced poor metabolism. Approximately 2 % of the Caucasian population and 15 % of the Asian population can be genetically phenotyped as **slow metabolizers** with respect to oxidative hepatic metabolism. It has been found that the AUC measurement in slow metabolizer subjects was approximately 1.5 times greater than in extensive metabolizer subjects for the same dose of moclobemide. This increase is within the normal range of variation (up to two times) typically seen in patients
Indications	Not labeled in the USA by the FDA. **Approved** in several **European countries** for the symptomatic relief of depressive illness The safety and efficacy has not been established in the pediatric population; therefore, its use is not recommended
Dosage	The administration of moclobemide should be initiated at 300 mg daily dose (in 2 divided doses) and increased gradually to a maximum of 600 mg/day if needed, carefully considering the clinical response and any evidence of intolerance. Individual patient response may allow for a reduction of the daily dose. As with other antidepressants, it should be kept in mind that there may be a lag time in therapeutic response
ADRs	Some of the most common ADRs (>1 %) which may occur include insomnia, dizziness, nausea, headaches, fatigue, orthostatic hypotonia, dry mouth, disturbed vision or paresthesias, hypersensitivity reactions, vertigo, excitement, inner restlessness, sweating, increase/loss of appetite, increased prolactin, or liver enzyme levels

Drug interactions	**Cimetidine** Cimetidine doubles the AUC of moclobemide and is expected to approximately double its steady-state concentrations. In patients receiving moclobemide concomitantly with cimetidine, a 50 % reduction in the dosage of moclobemide may be necessary **Tyramine** Studies conducted at the maximum recommended dose of 600 mg/day demonstrated that the mean dose of tyramine required to produce a 30 mmHg increase in systolic blood pressure: 148 ± 50 mg (76–200 mg) when moclobemide was administered immediately after tyramine. The threshold dose of tyramine was reduced to 84 ± 23 mg (54–112 mg) when the sequence of administration was reversed so that moclobemide was administered 1 h before tyramine. These findings indicate that the potentiation of tyramine may be minimized by administering moclobemide after, instead of prior to, a tyramine-enriched meal. There is limited experience in patients who took moclobemide before meals. Most clinical trial protocols specified that the drug be taken immediately after meals. Therefore, patients should be instructed to **take moclobemide** immediately **after meals** **Alcohol** Excessive consumption should be avoided. Alcohol interaction studies were performed at blood alcohol concentrations of 0.05 %. However, no studies were conducted at blood alcohol concentrations recognized as legally intoxicating **Sympathomimetics** Following multiple oral doses of moclobemide (total dose: 600 mg/day), a phenylephrine-induced increase in systolic blood pressure was potentiated (1.6 times) after intravenous administration. Patients should be advised to **avoid** the concomitant use of **sympathomimetic amines** (e.g., amphetamine- and ephedrine-like compounds contained in many proprietary cold, hay fever, or weight-reducing preparations), until further studies have been conducted Treatment with moclobemide does not necessitate special dietary restrictions. In clinical studies, it was demonstrated that up to 100 mg tyramine can be ingested safely during treatment with moclobemide 600 mg/day when it was given after meals. This amount of tyramine, 100 mg, corresponds to 1,000–2,000 g mild or 200 g strong cheese or to 70 g marmite yeast extract. As a safety measure, patients should be urged to report immediately the abrupt occurrence of any of the following symptoms: occipital headache, palpitations, neck stiffness, tachycardia or bradycardia, or other atypical or unusual symptoms not previously experienced Clinical interaction studies resulted in severe ADRs when moclobemide was coadministered with TCAs, SSRIs, nonselective MAO inhibitors, selective MAO-B inhibitors, meperidine, and thioridazine. Therefore, the concomitant use with these drugs is contraindicated There is no experience regarding the coadministration of moclobemide and buspirone or antipsychotics. Therefore, patients should be carefully monitored should concomitant administration be implemented
Contraindications	Patients with a known hypersensitivity to moclobemide or any compound of the product; patients in an acute confusional state; the combination with TCAs, SSRIs, nonselective MAO inhibitors, selective MAO-B inhibitors, meperidine, and thioridazine

4.7.15 Paroxetine

Pharmacodynamic properties	SSRI. The efficacy in the treatment of MDD, social anxiety disorder, OCD, panic disorder, generalized anxiety disorder, and post-traumatic stress disorder is presumed to be linked to potentiation of serotonergic activity in the CNS resulting from inhibition of neuronal reuptake of 5-HT Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of 5-HT into human platelets. In vitro studies in animals also suggest that it is a potent and highly selective inhibitor of neuronal 5-HT reuptake and has only very weak effects on noradrenaline and dopamine neuronal reuptake. In vitro radioligand binding studies indicate that paroxetine has little affinity for muscarinic, α_1, α_2, and β-adrenergic, dopamine (D_2), 5-HT_1, 5-HT_2, and histamine (H_1) receptors; antagonism of muscarinic, histaminergic, and α_1-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs
Pharmacokinetic properties	Mean t_{max} 5.2 h, mean $t_{1/2}$ 21 h; protein binding 93–95 %, bioavailability >90 % Paroxetine is extensively metabolized, and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part by CYP2D6
Indications	**FDA approved** (USA) in adults for: Acute and maintenance treatment of MDD Acute and maintenance treatment of OCD Acute treatment of panic disorder, with or without agoraphobia Social anxiety disorders (social phobia) Generalized anxiety disorder Post-traumatic stress disorder Safety and effectiveness in the pediatric population have not been established. Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with paroxetine, and the data were not sufficient to support a claim for use in pediatric patients **Approved in European countries** for the treatment of adults with: Major depressive episode OCD Panic disorder, with or without agoraphobia Social anxiety disorder (social phobia) Generalized anxiety disorder Post-traumatic stress disorder Paroxetine should not be used for the treatment of children and adolescents as controlled clinical trials have found paroxetine to be associated with increased risk for suicidal behavior and hostility. In addition, in these trials, efficacy has not been adequately demonstrated

Dosage	**MDD** The recommended initial, single dose is 20 mg/day, usually administered in the morning. As with all drugs effective in the treatment of MDD, the full effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week It is generally agreed that acute episodes of MDD require several months or longer of sustained pharmacological therapy. Whether or not the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown. Systematic evaluation of the efficacy of paroxetine has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg **OCD** The recommended, single dose in the treatment of OCD is 40 mg daily, usually administered in the morning. Patients should be started on 20 mg/day, and the dose can be increased in 10 mg/day increments. Dose changes should occur at intervals of at least 1 week. Patients were dosed in a range of 20–60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine in the treatment of OCD. The maximum dosage should not exceed 60 mg/day OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment **Panic disorder** The target dose is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10–60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine. The maximum dosage should not exceed 60 mg/day Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment **Social anxiety disorder** The recommended and initial dosage is 20 mg/day. In clinical trials, the effectiveness of paroxetine was demonstrated in patients dosed in a range of 20–60 mg/day Social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment **Generalized anxiety disorder** In clinical trials, the effectiveness was demonstrated in patients dosed in a range of 20–50 mg/day. The recommended starting dosage and the established effective dosage is 20 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week **Post-traumatic stress disorder** The recommended starting dosage and the established effective dosage is 20 mg/day. In one clinical trial, the effectiveness of paroxetine was demonstrated in patients dosed in a range of 20–50 mg/day. However, in a fixed dose study, there was no sufficient evidence to suggest a greater benefit for a dose of 40 mg/day compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at intervals of at least 1 week

ADRs	Common to all SSRIs: gastrointestinal disturbances, anxiety, sexual dysfunctions, impaired cognition, and the possibility of the **5-HT syndrome** onset with symptoms ranging from mild (increased heart rate, sweating, and over-response reflexes) to moderate (hypertension, hyperthermia, and agitation) to severe (large increases in heart rate and blood pressure, rhabdomyolysis, seizures, and disseminated intravascular coagulation) In placebo-controlled clinical trials conducted with **pediatric patients**, the following ADRs were reported in at least 2 % of pediatric patients treated with paroxetine and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation Decreased appetite and weight loss have been observed in association with the use of SSRIs. Consequently, **regular monitoring** of weight and growth should be performed in children and adolescents treated with an SSRI such as paroxetine **Events** reported **upon discontinuation of treatment** with paroxetine in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2 % of patients who received paroxetine and which occurred at a rate at least twice that of placebo, were emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain
Drug interactions	Common to all SSRIs: see Sects. 4.7.3 and 4.7.8 Clinical drug interaction studies showed that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine If concomitant use of paroxetine with certain other serotonergic drugs, i.e., triptans, TCAs, fentanyl, lithium salts, tramadol, buspirone, tryptophan, and St. John's wort, is clinically warranted, be aware of a potentially higher risk for 5-HT syndrome
Contraindications	The concomitant use with nonselective MAO inhibitors, thioridazine, and pimozide. In patients with a hypersensitivity to paroxetine or any of the inactive ingredients Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of **pregnancy** have an increased risk of congenital malformations, particularly cardiovascular malformations. When treating a pregnant woman with paroxetine, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when paroxetine is administered to a **nursing woman**

4.7.16 Reboxetine

Pharmacodynamic properties	Selective noradrenaline reuptake inhibitor, amplification of central effects of noradrenaline In vitro studies have shown that it has no significant affinity for adrenergic (α_1, α_2, β) and muscarinic receptors; antagonism of such receptors is associated with cardiovascular, anticholinergic, and sedative ADRs of other antidepressant drugs
Pharmacokinetic properties	t_{max} 2 h, $t_{1/2}$ ca. 13 h; protein binding 97 %, bioavailability 60 % Reboxetine is predominantly metabolized in vitro via cytochrome CYP3A4. Reboxetine inhibits both CYP2D6 and CYP3A4 with low binding affinities but has shown no effect on the in vivo clearance of drugs metabolized by these enzymes
Indications	Not labeled by the FDA in the USA Approved in **European countries** for the acute treatment of depressive illness/major depression and for maintaining the clinical improvement in patients initially responding to treatment in adults There are no data available on the use of reboxetine in children. It should not be used in the treatment of children and adolescents under the age of 18 years
Dosage	The recommended therapeutic dose is 4 mg twice a day, i.e., 8 mg/day administered orally. The full therapeutic dose can be given upon starting treatment. After 3–4 weeks, this dose can be increased to 10 mg/day in case of incomplete clinical response. The maximum daily dose should not exceed 12 mg. The minimum effective dose has not yet been established

ADRs	Very common ADRs (≥ 1/10) include dry mouth, constipation, nausea, and hyperhidrosis. Common ADRs (≥1/100 to <1/10) include decreased appetite, agitation, anxiety, headache, dizziness, paresthesia, akathisia, dysgeusia, accommodation disorder, tachycardia, palpitations, vasodilatation, hypotension, hypertension, rash, sensation of incomplete bladder emptying, urinary tract infection, dysuria, urinary retention, erectile dysfunction, ejaculatory pain, ejaculatory delay, and chills
Drug interactions	In vitro metabolism studies indicate that reboxetine is primarily metabolized by CYP3A4. Therefore, potent inhibitors of CYP3A4 (ketoconazole, nefazodone, erythromycin, and fluvoxamine) would be expected to increase plasma concentrations of reboxetine. In a study in healthy volunteers, ketoconazole, a potent inhibitor of CYP3A4, was found to increase plasma concentrations of the reboxetine enantiomers by approximately 50 %. Because of reboxetine's narrow therapeutic margin, inhibition of elimination is a major concern. Therefore, it should **not be given together with** drugs known to inhibit CYP3A4 such as **azole antifungal agents**, **macrolide antibiotics** such as erythromycin, or **fluvoxamine** Low reboxetine serum levels have been reported with the concurrent administration of CYP3A4 inducers such as phenobarbital and carbamazepine. Examples of other CYP3A4 inducers that may reduce the serum levels of reboxetine include but are not limited to phenytoin, rifampicin, and St. John's wort Reboxetine does not appear to potentiate the effect of **alcohol** on cognitive functions in healthy volunteers Concomitant use of **MAO inhibitors** including linezolid (an antibiotic which is a reversible nonselective MAO inhibitors) and methylene blue and reboxetine should be avoided in view of the potential risk (**tyramine-like effect**) based on their mechanisms of action Although data are not available from clinical studies, the possibility of hypokalemia with concomitant use of potassium-losing diuretics should be considered
Contraindications	Known hypersensitivity to reboxetine or any of the components of the product No clinical trial data on exposure to reboxetine during **pregnancy** are available. However, postmarketing safety data on a very limited number of exposed pregnancies indicate no adverse effects on pregnancy or on the health of the fetus/newborn child. Animal studies in general do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, or parturition. Some impairment of growth and development has been noted in rat neonates. Therefore, reboxetine should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing fetus Reboxetine is excreted in breast milk. The level of active substance transferred in breast milk is anticipated to be very low; however, there is insufficient information to exclude a risk to the nursing infant. The use of reboxetine during **breast-feeding** can be considered if the potential benefits outweigh the risk for the child

4.7.17 Sertraline

Pharmacodynamic properties	SSRI. The mechanism of action is presumed to be linked to its inhibition of CNS neuronal uptake of 5-HT. Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of 5-HT into human platelets. In vitro studies in animals also suggest that it is a potent and selective inhibitor of neuronal 5-HT reuptake and has only very weak effects on noradrenaline and dopamine neuronal reuptake In vitro studies have shown that sertraline has no significant affinity for adrenergic (α_1, α_2, β), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT_2), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain noradrenaline receptors, as has been observed with other drugs effective in the treatment of MDD. It does not inhibit MAO

Pharmacokinetic properties	t_{max} 4.5–8.4 h, $t_{1/2}$ ca. 26 h; protein binding 98 %, bioavailability 70 % Relative to the adults, both the 6–12-year-olds and the 13–17-year-olds showed about 22 % lower AUC (0–24 h) and c_{max} values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid excessive plasma levels Sertraline undergoes extensive first-pass metabolism. The principal initial pathway of metabolism is *N*-demethylation. In vitro studies have found that multiple CYP isoforms can demethylate sertraline: CYP2D6, CYP2C9, CYP2B6, CYP2C19, and CYP3A4; however, in vivo studies in humans have not yet clearly defined the matter. *N*-Desmethylsertraline has a plasma terminal $t_{1/2}$ of 62–104 h. Both in vitro biochemical and in vivo pharmacological testing have shown *N*-desmethylsertraline to be substantially less active than sertraline
Indications	**FDA approved** (USA) in adults for: Acute and maintenance treatment of MDD Acute and maintenance treatment of OCD in adults and pediatric patients aged 6–17 years Acute and maintenance of panic disorder, with or without agoraphobia, in adults Post-traumatic stress disorder Premenstrual dysphoric disorder in adults Social anxiety disorder in adults Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established. Two placebo-controlled trials ($n=373$) in pediatric patients with MDD have been conducted with sertraline, and the data were not sufficient to support a claim for use in pediatric patients Sertraline is approved for the treatment of depression; in addition, it is approved in some **European countries** for the treatment of social anxiety disorder, panic disorder (with or without agoraphobia disorder), post-traumatic stress disorder, and OCD. In some European countries, OCD is also indicated in children and adolescents (aged 6–17 years)
Dosage	**Dosage for children and adolescents with OCD** Treatment should be initiated with a dose of 25 mg once daily (either in the morning or evening) in children (aged 6–12 years) and at a dose of 50 mg once daily in adolescents (aged 13–17 years) While a relationship between dose and effect has not been established for OCD, patients were dosed in a range of 25–200 mg/day in the clinical trials demonstrating the effectiveness of sertraline for pediatric patients (6–17 years) with OCD. Patients not responding to an initial dose of 25 or 50 mg/day may benefit from dose increases up to a maximum of 200 mg/day. For children with OCD, their generally lower body weights compared to adults should be taken into consideration in advancing the dose in order to avoid excess dosing. Given the 24 h $t_{1/2}$ of sertraline, dose changes should not occur at intervals of less than 1 week **Dosage for adults** MDD and OCD. Sertraline should be administered initially at a dose of 50 mg once daily Post-traumatic stress disorder and social anxiety disorder: initiation with a dose of 25 mg once daily. After 1 week, the dose should be increased to 50 mg once daily While a relationship between dose and effect has not been established for MDD, OCD, panic disorder, post-traumatic stress disorder, or social anxiety disorder, patients were dosed in a range of 50–200 mg/day in the clinical trials demonstrating the effectiveness of sertraline for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 h $t_{1/2}$ of sertraline, dose changes should not occur at intervals of less than 1 week

ADRs	Common to all SSRIs: gastrointestinal disturbances, anxiety, sexual dysfunctions, impaired cognition, and the possibility of the **5-HT syndrome** onset with symptoms ranging from mild (increased heart rate, sweating, and over-response reflexes) to moderate (hypertension, hyperthermia, and agitation) to sever (large increases in heart rate and blood pressure, rhabdomyolysis, seizures, and disseminated intravascular coagulation) Significant **weight loss** may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1–2 pound weight loss versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss During marketing of sertraline and other SSRIs and SNRIs, there have been spontaneous reports of ADRs occurring upon **discontinuation** of these drugs, particularly when abrupt, including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms
Drug interactions	Common to all SSRIs: see Tables 4.7.3 and 4.7.8 Clinical drug interaction studies showed that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including other SSRIs and TCAs If concomitant use of sertraline with certain other serotonergic drugs, i.e., triptans, TCA, fentanyl, lithium salts, tramadol, buspirone, tryptophan, and St. John's wort, is clinically warranted, be aware of the potentially increased risk for 5-HT syndrome Because sertraline is tightly bound to plasma protein, the administration to a patient taking another drug, tightly bound to protein (e.g., warfarin, digitoxin), may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound sertraline by other tightly bound drugs
Contraindications	The concomitant use with nonselective MAO inhibitors and pimozide in patients with a hypersensitivity to sertraline or any of the inactive ingredients Infants exposed to SSRIs in **pregnancy** may have an increased risk for **persistent pulmonary hypertension of the newborn** (PPHN). PPHN occurs in 1–2/1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiological studies suggest a positive statistical association between SSRI use (including sertraline) in pregnancy and PPHN. Other studies do not show any association. Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of MDD, who either were on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their MDD compared to those women who remained on antidepressant medication throughout pregnancy It is not known whether, and if so to what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sertraline is administered to a **nursing woman**

4.7.18 Venlafaxine

Pharmacodynamic properties	SNRI. The mechanism of the antidepressant action is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, *O*-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal 5-HT and noradrenaline reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α_1-adrenergic receptors in vitro. Pharmacological activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess MAO inhibitory activity and have virtually no affinity for opiate of benzodiazepine-sensitive receptors

Pharmacokinetic properties	Mean t_{max} 2 h (immediate release), mean t_{max} 5.5 h (extended-release capsules); mean $t_{1/2}$ 5 h (venlafaxine), mean $t_{1/2}$ 11 h (ODV), protein binding 27 %, bioavailability 40–45 %; metabolism by CYP3A3/4, CYP2C9, CYP2C19 and CYP2D6
	Venlafaxine undergoes extensive hepatic metabolism. In vitro and in vivo studies indicate that it is biotransformed to its major active metabolite, ODV, by CYP2D6. In vitro and in vivo studies indicate that venlafaxine is metabolized to a minor, less active metabolite, *N*-desmethylvenlafaxine, by CYP3A4. In vitro and in vivo studies indicate that it is a weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9 or CYP3A4
	Patients with low CYP2D6 levels ("**poor metabolizers**") had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 (extensive metabolizers). The differences between the CYP2D6 poor and extensive metabolizers, however, are not expected to be clinically important because the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equiactive and equipotent
Indications	**Approved by FDA** (USA) and in **European countries** in adults for:
	Acute and maintenance treatment of MDD
	Acute and maintenance treatment of generalized anxiety disorder
	Treatment of social anxiety disorder (social phobia)
	Panic disorder
	Safety and effectiveness in the pediatric population have not been established. Two placebo-controlled trials in 766 pediatric patients with MDD and two placebo-controlled trials in 793 pediatric patients with generalized anxiety disorder have been conducted with extended-release capsules of venlafaxine, and the data were not sufficient to support a claim for use in pediatric patients
Dosage	**MDD**
	The recommended starting dose for prolonged-release venlafaxine is 75 mg given once daily. Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 375 mg/day. Dosage increases can be made at intervals of 2 weeks or more. If clinically warranted due to symptom severity, dose increases can be made at more frequent intervals, but not less than 4 days
	Antidepressive medicinal products should continue for at least 6 months following remission
	Generalized anxiety disorder
	The recommended starting dose for prolonged-release venlafaxine is 75 mg given once daily. Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 225 mg/day. Dosage increases can be made at intervals of 2 weeks or more
	Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly, on a case-by-case basis
	Social anxiety disorder
	The recommended dose for prolonged-release venlafaxine is 75 mg given once daily. There is no evidence that higher doses confer any additional benefit
	However, in individual patients not responding to the initial 75 mg/day, increases up to a maximum dose of 225 mg/day may be considered. Dosage increases can be made at intervals of 2 weeks or more
	Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly, on a case-by-case basis
	Panic disorder
	It is recommended that a dose of 37.5 mg/day of prolonged-release venlafaxine be used for 7 days. Dosage should then be increased to 75 mg/day. Patients not responding to the 75 mg/day dose may benefit from dose increases up to a maximum dose of 225 mg/day. Dosage increases can be made at intervals of 2 weeks or more
	Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly, on a case-by-case basis

ADRs	The most commonly (>1/10) reported ADRs in clinical studies were nausea, dry mouth, headache, and sweating (including night sweats)
	Other common ADRs (≥1/100 to <1/10) include sleep disturbance, increased nervousness, agitation, gastrointestinal complaints (including obstipation), increased blood pressure, tachycardia and orthostatic hypotonia, hypertonia, altered liver function, appetite disturbances, hyponatremia, elevated prolactin and cholesterol levels, extrapyramidal motor reactions, visual disturbances, paresthesias, trembling, and exanthemata
	In general, the ADR profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (aged 6–17 years) was similar to that seen for adults. As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed. Particularly, the following ADRs were observed in **pediatric patients**: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia
	Although no studies have been designed to primarily assess the impact of venlafaxine on growth, development, and maturation of children and adolescents, the studies that have been done suggest that it may adversely **affect weight and height**. Should the decision be made to treat a pediatric patient with venlafaxine, regular monitoring of weight and height is recommended during treatment, particularly if it is to be continued long term
	Dose-related **increases** in **blood pressure** have been commonly reported. In some cases, severely elevated blood pressure requiring immediate treatment has been reported in postmarketing experience. All patients should be carefully screened for high blood pressure, and preexisting hypertension should be controlled before initiation of treatment. Blood pressure should be reviewed periodically, after initiation of treatment and after dose increases. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g., those with impaired cardiac function
Drug interactions	**Effect of venlafaxine on other drugs**
	Clinical interaction studies resulted in severe ADRs when venlafaxine was coadministered with nonselective MAO inhibitors. Therefore, the concomitant use of moclobemide 5-HT is contraindicated
	As with other serotonergic agents, the **5-HT syndrome**, a potentially life-threatening condition, may occur, particularly with concomitant use of other agents that may affect the 5-HT neurotransmitter system (including triptans, SSRIs, SNRIs, lithium salts, sibutramine, tramadol, or St. John's wort), with medicinal agents that impair metabolism of 5-HT (such as MAO inhibitors) or with 5-HT precursors (such as tryptophan supplements). If concomitant treatment with venlafaxine and an SSRI, an SNRI, or a 5-HT receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use with 5-HT precursors (such as tryptophan supplements) is not recommended
	The risk of using venlafaxine in combination with other **CNS-active substances** has not been systematically evaluated. Consequently, caution is advised when it is taken in combination with other CNS-active substances
	Effect of other medicinal products on venlafaxine
	Concomitant use of **CYP3A4 inhibitors** (e.g., atazanavir, clarithromycin, indinavir, itraconazole, voriconazole, posaconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin) and venlafaxine may increase levels of venlafaxine and ODV. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly
	A pharmacokinetic study with haloperidol has shown a 42 % decrease in total oral clearance, a 70 % increase in AUC, and an 88 % increase in c_{max}, but no change in $t_{1/2}$ for **haloperidol**. This should be taken into account in patients treated with haloperidol and venlafaxine concomitantly. The clinical significance of this interaction is unknown
	Venlafaxine increased the **risperidone** AUC by 50 % but did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). The clinical significance of this interaction is unknown

Contraindications	The concomitant use with nonselective MAO inhibitors. Venlafaxine must be discontinued for at least 7 days before starting treatment with an irreversible MAO inhibitor
	In patients with a hypersensitivity to venlafaxine or any of the inactive ingredients
	Neonates exposed to venlafaxine, other SNRIs, or SSRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with the 5-HT syndrome. When treating a **pregnant woman** with venlafaxine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment
	Venlafaxine and ODV are excreted in human milk. Because of the potential for serious ADRs in **nursing infants**, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

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Antipsychotics

5

Manfred Gerlach, Claudia Mehler-Wex,
and Benno G. Schimmelmann

Contents

M. Gerlach, PhD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Laboratory for Clinical Neurobiology and Therapeutic Drug Monitoring, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: manfred.gerlach@uni-wuerzburg.de

C. Mehler-Wex, MD
Department of Child and Adolescent Psychiatry and Psychotherapy, University of Ulm, Steinhövelstr. 5, 89075 Ulm, Germany

HEMERA-Klinik, Schönbornstr. 16, 97688 Bad Kissingen, Germany
e-mail: mehler-wex@hemera.de

B.G. Schimmelmann, MD
University Hospital of Child and Adolescent Psychiatry, University of Bern, Bolligenstr. 111, 3000 Bern, Switzerland
e-mail: benno.schimmelmann@gef.be.ch

5.1 Definition

Antipsychotics (previous name neuroleptics) are psychopharmacological agents employed primarily in the treatment of schizophrenia spectrum disorders, psychotic symptoms in other disorders (including affective and organic disorders), and mania. However, antipsychotics are also used in the treatment of children and adolescents with tic disorders, irritability, agitation, and aggression associated with autistic disorder and other pervasive developmental disorders, as well as in youths with disruptive behavior disorders

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with and without mental retardation (mostly off-label use, see Sect. 2.1.2).

Until the middle of the twentieth century, there were few options to treat most psychiatric disorders, particularly schizophrenia. It was only following the discovery of chlorpromazine's psychoactive effects by accident in 1952 that fundamental advances in the treatment of psychiatric patients were achieved (including reduction of the need for coercive measures, simplification of care and accommodation, reduction of the length of hospital treatment, facilitation of reintegration into society). In addition, this discovery also led to further research that resulted in the initiation of psychopharmacology as a discipline.

5.2 Classification

The history of antipsychotic drug therapy has been described in detail elsewhere (Lopez-Munoz et al. 2005). Here, we will briefly focus on the conceptualization of chlorpromazine's actions (Carpenter and Davis 2012) that finally result in the classification of antipsychotics as well as anxiolytics and sedative-hypnotics (see Chap. 6). The **initial conceptualization** of chlorpromazine's action focused on its so-called tranquilization effect and antianxiety and anti-aggressive effects. Meprobamate was introduced in 1955 and had antianxiety properties, but it was found out soon that it was ineffective in schizophrenia. This led to the conceptualization of **major tranquilizers** and minor tranquilizers. The major tranquilizer concept suggested that therapeutic success was based on calming the patient with a reduction of aggression, agitation, violence, and anxiety and led to the use of major tranquilizers in a broad range of conditions where "minor tranquilizers" such as meprobamate or barbiturates were not adequate. Recognizing that the primary effect was reduction of psychotic symptoms not secondary to anxiety reduction resulted in a more focused application in schizophrenia and in the use of the term "antipsychotic."

The discovery of the therapeutic properties of chlorpromazine was soon followed by the description of its tendency to produce extrapyramidal motor adverse drug reactions (ADRs) including acute dystonic reactions, akathisia, parkinsonism virtually indistinguishable from classical Parkinson's disease, and tardive dyskinesia which tends to occur after months to years of use of antipsychotic drugs.

Once chlorpromazine was observed to be an effective antipsychotic agent, it was tested preclinically to uncover its mechanism of antipsychotic action. Early in the testing process, chlorpromazine and other antipsychotic agents were all found to cause neurolepsis, known as an extreme slowness or absence of motor movement as well as behavioral indifference in experimental animals. The original antipsychotics were first discovered due to their ability to produce this effect in experimental animals, thus called **neuroleptics**, capturing both the tranquilization and the extrapyramidal motor ADRs. The term neuroleptic is derived from the Greek "νευρον" (neuron, originally meaning "sinew," but today refers to neurons) and "λαμβανω" (lambano for "take hold of") meaning "to seize the neuron." Until clozapine was approved for clinical use in the early 1970s, many members of the psychiatric community believed that a drug could not have any antipsychotic effect without producing extrapyramidal motor ADRs. It was claimed that the neuroleptic dose that produced minimal subclinical rigidity and hypokinesis (i.e., "the neuroleptic threshold") was the minimal dose necessary for a therapeutic antipsychotic effect (therefore the term typical neuroleptic) and that this effect manifested itself by micrographic handwriting changes (Haase 1954; Haase and Janssen 1965).

With the subsequent development of clozapine and other second-generation (atypical) antipsychotic drugs (e.g., amisulpride, olanzapine, quetiapine, risperidone), which possess reduced extrapyramidal motor ADRs, the term neuroleptics no longer correctly categorizes all agents with antipsychotic effects; therefore, the **term antipsychotics** is **more accurate** and will be used in this chapter.

From the **clinical viewpoint** and in particular in view of their differential therapeutic effects, the antipsychotics can be classified into:

- Low-potency antipsychotics
- Medium-potency antipsychotics
- High-potency antipsychotics

Table 5.1 shows a number of antipsychotics according to their neuroleptic potency, assessed as described above. **Chlorpromazine** serves as the **reference medication**, its neuroleptic potency being defined as 1.0. Extrapyramidal motor ADRs increase with rising neuroleptic potency of the typical first-generation antipsychotics, whereas the sedative and vegetative ADRs decrease; this applies only to lesser degree (or not at all) to second- and third-generation antipsychotics (see below). However, it has to be mentioned that individual response to antipsychotics can be very different. The antipsychotic effect is in principle the same; however, because of their vegetative ADRs, low-potency antipsychotics cannot be dosed high enough to achieve a full antipsychotic effect.

Table 5.1 Classification of antipsychotics according to antipsychotic potency

1. Low-potency antipsychotics
Amisulpride
Levomepromazine
Melperone
Promethazine
Sulpiride
Thioridazine
2. Medium-potency antipsychotics
Clopenthixol
Clozapine
Perazine
Ziprasidone
Zotepine
Zuclopenthixol
3. High-potency antipsychotics
Benperidol
Bromperidol
Flupentixol
Fluphenazine
Fluspirilene
Haloperidol
Olanzapine
Perphenazine
Pimozide
Risperidone

From Mutschler et al. (2008)

According to their preclinical neuroleptic properties and the frequency of extrapyramidal motor ADRs at therapeutic levels, antipsychotics are **broadly divided** into three groups:

- typical (classical, conventional) first-generation,
- atypical second-generation, and
- typical third-generation antipsychotics.

Typical antipsychotics include agents with a tricyclic structure (chlorpromazine, fluphenazine, flupentixol, levomepromazine, promethazine, thioridazine) as well as the butyrophenones (haloperidol, melperone) and diphenylbutylpiperidines (fluspirilen, pimozide) (Fig. 5.1).

The atypical antipsychotics include the more recent agents with a tricyclic chemical structure (clozapine, olanzapine, quetiapine), benzamide (amisulpride, sulpiride), benzisoxazole (risperidone), and benzisothiazole (iloperidone, ziprasidone) derivatives, as well as antipsychotics with other chemical structures (aripiprazole) (Fig. 5.2).

Atypical **second- and third-generation antipsychotics** are associated with less extrapyramidal motor ADRs and a lower liability for tardive dyskinesia. However, this advantage is minimized when typical antipsychotics are used in low to moderate doses and when anticholinergic drugs are co-administered. Atypical second- and third-generation antipsychotics were **believed to have a superior effect** on negative (e.g., lack of initiative, loss of interest) and cognitive symptoms of schizophrenia when compared to typical antipsychotics. However, this superiority is controversial and not clearly demonstrated in clinical studies (see Sect.. 5.4.2). Only amisulpride, clozapine, olanzapine, and risperidone were found to be better than typical first-generation antipsychotic drugs for overall efficacy, with small to medium effect sizes (definition see Sect. 1.1) in adult patients with chronic schizophrenia (Keefe et al. 2007; Leucht et al. 2009; Mishara and Goldberg 2004). However, except for clozapine and in part for olanzapine, this advantage has not been demonstrated in children and adolescents so far (Schimmelmann et al. 2013).

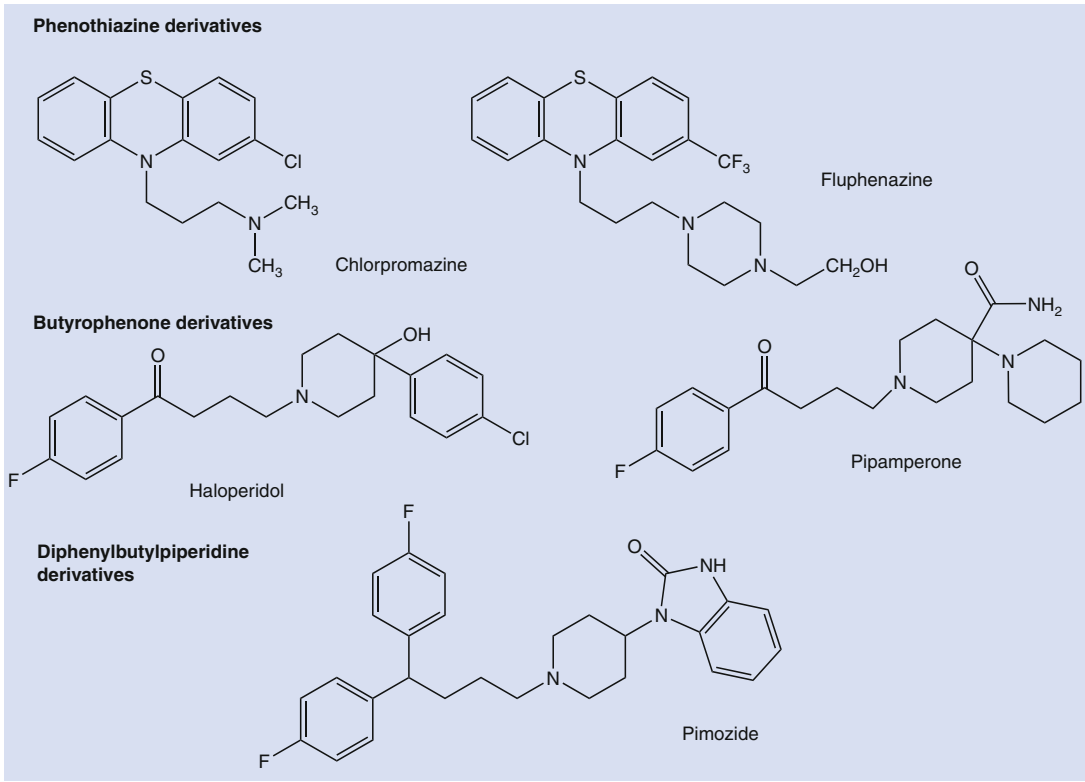

Fig. 5.1 Structural formulas of some first-generation antipsychotics

5.3 Mechanisms of Action

The pathogenesis of schizophrenic and other psychoses, like the mechanism of action of antipsychotics, has been only incompletely elucidated. Schizophrenia is a heterogeneous syndrome and the precise molecular pathology has not yet been established for any disease entity within the syndrome. A number of genetic and environmental factors (including maternal viral infections, complications during pregnancy or birth, cannabis use) that might be relevant to schizophrenia have been identified (Brown 2011; Gebicke-Haerter 2012; Khandaker et al. 2012). The neurodevelopmental hypothesis of schizophrenia (Marenco and Weinberger 2000) proposes that early-onset schizophrenia in particular (beginning in childhood or early adolescence) is the consequence of aberrant neurogenesis. This model is supported by numerous neurobiological abnormalities that are often more marked in younger than older patients, including brain atrophy, abnormal cortical cytoarchitecture, and neurotrophic factor deficits.

As described above, the earliest effective treatments for schizophrenia and other psychotic illnesses result from serendipitous clinical observations rather than from scientific knowledge of the neurobiological basis of psychosis or the mechanism of action of effective antipsychotic agents. The discovery of chlorpromazine's psychoactive effects led to further research and challenged basic scientists to determine the mechanism of action. Carlsson and Lindqvist (1963) found increased metabolites of dopamine and noradrenaline following low doses of chlorpromazine and haloperidol, respectively, in the mouse brain and suggested that this effect is induced by a compensatory activation of monoaminergic neurons after the blockade of monoaminergic receptors. This finding was the foundation of the **dopamine hypothesis** of schizophrenia, a hypothesis that provided the basis for the discovery of all antipsychotic agents approved for the treatment of schizophrenia during the past 60 years, and remains a basis for much schizophrenia research today.

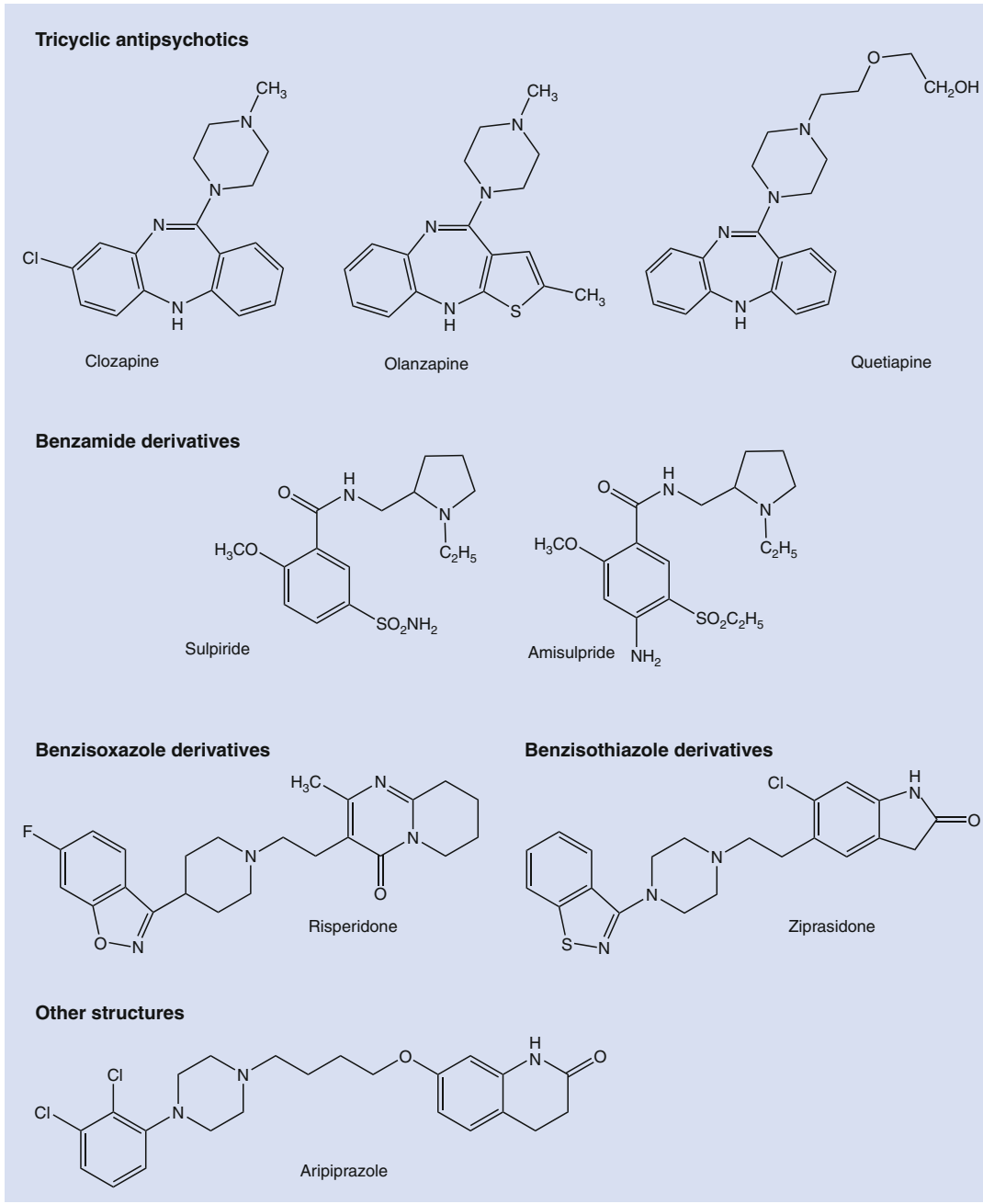

Fig. 5.2 Structural formulas of some second- and third-generation antipsychotics

Both postmortem and brain imaging investigations have provided indications that the mesolimbic **dopaminergic system** (see Sect. 1.3.2.1) is **overactive** in patients with a psychosis (see for a review: Carlsson 2006). The overactivity of this system has been associated with the positive symptoms of psychosis. High doses of dopaminomimetics, such as L-DOPA (the metabolic precursor of dopamine) and amphetamines (which release dopamine), can elicit a paranoid psychosis. In addition, systemic administration of dopamine-releasing psychostimulants such as amphetamine and methylphenidate prescribed to active schizophrenic patients may worsen the psychosis. However, other neurotransmitter systems that interact with dopaminergic transmission

(especially that of glutamate, in the context of a glutamate deficit, but also serotonergic and GABAergic systems) are also affected in patients with schizophrenia (Benes 2009).

Almost all **antipsychotics** are **antagonists of the dopamine D_2-receptor family** (molecular subtypes $D_{2–3}$; Tables 5.2 and 5.3). The role of neuroreceptors as biological targets of antipsychotics has been discussed in Sect. 1.3.2.1 and 1.4.2. It has been demonstrated in in vitro studies that there is a remarkable correlation between the ability of first-generation antipsychotics to block dopamine D_2 receptors and the dose used in treating patients with schizophrenia (Creese et al. 1976; Seeman and Lee 1975). In vitro studies also demonstrated that first-generation antipsychotics such as haloperidol bind tightly to the D_2-receptor family and dissociate slowly (Kapur and Seeman 2000). In contrast, second-generation antipsychotics have faster dissociation rates. Kapur and Seeman (2001) hypothesized that dissociation from the dopamine D_2 receptors quickly makes an antipsychotic agent more accommodating of physiological dopamine neurotransmission, permitting an antipsychotic effect without extrapyramidal motor ADRs and hyperprolactinemia as well as conferring benefits along a variety of clinical dimensions such as cognitive and secondary negative symptoms. However, this theory could not be confirmed by clinical studies

Table 5.2 Receptor binding affinities (nM) to dopamine receptor subtypes expressed as equilibrium constant (K_i) of haloperidol and atypical second-generation antipsychotics

Subtype	HAL	CLO	OLA	QUE	RIS	ZIP
D_1	210	85	31	460	430	525
D_2	1	160	44	580	2	4
D_3	2	170	50	940	10	7
D_4	3	50	40	1,900	10	32

Adapted from Tamminga (2006)
K_i the amount of the antipsychotic needed to block 50 % of the receptors in vitro. Therefore, a lower number denotes stronger affinity and binding to the respective receptor
CLO clozapine, *HAL* haloperidol, *OLA* olanzapine, *QUE* quetiapine, *RIS* risperidone, *ZIP* ziprasidone

Table 5.3 Receptor binding affinities (nM) expressed as equilibrium constant (K_i) of selected typical first-generation and atypical second-/third-generation antipsychotics

	Typical first-generation antipsychotics			Atypical second-/third-generation antipsychotics								
Receptor subtype	CPZ	HAL	PER	ARI	ASE	CLO	ILO	OLA	PALI	QUE	RIS	ZIP
D_2	2.0	2.6	1.4	0.66[a]	1.3	210	3.3	20	2.8	770	3.8	2.6
5-HT_{1A}	3,115	1,800	421	5.5[a]	2.5	160	33	610	480	300	190	1.9[a]
5-HT_{2A}	8.0	61	5	8.7	0.06	2.59	0.2	1.5	1.2	31	0.15	0.12
5-HT_{2c}	25.0	4,700	132	22	0.03	4.8	14	4.1	48	3,500	32	0.9
α_1	2.6	17	10	26	1.2	6.8	0.31	44	10	8.1	2.7	2.6
α_2	750	600	500	74	1.2	158	3	280	80	80	8	154
H_1	0.2	260	8	30	1.0	3.1	12.3	0.08	3.4	19	5.2	4.6
M_1	25.0	>10,000	1,500	6,780	8,128	1.4	4,898	2.5	>10,000	120	>10,000	300
M_2	150	>10,000	NA	3,510	NA	204	3,311	622	>10,000	630	>10,000	>3,000
M_3	67	>10,000	1,848	4,680	NA	109	>10,000	126	>10,000	1,320	>10,000	>1,300
M_4	40	>10,000	NA	1,520	NA	27	8,318	350	>10,000	660	>10,000	>1,600

Adapted from Correll (2011)
K_i, the amount of the antipsychotic needed to block 50 % of the receptors in vitro. Therefore, a lower number denotes stronger affinity and binding to the respective receptor
ARI aripiprazole, *ASE* asenapine, *CLO* clozapine, *CPZ* chlorpromazine, *HAL* haloperidol, *ILO* iloperidone, *OLA* olanzapine, *PALI* paliperidone, *PER* perphenazine, *QUE* quetiapine, *RIS* risperidone, *ZIP* ziprasidone, *NA* not assessed
α_1, α_2 subtypes of the adrenoceptor, D_2 molecular dopamine receptor subtype of the D_2-receptor family, H_1 histamine receptor subtype, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} subtypes of the serotonin receptor, $M_{1–4}$ molecular subtypes of muscarinic cholinoceptors
[a]Partial agonism

that do not clearly demonstrate a superiority of second- and third-generation antipsychotics on negative and cognitive symptoms of schizophrenia when compared with typical antipsychotics (Keefe et al. 2007; Leucht et al. 2009; Mishara and Goldberg 2004).

It is believed that through the blockade of dopamine D_2 receptors in the mesolimbic dopaminergic system, the effects of overactive dopaminergic neurons in the area tegmentalis ventralis are dampened and dopaminergic neurotransmission normalized. In contrast, antagonism of dopamine D_2 receptors in the striatum and the tuberoinfundibular areas, respectively, leads to the presentation of extrapyramidal motor ADRs, such as parkinsonism, akathisia, dystonia and tardive dyskinesia, and increased prolactin concentrations.

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging studies have demonstrated the importance of **dopamine D_2-receptor occupancy** as a **predictor of antipsychotic response** and the **occurrence of extrapyramidal motor ADRs** in schizophrenic patients (see Miyamoto et al. 2005; Seeman 2002 for a review). Such studies have shown that antipsychotic effects are associated with a striatal dopamine D_2-receptor occupancy of 65–70 % and that D_2-receptor occupancy greater than 80 % significantly increases the risks of extrapyramidal motor ADRs. Recent imaging studies have also revealed that therapeutic doses of first-generation antipsychotics produce high blockade of the dopamine D_2-receptor family equally in limbic cortical areas and the striatum (see Miyamoto et al. 2005). Thus, a threshold between 65 and 80 % occupancy seems to provide the therapeutic window to minimize the risk of extrapyramidal motor ADRs for first-generation antipsychotics. For second-generation antipsychotics a similar dopamine D_2-receptor occupancy was shown to be important for antipsychotic response and minimization of extrapyramidal motor ADRs. Clozapine and quetiapine, however, exhibited lower levels of dopamine D_2-receptor occupancy (less than 70 %) at therapeutically effective doses (Miyamoto et al. 2005), suggesting that a threshold level of D_2-receptor occupancy (and possibly antagonism) alone cannot fully explain the therapeutic efficacy.

In addition to the blockade of dopamine D_2 receptors, **second- and third-generation antipsychotics** have, in general, a **wide range of neuroreceptor effects**, including action at several adrenoceptors, muscarinic, histamine, and serotonin receptors (Table 5.3). It is hypothesized that the interaction with these neuroreceptors also contributes to their antipsychotic effects and their specific ADR profile. In particular, the antagonism of serotonin 5-HT_2 receptors is discussed to be associated with the superior responses to clozapine and the lower propensity to cause extrapyramidal motor ADRs for atypical antipsychotics. The sedative effect of some antipsychotics is believed to relate to the blockade of the histamine H_1 receptor.

Third-generation antipsychotics such as aripiprazole (approved for treatment of schizophrenia in Europe and the USA) and bifeprunox (which was under development as a treatment for schizophrenia, but in 2009 all development activities were stopped) differ from previously described first- and second-generation antipsychotics in that they act as **partial agonists/antagonists** at the D_2-receptor family (Lieberman 2004). Both agents are members of the pharmacological class of partial dopamine receptor agonists (for definition of partial agonists, see Sect. 1.4.2.1). Even at high concentrations they exert only a small agonist effect at the receptor, smaller than that of a (full) agonist. Partial agonists act in a dualistic manner, because they alter the concentration balance of inactive to active receptor. That is, they possess both agonist and antagonist properties: in the presence of concentrations of a full agonist that elicits a greater response than that of a partial agonist, the latter reduces the effect of the full agonist (partial antagonism); at low concentrations or the absence of a full agonist, a partial agonist acts, in contrast, as a receptor agonist. Partial dopamine receptor agonists should thus modulate not only the positive symptoms of schizophrenia, which are believed to be caused by excessive activity of the mesolimbic dopaminergic system, but also the negative symptoms, attributed to reduced activity of the mesocortical

dopaminergic system. However, this theory has not been confirmed by clinical studies that do not clearly demonstrate a superiority of aripiprazole on negative and cognitive symptoms of schizophrenia when compared with typical and atypical second-generation antipsychotics (see Sect. 5.4.2).

5.4 Clinical Psychopharmacology

5.4.1 Indications

Antipsychotics are used in the treatment of children and adolescent with a range of psychiatric conditions and symptoms, including:

- Schizophrenia
- Schizoaffective disorders, such as paranoid and paranoid-hallucinatory states as well as of chronic schizophrenia
- Acute psychotic syndrome
- Agitation
- Anxiety and stress-related states
- Insomnia
- Impulse control disorders
- Autoaggressive behavior
- Tic disorders
- Withdrawal syndromes (drugs of abuse, medications), alcoholic delirium
- Bipolar disorder

Table 5.4 summarizes US Food and Drug Administration (FDA)-approved indications of antipsychotics in children and adolescents. Although it has been shown that clozapine is superior to olanzapine in reducing psychosis cluster scores and negative symptoms (see Sect. 5.4.2), it is considered a second- or third-line option in the treatment of schizophrenia because of potentially severe ADRs, namely, the risk of agranulocytosis and a convulsant effect. According to the guidelines by the

Table 5.4 Pediatric indications of antipsychotics approved by the US Food and Drug Administration (FDA)

Medication	Approved indication	Age for which it is approved
Aripiprazole	Schizophrenia	13–17 years
	Bipolar I disorder	6–17 years
	Irritability/aggression associated with autistic disorder	6–17 years
Clozapine	None	
Haloperidol	Psychosis	≥3 years
	Tourette's disorder	≥3 years
	Hyperactivity, severe behavioral problems, and hyperexcitability	≥3 years
Olanzapine	Schizophrenia	13–17 years
	Manic or mixed episodes of bipolar I disorder	13–17 years
Paliperidone	Schizophrenia	13–17 years
Pimozide	Tourette's disorder	≥12 years
Quetiapine	Schizophrenia	13–17 years
	Short-term treatment of manic episodes of bipolar I disorder	13–17 years
	Adjunct to lithium and valproate for short-term treatment of manic episodes of bipolar I disorder	13–17 years
Risperidone	Schizophrenia	13–17 years
	Bipolar I disorder	6–17 years
	Irritability/aggression associated with autistic disorder[a]	6–17 years

[a]Interestingly, the European Medicines Agency (EMA) adopted the indication for risperidone for the use in autistic disorder as follows (EMEA/H/A-30/911): risperidone is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors require pharmacological treatment

American Academy of Child and Adolescent Psychiatry (AACAP), it is generally used only after therapeutic trials of at least two other antipsychotic medications: one or both of which should be an atypical agent (AACAP Official Action 2001).

High-potency antipsychotics have been increasingly employed "off-label" for the symptomatic treatment of clinical aggressive, autoaggressive, stressed, and agitated states (Table 5.5), because the regulatory drugs agencies do not consider aggressive behavior as a distinct disease and standardized clinical national and international guidelines are still controversial (Comai et al. 2012). In specific clinical situations these antipsychotics are also used at low doses, well below the antipsychotic threshold, in the treatment of anxiety and anxious-depressive states as well as for facilitating sleep (see Table 5.5). Medium-potency antipsychotics are chiefly used as adjuvant sedative agents or to assist with mild mental confusion. The antipsychotic efficacy of low-potency antipsychotics is smaller, but their sedative effect greater, so that they are used for sedative purposes or to reduce tension in various psychiatric disorders.

As described in Chap. 6, the current guidelines do not recommend low-potency antipsychotics for the pharmacological treatment of children and adolescents with anxiety disorders and second-generation antipsychotics such as quetiapine and olanzapine, which might be suitable for patients with comorbid insomnia, who can benefit from the primary action of these drugs as well as from the sedating effect.

5.4.2 Clinical Effects and Efficacy

The clinical and ADR profiles of antipsychotics derive from their affinities for different neurotransmitter receptors (Tables 5.2 and 5.3). As already mentioned, there is a relationship between the antipsychotic potency of antipsychotics, their in vitro and in vivo affinity for the dopamine D_2-receptor family, and the occurrence of extrapyramidal motor ADRs. The sedative effect of some antipsychotics is believed to be related to blockade of the histamine H_1 receptor.

Antipsychotics **cannot cure psychiatric disorders**, but modulate so-called target symptoms, such as hallucinations, delusions, ego disturbances, mania, impulsivity, aggression, or anxiety and stress states. These target symptoms ultimately determine the choice of antipsychotics.

Following administration of an antipsychotic drug, the first clinically evident effect is sedation, which is, however, particularly desirable in psychosis-related, acutely aggressive, or anxiety-tinged agitation states, in order to achieve rapid relief of tension or anxiety for the patient, with improved capacity for emotional distancing. The **antipsychotic efficacy** of the drug develops immediately or, more commonly, becomes clinically significant only **after a period of a few days to two weeks**. The reasons are not entirely known. As antipsychotics principally act via G protein-coupled receptors, the delayed onset of efficacy is perhaps best explainable by the induction of regulatory effects and functional changes via modulation of gene expression in target neurons (see Sect. 1.2.6).

The current evidence for the efficacy and safety of antipsychotics in the treatment of schizophrenia, bipolar disorders, and neuropsychiatric disorders, associated with aggression in children and adolescents, has been described in detail in various systematic reviews (Amor 2012; Correll et al. 2010, 2011; Fraguas et al. 2011; Goldstein et al. 2012; Liu et al. 2011; Masi and Liboni 2011; Nevels et al. 2010; Pringsheim and Gorman 2012; Seida et al. 2012). Clinical studies carried out to demonstrate the efficacy and safety of antipsychotics in children and adolescents with anxiety disorders and insomnia are discussed in Chap. 6.

Efficacy and Safety of First-Generation Antipsychotics Compared to Placebo

There have been only a few clinical studies of first-generation antipsychotics in children and adolescents that satisfy current scientific standards and no long-term studies that examine safety and long-term ADRs. Older, small, and underpowered active-controlled trials have examined efficacy of first-generation antipsychotics in the treatment of early-onset schizophrenia spectrum disorders.

Table 5.5 Psychiatric indications for antipsychotics and therapeutic recommendations for their use in children and adolescents

Indication	Appropriate antipsychotic
Alcoholic delirium (especially with high blood alcohol levels)	High-potency first-generation antipsychotics
	Haloperidol 5–10 mg i.v. can be repeated several times
Autoaggressive behavior with intellectual disability, autism, or developmental disorder	Good experience with long-term employment of risperidone 0.5–2 mg p.o. (at night)
	Also possible: quetiapine 50–300 mg, ziprasidone 20–60 mg
Delusional depression	Low dosage of high-potency first-, or second-generation antipsychotics
	Risperidone 0.5–2 mg p.o. evenings
Disorders of schizophrenic type	High-potency first-, or second-generation antipsychotics
	Acute treatment: haloperidol 5–10 mg i.v., olanzapine 10 mg i.m. or as orodispersible tablet
	Long-term treatment: second- and third-generation antipsychotics
Impulse control disorders (such as ADHD)	Sedative or second- and third-generation antipsychotics
	Longer-term therapy: risperidone 0.25–2 mg/day
Insomnia	Low-potency first-generation antipsychotics (for example, levomepromazine 25–50 mg p.o. at night)
Motor agitation, agitation states (destructive behavior that pose a potential threat to self or others, and refusal to accept medication)	Medium- to high-potency first- or second-generation antipsychotics or sedative antipsychotic agents
	Acute treatment: haloperidol 5–10 mg i.v., olanzapine 5–10 mg i.m., ziprasidone 10 mg i.m., levomepromazine 50 mg i.m.
Paranoid ideation in anorexia nervosa (distorted body schema perception, weight phobia, etc.)	Smaller open studies with positive findings regarding low dosages of second-generation antipsychotics, such as olanzapine 2.5–10 mg/day or quetiapine ca. 150–300 mg p.o. medium term
Phase prophylaxis	Quetiapine or olanzapine (low dosage)
Psychomotor tension (aggression, anxious restlessness)	Medium- to low-potency first-generation or sedative second-generation antipsychotics
	For example, levomepromazine up to 4×50 mg p.o.
Schizoaffective disorders	Second- and third-generation antipsychotics
Manic phases, manic disinhibition	Olanzapine (up to 20 mg p.o. at a time), quetiapine (increased by increments over several days to ca. ≥400 mg/day)
Tics (also: Tourette's syndrome) Stereotypies, dyskinesias, choreoathetotic movement disorders	Tiapride 150–300 mg/day p.o. (broken into 3 individual doses)
	Risperidone 0.5–3 mg/day (divided into 2–3 individual doses, gradually increasing dosage slowly)
Acute or chronic pain states	Low-potency first-generation antipsychotics (for serotoninergic effect)
	Levomepromazine, thioridazine p.o.
Uncontrolled urge to move and inner tension in anorexia nervosa	Low dose second- and third-generation antipsychotics or melperone 4×25 mg/day p.o.

ADHD attention deficit/hyperactivity disorder, *i.m.* intramuscular, *i.v.* intravenous, *p.o.* per os

A ten-week, double-blind, placebo-controlled, crossover design study, in which 12 children (age range 5.5–11.75 years) completed a two-week placebo baseline period followed by an eight-week double-blind treatment (placebo for four weeks followed by haloperidol 1.8 mg for four weeks, or alternatively haloperidol for four weeks followed by placebo for four weeks) revealed that **haloperidol** is superior to placebo in the reduction of target positive symptoms (Spencer et al. 1992). The ADRs from haloperidol use were mostly drowsiness, dizziness, and extrapyramidal motor ADRs as well as other motor abnormalities, including dystonic reactions, which were resolved with dosage titration. The efficacy of haloperidol was supported in a three-arm, parallel-group study that compared mean daily doses of loxitane (87.5 mg), haloperidol (9.8 mg), and placebo in 75 adolescents over a period of four weeks: both loxitane and haloperidol were shown to be superior to placebo (Pool et al. 1976).

In another study, 21 schizophrenic adolescents (mean age 15.5 years) who were administered **thiothixene** or **thioridazine** (mean daily dose 16.2 and 178 mg, respectively) were compared over a six-week duration (Realmuto et al. 1984). Only nine of 21 subjects responded to both treatments, although both resulted in high levels of sedation. As sedation necessitated dose reductions, which led to severely limited therapeutic responses, the authors concluded that high-potency antipsychotics might be preferable to more sedating low-potency drugs in this population.

All these studies found significant extrapyramidal motor symptoms affecting 70 % of those treated with haloperidol or loxitane and 50 % of those treated with thiothixene. Indeed, the increased likelihood to cause extrapyramidal motor ADRs has led to decreased use, especially for children and adolescents.

First-generation antipsychotics such as **haloperidol** have been used extensively to treat aggression in psychiatric patients although a systematic review of the pharmacotherapy for the treatment of aggressive behavior in general adult psychiatry demonstrated that there is weak evidence of efficacy for antipsychotic agents in the treatment of **aggression** (Goedhard et al. 2006). There is only one double-blind placebo-controlled study (Campbell et al. 1984) in 61 treatment-resistant, hospitalized children (age 5.2–12.9 years) with conduct disorder, showing the superiority of haloperidol (1.0–6.0 mg/day) to placebo in decreasing behavioral symptoms.

Tiapride is a selective antagonist of dopamine D_2 receptors with weak antipsychotic properties that is used commonly in Europe for the treatment of tics. However, it is not available in the USA. In a pair of six-week controlled studies enrolling 27 children with Tourette's syndrome, at doses ranging from 4 to 6 mg/kg/day, it was found that tiapride is superior to placebo and produces a 44 % decrease in videotaped tic counts (Eggers et al. 1988).

Efficacy and Safety of Second- and Third-Generation Antipsychotics Compared to Placebo

In contrast to first-generation antipsychotics, the **efficacy** of second- and third-generation antipsychotics is **well established** in children and adolescents with schizophrenia, bipolar I disorder, tic disorders, and irritability, agitation, and aggression associated with autistic disorder and other pervasive developmental disorders as well as in youths with disruptive behavior disorders with and without mental retardation. There are several randomized, placebo-controlled antipsychotic trials showing that aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone were superior to placebo in children and adolescents (see Amor 2012; Correll et al. 2010, 2011; Fraguas et al. 2011; Goldstein et al. 2012; Liu et al. 2011; Masi and Liboni 2011; Nevels et al. 2010; Pringsheim and Gorman 2012; Schimmelmann et al. 2013; Seida et al. 2012 for a review). These studies have been the basis for the FDA approval of the four most prescribed second-generation antipsychotics in children and adolescents (see Table 5.4).

Efficacy in Early-Onset Schizophrenia and Schizoaffective Disorders

In a six-week, international, multisite, placebo-controlled study ($N = 107–302$ per study), aripiprazole (10 or 30 mg/day), olanzapine (2.5–20 mg/day),

paliperidone (1.5, 3, or 6 mg/day, dependent on weight, and 6 or 12 mg/day, dependent on weight), quetiapine (400 or 800 mg/day), and risperidone (1–3 or 4–6 mg/day) were all superior to placebo in adolescents (aged 13–17 years) regarding the primary outcome, the change in the Positive and Negative Syndrome Scale (PANSS) total score (reviewed in Correll et al. 2011). A post hoc analysis of randomized clinical trial data revealed a reduction in items in the negative symptom scores (PANSS hostility, uncooperativeness, and poor impulse control) at a higher dose of aripiprazole (30 mg/day) after a six-week treatment (Robb et al. 2010).

In an additional study, risperidone (1.5–6 mg/day) was superior to a pseudo-placebo of risperidone (0.15–0.6 mg/day). By contrast, paliperidone (1.5 and 6 mg or 12 mg/day, dependent on weight) was not different from the placebo, but response rates were significantly higher in both the medium- and high-dose arms (reviewed in Correll et al. 2011). Moreover, according to data available to date, one **trial** comparing **ziprasidone** with placebo (40–80 mg/day target dose in patients weighing <45 kg and 80–160 mg/day in the others) was **discontinued** by the sponsor due to the lack of efficacy as determined in an interim analysis that revealed significant regional differences with higher placebo response rates in South America and Asia than in the USA and Europe (Correll et al. 2011). Interestingly, the only studies/dose arms that failed in adolescent schizophrenia had a weight-based dosing schedule. Pooled numbers needed to treat (definition, see Sect. 1.1) based on the response rates for each of these antipsychotics ranged from four (risperidone) to ten (quetiapine), translating into moderate to small effect sizes, which were statistically significant, except for olanzapine, which included the fewest participants (Correll et al. 2011).

Efficacy in Children and Adolescents with Bipolar I Disorder with Manic or Mixed Episode

A variety of randomized, placebo-controlled trials demonstrated efficacy of second- and third-generation antipsychotics in children and adolescents with bipolar I mania. Five studies with subjects aged ten to 17 years showed superior efficacy of antipsychotic monotherapy compared to placebo regarding reduction in the Young Mania Rating Scale (YMRS) score (reviewed in Correll et al. 2011). In one international, multisite, placebo-controlled trial, each lasting either three weeks (olanzapine, quetiapine, risperidone) or four weeks (aripiprazole, ziprasidone), aripiprazole (10 or 30 mg/day), olanzapine (2.5–20 mg/day), quetiapine (400 or 600 mg/day), risperidone (0.5–2.5 or 3–6 mg/day), and ziprasidone (20–160 mg/day) were all superior to placebo in children and adolescents (age ten to 17 years; 13–17 years for olanzapine) regarding the primary outcome, the change in the YMRS total score (reviewed in Correll et al. 2011). In children and adolescents with bipolar I disorder mania, numbers needed to treat of the pooled dose arms for "response" (defined as at least a 50 % reduction in the YMRS total score) compared to placebo ranged from three to four, corresponding to large to moderate effect sizes.

Efficacy in Autistic Disorder

Several randomized, placebo-controlled studies in children and adolescents with autism spectrum disorders have been reported. In five adequately powered (>30 patients) trials (reviewed in Correll et al. 2011), aripiprazole and risperidone (5, 10, and 15 or 5–15 mg/day) showed superior efficacy compared to placebo regarding the primary outcome, the irritability subscale score of the Aberrant Behavior Checklist (ABC), in patients with autistic disorder (aged six to 17 years in the aripiprazole study; two to nine, five to 12, and five to 17 years in the risperidone studies). While stereotypic behaviors also improved, the core deficits of verbal and nonverbal communication were not altered by antipsychotic treatment. The pooled effect sizes against placebo were moderate to large, i.e., 0.7–0.8 for risperidone and 0.5–0.8 with aripiprazole (reviewed in Correll et al. 2011). Numbers needed to treat in order to have a study-defined "response" in autism spectrum disorders ranged from two to four for risperidone; four in a small study of eleven patients treated with olanzapine, and four to seven in two studies, with aripiprazole, with greater efficacy in the

higher dose arms in the flexible-dose study (reviewed in Correll et al. 2011). In addition to the acute phase trials, in two placebo-controlled relapse prevention studies, risperidone was significantly superior to placebo in maintaining efficacy in the ABC irritability subscore.

To date, only one randomized study has examined the effects of **parent training added to risperidone** versus risperidone monotherapy for maladaptive and irritable behavior (Aman et al. 2009). This 24-week, randomized, parallel-groups clinical trial enrolled 124 children (aged four to 13 years) with pervasive developmental disorders plus frequent tantrums, self-injury, and aggression. The subjects received risperidone monotherapy from 0.5 to 3.5 mg/day (with switch to aripiprazole if risperidone was ineffective). Risperidone plus parent training resulted in a greater reduction of maladaptive behaviors than medication treatment alone. Moreover, the risperidone dose requirements were lower in the combination treatment group.

Efficacy in Disruptive Behavior Disorders

Several placebo-controlled studies were carried out with risperidone in children and adolescents (age range over all studies: five to 15 years) with aggressive behaviors associated with conduct disorder, disruptive behavior disorders, attention deficit/hyperactivity disorder (ADHD), and/or mental retardation/subaverage intelligence. All studies demonstrated that the antipsychotic agent was superior to placebo regarding the study-defined response measure with moderate to large effect sizes (numbers needed to treat: two to five; reviewed in Correll et al. 2011). In addition, risperidone also showed superior efficacy for relapse prevention compared to placebo in one large, six-month placebo-substitution trial in children and adolescents (Reyes et al. 2006).

Efficacy in Tourette's Disorder

The efficacy and safety of risperidone and ziprasidone were shown in two randomized, placebo-controlled trials in children and adolescents with Tourette's syndrome and chronic tic disorders. In a 56-day study with 28 subjects (aged seven to 17 years), ziprasidone (initiated at a dose of 5 mg/day and flexibly titrated to a maximum of 40 mg/day) was superior to placebo in reducing the global severity and total tic scores on the Yale Global Tic Severity Scale (Sallee et al. 2000). No clinically significant effects were observed on specific ratings of extrapyramidal motor symptoms, akathisia, or tardive dyskinesia.

In an eight-week trial (mean daily dose of risperidone: 2.5 ± 0.85 mg/day) with 34 medication-free patients (26 children and eight adults, ranging in age from six to 62 years), the 12 children randomized to risperidone showed a 36 % reduction in tic symptoms compared to an 11 % decrease in the 14 children on placebo (Scahill et al. 2003). Two children on risperidone showed acute social phobia, which resolved with dose reduction in one subject, but resulted in medication discontinuation in the other. A mean increase in body weight of 2.8 kg was observed in the risperidone group compared to no change in placebo. No extrapyramidal motor ADRs and no clinically significant alterations in cardiac conduction times or laboratory measures were observed.

Comparison of Typical First-Generation and Atypical Second- and Third-Generation Antipsychotics

Guidelines by the AACAP recommended the use of antipsychotic agents for schizophrenia spectrum disorders in children and adolescents, with a preference for second- and third-generation antipsychotics that might be more useful for negative symptoms (AACAP 2001). On the basis of the broadened use of second- and third-generation antipsychotics in nonpsychotic disorders and off-label indications, in particular, antipsychotic prescribing has increased substantially in children and adolescents. Unfortunately, there is no or, at best, weak evidence for the use of these agents for various forms of mental disorders.

Three comprehensive systematic reviews of antipsychotics in children and adolescents across many conditions showed that scientific evidence for most comparisons is low or insufficient, particularly for first-generation antipsychotics versus second- and third-generation antipsychotics (Fraguas et al. 2011; Seida et al. 2012; Zuddas

et al. 2011). The lack of evidence results in the high risk of bias and the lack of consistency and precision in these studies (Seida et al. 2012). Nearly all trials revealed a high risk of bias due to inadequate allocation concealment and blinding. Approximately 80 % of the trials were funded by industry, representing a potential risk for bias. Most cohort studies did not check potential confounders in the design and analyses. The lack of consistency results from the various scales and surrogate measures used to assess outcomes. Precision was often poor due to the small sample sizes (ranging from eleven to 42 per treatment group), which might give an indication of the insufficient power to detect differences between groups.

Early-Onset Schizophrenia and Schizoaffective Disorders and Bipolar I Disorder

In the systematic review by Fraguas et al. (2011), in total, 34 studies with 2,719 children and adolescents were included. These studies, which were investigator-initiated and federally funded, lasted between three weeks and 12 months, with most studies (79.4 %) lasting three months or less. Nine studies ($N=788$) were carried out in patients with schizophrenia, six ($N=719$) in subjects with bipolar disorder, and 19 ($N=1,212$) in a mixed population. Data on efficacy showed that, except for **clozapine being superior for refractory schizophrenia**, there were no significant differences between second- and third-generation antipsychotics and first-generation antipsychotics in children and adolescents with psychotic disorders and bipolar disorder (Fraguas et al. 2011). This lack of difference in clinical efficacy was independent of the diagnosis, suggesting that the clinical efficacy of second- and third-generation antipsychotics could not be distinguished, at least not as measured by the clinical scales and the use of relatively small samples. However, these results, which are based on group means, do not imply that second-generation or first-generation antipsychotics have identical efficacy in individuals.

All head-to-head studies that compared antipsychotics in children and adolescents with schizophrenia or psychosis showed that symptom response was not significantly different between olanzapine and risperidone, between olanzapine or risperidone and haloperidol or molindone (approved by the FDA for the treatment of individuals with schizophrenia in adolescents as young as 12 years of age, but has not been studied for early-onset schizophrenia), or between olanzapine and quetiapine. By contrast, in small-scale studies with only ten to 21 patients per treatment group, lasting between six and 12 weeks, clozapine was superior to haloperidol, standard dosing of olanzapine, or "high-dose" (up to 30 mg/day) olanzapine, with a number needed to treat of three for response to the "high-dose" olanzapine, representing a large effect size (Correll et al. 2011).

In contrast to efficacy data, **safety assessments showed** relevant **differences** between second- and third-generation antipsychotics (Fraguas et al. 2011). Mean **weight gain** ranged from 3.8 to 16.2 kg in patients treated with olanzapine ($N=353$), from 0.9 to 9.5 kg in subjects receiving clozapine ($N=97$), from 1.9 to 7.2 kg in those on risperidone ($N=571$), from 2.3 to 6.1 kg among patients taking quetiapine ($N=133$), and from zero to 4.4 kg in those treated with aripiprazole ($N=451$).

Prolactin concentrations increased the most in subjects on risperidone (mean change ranging from 8.3 to 49.6 ng/mL), followed by olanzapine (−1.5 to + 13.7 ng/mL). Treatment with aripiprazole was associated with decreased prolactin levels, while clozapine and quetiapine were found to be mostly neutral.

With respect to **extrapyramidal motor ADRs**, second- and third-generation antipsychotics were associated with less parkinsonism and akathisia than first-generation antipsychotics. Most of the studies comparing extrapyramidal motor ADRs between second and third-generation antipsychotics found no significant differences.

Nonpsychotic Disorders

As discussed above, the randomized double-blind studies showed that first-generation antipsychotics are effective in ameliorating nonpsychotic psychiatric disorders in children and adolescents. Currently, no comparison studies among different second- and third-generation antipsychotics have been carried out in children and adolescents with nonpsychotic disorders (Zuddas et al. 2011).

As for schizophrenia, it was demonstrated in comprehensive systematic reviews that the different second- and third-generation antipsychotics show a similar efficacy for specific nonpsychotic disorders, but significantly differ in their safety profile. In children and adolescents with bipolar, autistic, or disruptive behavior disorders, efficacy of second- and third-generation antipsychotics on mania, extreme mood variability, irritability, and aggression, measured as effect size or numbers needed to treat, appears greater than for psychotic symptoms of schizophrenia: average numbers needed to treat for nonpsychotic disorders is two to five, whereas for schizophrenia it varies between three for risperidone and ten for olanzapine, quetiapine, and aripiprazole (Zuddas et al. 2011).

In randomized studies, ADRs were usually relatively minor, easily predictable, and manageable, whereas long-term open-label studies have indicated that some ADRs, such as the **metabolic effects**, might be severe and potentially life-threatening in the long term (Zuddas et al. 2011). Based on these findings, the authors suggested that the choice of a specific treatment should be guided primarily by the safety profile of specific antipsychotics, considering specific risk factors (i.e., obesity and BMI, family history of diabetes or cardiovascular disorder) for the single patient.

5.4.3 Recommended Dosages

The adjustment of antipsychotic dosage must be undertaken on an individual basis, as response varies widely between patients. Weight-based dosing schedules are not recommended. The maintenance dosage must therefore be individually determined, and the antipsychotic dosages listed in Table 5.5 must be regarded only as guidelines. For child and adolescent psychiatry, the mentioned dearth of clinical studies, in particular with first-generation antipsychotics, and the frequent lack of approval for the use of these medications in these age groups mean that therapy should commence with especially low dosages and the dosage should be carefully increased by small increments ("**start low, go slow, but go if needed**"). This particularly applies to younger children and those of low body weight. Therapeutic drug monitoring (TDM, see Sect. 2.3) may be appropriate under certain circumstances (see Sect. 5.6).

In order to guarantee reliable effective drug levels in patients with compliance problems, **slow-release preparations** (e.g., paliperidone ER, for extended release, or quetiapine prolong) and depot preparations can be employed. Administration of paliperidone ER enables more consistent medication release throughout the day. **Depot preparations** are antipsychotics esterified in an oily solution that can be administered by intramuscular (i.m.) injection. Depot preparations are effective, depending upon dosage, for one to four weeks and spare the patients the need to take tablets daily. However, any ADRs that occur can be problematic, as the depot form means that they will persist longer. The fine adjustment of dosage is also difficult and time-consuming, so that depot antipsychotics are not suitable for acute medication. However, their use in children and adolescents may be appropriate, after symptom control and oral dosages of an antipsychotic were stabilized and particularly if nonadherence is a problem.

In case of **nonadherence**, it is advisable to initially adjust drug dosage by oral administration, possibly under hospital conditions and with checks of the patient's mouth. If it seems appropriate to switch to depot medication, this should occur after a sufficient dosage has been achieved with oral administration. The depot form should, if possible, consist of the same medication (e.g., flupentixol 10 mg/day orally (p.o.) corresponds to flupentixol decanoate 40 mg/2 weeks i.m.; haloperidol decanoate is given at 15–20-fold higher dosages of the oral dosage every four weeks i.m.). Higher plasma levels, with a consequently increased risk of ADRs, can ensue directly after injection of the slow-release preparation. First-generation antipsychotics as well as second- and third-generation antipsychotics, such as aripiprazole (in the USA), olanzapine, paliperidone, and risperidone, are currently available in depot preparations. These antipsychotic depot formulations differ regarding their injection interval (every two

weeks for risperidone, every four weeks for the others) and need for overlap with oral antipsychotics (three weeks for risperidone, two weeks with aripiprazole, no overlap required for olanzapine and paliperidone) although a second booster injection after one week is needed with paliperidone. Due to the risk of a **postinjection delirium/sedation syndrome**, which is unique to **olanzapine**, and in view of the fact that risk does not decrease with the duration of treatment, olanzapine depot should only be considered for the treatment of refractory patients and for those whom a three-hour observation period after the injection can be assured. Nevertheless, there is only limited clinical experience, and there are no controlled studies regarding depot antipsychotics in pediatric patients.

The **combination** of high- and low-potency **antipsychotics** is frequently the **clinical standard**, particularly at the beginning of the treatment, in order to achieve sedation or reduction of tension. Benzodiazepines are often administered in parallel. In chronic courses, which usually become manifest only during adulthood, high-potency first-generation antipsychotics are sometimes combined with an effective second- and third-generation agent. Particular restrictions regarding the use of clozapine must, however, be observed (see below, Sect. 5.4.6). Combinations of second- and third-generation antipsychotics are, in general, to be preferred.

5.4.4 Adverse Drug Reactions (ADRs)

Studies comparing rates of antipsychotic ADRs in children and adolescents with those in similar studies of adults indicate that **children and adolescents are at higher risk** for developing a number of antipsychotic-induced ADRs (Correll 2008). These include higher rates of sedation, extrapyramidal motor ADRs (except for akathisia), withdrawal dyskinesia, prolactin elevation, weight gain, and at least some metabolic abnormalities. By contrast, tardive dyskinesia and diabetes are less likely to occur in children and adolescents compared to adults. However, this is a very probable result due to the short follow-up periods in children and adults and the presence of an accumulated risk and added lag time in adults. This raises concerns about a potential shortening of the time until these long-term complications occur when antipsychotic treatment is initiated during childhood.

Antipsychotic's safety profile is **crucial for the treatment strategy** in children and adolescents with schizophrenia or bipolar disorder, because of the long-term course of pharmacological therapy. Second- and third-generation antipsychotics are considered safer than first-generation agents, although they are frequently associated with ADRs, including weight gain and metabolic complications, elevation in prolactin levels, extrapyramidal motor ADRs, sedation, and cardiac effects that require careful monitoring (Amor 2012; Fraguas et al. 2011; Masi and Liboni 2011).

Relationship Between Receptor Binding and ADR Profile

Antipsychotics exhibit widely varying receptor binding profiles (Table 5.3), and this is reflected in different ADRs (Table 5.6). As discussed above, the dopamine D_2-receptor occupancy is a predictor not only of antipsychotic response but also of the occurrence of extrapyramidal motor ADRs, resulting from the blockade of nigrostriatal dopamine receptors. Vegetative ADRs are caused by inhibition of adrenergic α_1 and muscarinic acetylcholine receptors, and the reduced sympathetic and/or parasympathetic transmission that ensues. The antagonism of serotonin 5-HT_2-receptors is associated with the lower propensity to cause extrapyramidal motor ADRs for second- and third-generation antipsychotics.

ADRs During the Dose Adjustment Phase

During the dose adjustment phase and also when switching medications, **tiredness, diminished concentration, and orthostatic symptoms** are particularly common, but usually transitory ADRs. Other ADRs can also moderate or even cease in the course of therapy with antipsychotics. The positive effects and ADRs of an antipsychotic agent must be weighed against each other when deciding whether to continue with the

Table 5.6 Non-dopaminergic pharmacodynamic effects and the resultant adverse drug reactions (ADRs) of antipsychotics

Site of action	Symptoms	Recommended therapy
Acetylcholine M_{1-5}-receptors	Mouth and nasal dryness	Moistening of the mucous membranes (increased fluid intake, sugar-free sweets, etc.)
	Accommodation disturbances	Often resolves without intervention
	Obstipation (**caution**: paralytic ileus)	Drinking, high-fiber diet
	Micturition problems, (caution: acute urinary retention)	Cholinergic agent, such as carbachol 0.25 mg i.m. or i.v., carbachol 1–4 mg/day p.o.; or ACh-esterase inhibitor, such as distigmine 2.5–5 mg p.o.
	Salivation	Anticholinergic, such as pirenzepine 25–100 mg/day
	Memory disturbances	
	Caution: glaucoma attack	
Histamine H_1-receptor	Sedation, tiredness	Usually transitory
	Weight gain (?)	See last line under 5-HT_2
	Caution: intensification of other centrally depressant agents	
Adrenergic α_1-receptor	Hypotonia, orthostatic dysregulation, vertigo	Kneipp therapy, possibly dihydroergotamine 2–6 mg/day or etilefrine 20–60 mg/day
	Reflex tachycardia	β-Adrenoceptor antagonist, such as propranolol 10–30 mg/day
	Sedation	Usually transitory
	Nasal congestion	Nose drops, for example, xylometazoline
	Cave: intensification of the effects of other adrenergic α_1-receptor antagonists	
Serotonin 5-HT_2-receptor	Sedation	Usually transitory
	Increased appetite	Diet, physical activity program; possible switch to an antipsychotic agent with lower risk of weight gain (see Sect. 5.4.4.7)
	Weight gain	
	Beneficial effect: Reduced risk of extrapyramidal motor ADRs and increased prolactin secretion	

ACh acetylcholine, *i.m.* intramuscular, *i.v.* intravenous, *p.o.* per os
(?) context not clarified

medication. The persistence of some ADRs can indicate that a supplementary medication is appropriate. Corresponding recommendations are included in Table 5.6.

During the first two to four weeks of antipsychotic treatment, the gall duct epithelium can swell, and signs of intrahepatic cholestasis arise as an allergic response. The resulting rise in transaminase and alkaline phosphatase activity is usually transitory and often accompanied by other allergic symptoms (urticaria, eosinophilia, etc.). It is not usually necessary to discontinue or switch medication (exception: signs of icterus), as in the course of therapy, desensitization appears to develop.

Extrapyramidal Motor ADRs

As discussed above, the potential risk of extrapyramidal motor ADRs is higher for first-generation antipsychotics than for second- and third-generation agents. Extrapyramidal motor ADRs are characterized by the symptoms listed in Table 5.7.

In the systematic review by Fraguas et al. (2011), in which 34 short-term studies with 2,719 children and adolescents with schizophrenia and bipolar I disorder were included, it was found that treatment with second- and third-generation antipsychotics resulted in less parkinsonism and akathisia than with first-generation antipsychotics (taking haloperidol and molin-

Table 5.7 Extrapyramidal motor adverse drug reactions during antipsychotic therapy

Motor symptom	Clinical manifestations	Symptoms
Early dyskinesias	Orofacial dyskinesias	Oculogyric crises (ocular turning)
		Tongue-throat spasms
		Rabbit syndrome (twitching of the nasolabial transition)
	Neck and shoulder dystonias, less commonly trunk dystonias	Retrocollis
		Torsion dystonia
	Opisthotonos	
Antipsychotic-induced parkinsonism	Parkinson-like symptoms	Rigor (cogwheel phenomenon)
		Hypokinesia
		Tremor
Akathisia		Inability to sit still
		Scuttling movements
		Restless wandering
		"Tingling" of the soles
Late dyskinesias (tardive dyskinesias)		Rolling tongue, sucking, lip-smacking
		Grimacing
		Athetotic movements
Neuroleptic malignant syndrome		Rigor
		Stupor
		Disturbances of consciousness
		Vegetative symptoms
		High fever

done as the reference first-generation antipsychotics). **Head-to-head comparisons** between second- and third-generation antipsychotics resulted in only one study with the significant finding that risperidone causes more rigidity than olanzapine. None of the remaining antipsychotic comparisons in this area reached significance. However, the methodological discrepancies with regard to patient population, heterogeneous assessment instruments, follow-up periods, titration schedules, and maximum doses between the studies included in this review make it impossible to draw an unambiguous conclusion. Indeed, second- and third-generation antipsychotics are not free from extrapyramidal motor ADRs either. Treatment with **risperidone** has been associated with **higher tremor and dystonia rates** than other second-generation antipsychotics (Fraguas et al. 2011).

A review of chronic extrapyramidal motor ADRs of second-generation antipsychotics in children and adolescents has shown relatively low one-year tardive dyskinesia rates of 0.4 % (Correll and Kane 2007). However, these results are limited as to the small sample size of studies with second-generation antipsychotics other than risperidone and by the fact that relatively low doses were used, which could have obscured a potentially greater risk for tardive dyskinesia in children and adolescents treated with higher total doses of second- and third-generation antipsychotics and for longer durations (Correll and Kane 2007).

With regard to extrapyramidal motor ADRs, **it should be noted** that:

- Ninety percent occur within the first five days after initiation of treatment or following a dosage increase.
- Extrapyramidal motor symptoms are particularly stigmatizing and can frighten the patient, undermining patient's compliance. Prior explanation is therefore essential for the patient and his or her family, and extrapyramidal motor symptoms should be treated as soon as they appear (Table 5.8).
- The development of prolonged patient response times, disjointed thoughts, and apparent absence states make it difficult to differentiate from primary psychiatric, formal

Table 5.8 Therapy of extrapyramidal motor adverse drug reactions

Manifestation form	Recommended intervention
Early dyskinesias	Anticholinergics, for example, biperiden or benztropine
Acute	For severe dyskinesia: biperiden 2 mg i.v. (can be repeated after several minutes to treat residual symptoms) or benztropine 0.05 mg/kg one to two times a day
	For mild indications: biperiden non-retard 2 mg p.o.
Prophylaxis	Biperiden as slow-release preparation daily 2–4 mg in the morning (p.o.)
Antipsychotic-induced parkinsonism	Anticholinergics, for example, biperiden as slow-release preparation daily 2–4 mg in the morning p.o.
Akathisia	In most cases: anticholinergics, for example, biperiden (procedure as for early dyskinesias)
	Alternatively: benzodiazepines
	Alternatively: β-adrenoceptor antagonists, for example, propranolol 20 mg/day, increased as required in 20 mg/day increments to max. 100 mg
Late dyskinesias (tardive dyskinesias)	Where possible, immediate switch to clozapine (because of very low risk for extrapyramidal motor ADRs)
	Alternatively: switch to second- and third-generation antipsychotics with potentially lower risk for extrapyramidal motor ADRs (e.g., olanzapine, quetiapine)
Neuroleptic malignant syndrome	Discontinuation of antipsychotic therapy, administration of dopamine receptor agonists (e.g., bromocriptine 7.5–16 mg/day) or the muscle relaxant dantrolene 4–10 mg/kg body weight/day

i.v. intravenous, *p.o.* per os

cognitive symptoms, which can also be indications of early dyskinesia.

- Affected patients frequently attempt to conceal clearly visible dyskinesias by integrating them into their existing delusional system.
- Extrapyramidal motor ADRs can also reappear after long-term stabile antipsychotic treatment, for example, as the result of stress. Under these circumstances there is a danger that the therapist will misinterpret the situation as a relapse into schizophrenic, catatonic symptoms and increase the antipsychotic dosage, thus exacerbate the dyskinesias.
- The exacerbation of extrapyramidal motor ADRs by demanding or stressful situations can be used for early detection (e.g., setting computational tasks increase discrete dyskinesias) or indicate that the patient is struggling to cope.
- The intravenous (i.v.) administration of anticholinergics is appropriate emergency relief for acute dyskinesia, immediately resolving the symptoms (e.g., 2 mg biperiden (licensed in European countries) or benztropine (FDA approved for the therapy of all forms of parkinsonism in patients over 3 years) 0.02–0.05 mg/kg one to two times a day).
- Children and adolescents should be particularly closely monitored as to the development of extrapyramidal motor ADRs and be orally treated at the first signs of their appearance with long-acting formulations of biperiden or benztropine, in order to ensure that further symptomatic progression, which would increase anxiety, is forestalled.
- Cautious reduction of antipsychotic dosage or switching to a second- or third-generation antipsychotic agent after fading of the acute phase, to the degree allowed by the clinical situation, is advisable.

Tardive Dyskinesias

The so-called tardive dyskinesias, another manifestation of extrapyramidal motor ADRs (Table 5.7), are involuntary rhythmic "chewing movements" of the mouth and tongue but also involuntary movements of the neck, trunk, and extremities. Late dyskinesias, in contrast to early dyskinesias, arise in around 20 % of patients only months after the commencement of antipsychotic therapy; their incidence declines significantly from about the fifth year of treatment. The symptoms cease during sleep. In contrast to medication-induced hypokinetic parkinsonism, late dyskinesias are a hyperkinetic phenomenon. The etiology of this ADR is not known. It has been suggested that postsynaptic dopamine D_2-receptor blockade results in increased

dopamine receptor numbers ("receptor upregulation") or receptor sensitivity to stimulation ("supersensitivity"; see Sect. 1.4.2). This phenomenon can be further amplified by inhibition of dopamine autoreceptors.

Risk factors for late dyskinesias are:

- Female gender
- Advanced age
- Extended therapy with high dosages of the antipsychotic agent
- Supplementary or prophylactic anticholinergic therapy
- Concomitant therapy with lithium salts
- Structural brain damage

The average prevalence of late dyskinesias during antipsychotic therapy across all age groups is 24 %, whereby the figures vary between 0.5 and 70 % (Kulkarni and Naidu 2003). The onset of symptoms is usually between the third month and third year of treatment. There are no secure prevalence figures for children and adolescents.

There is currently **no satisfactory therapy** for antipsychotic-induced late dyskinesias, so that avoiding these ADRs by adopting the lowest possible yet sufficiently effective dosages is particularly important. At the first signs of late dyskinesia, the prognostically most favorable approach is to switch as quickly as possible to the only "genuine" atypical antipsychotic agent, clozapine.

Neuroleptic Malignant Syndrome

A particularly ominous but **rare ADR** is the neuroleptic malignant syndrome. Early indications include the increase of extrapyramidal motor ADRs (above all, rigidity), accompanied by fever and changes in cardiovascular parameters (vegetative dysautonomia with tachycardia, disturbed cardiac rhythm, hyperhidrosis). Disturbed consciousness, ranging to stupor, is common. Less frequent symptoms include muscular cramp, myoclonus, and pyramidal symptoms. Agitation states are seldom. Monitoring of the blood picture, urine, and hepatic function indicates an increased creatinine kinase activity and erythrocyte sedimentation rate, leukocytosis, elevated transaminase activity, and myoglobinuria with dark coloration of the urine. As in some cases laboratory values can still lie within the normal range, but the **clinical picture** is **decisive for diagnosis**.

Despite treatment (see Table 5.8), the mortality rate is up to 20 % (Madaan et al. 2008), the cause of death usually being rhabdomyolysis-related renal failure. Early recognition as well as timely intervention and the prevention of complications are important clinical components in the management of neuroleptic malignant syndrome in children and adolescents.

The incidence of the neuroleptic malignant syndrome in an inpatient psychiatric population of antipsychotic-treated patients varied between 0.07 and 2.4 % (Schatzberg et al. 2003). In children under six years of age, the syndrome could develop after as little as a single antipsychotic administration. This syndrome has been reported to occur with second- and third-generation antipsychotics, including risperidone, olanzapine, and aripiprazole (Madaan et al. 2008; Masi and Liboni 2011). Studies have shown that 66 % of the cases occur during the first two weeks of therapy and 96 % within the first 30 days. The mean recovery time ranges from seven to ten days, with low estimates of mortality of 10 % and high estimates of 20 % (Madaan et al. 2008). Although clozapine is associated with few extrapyramidal motor ADRs, clozapine-induced neuroleptic malignant syndrome can still occur, but with fewer extrapyramidal motor symptoms and a lower increase in creatine kinase levels (Madaan et al. 2008).

The neuroleptic malignant syndrome requires the **immediate discontinuation** of the antipsychotic drug as well as adequate **volume substitution** and **symptomatic fever reduction**. An internist case conference and transfer to an intensive care unit should be immediately organized. The most effective agents in the treatment of neuroleptic malignant syndrome have proved to be dantrolene (p.o. for children from five years, beginning with 1 mg/kg body weight, can be increased to max. 200 mg/day; from 50 kg body weight, beginning with 2×25 mg/day, can be increased to max. 400 mg/day; i.v., 2.5 mg/kg body weight, max. daily dosage 10 mg/kg body weight) and bromocriptine (10–30 mg/day, max. 60 mg/day) (Silva et al. 1999).

With regard to **differential diagnosis**, neuroleptic malignant syndrome must be distinguished from **pernicious catatonia**, characterized by fever, stupor, postural stereotypies, catalepsy, and negativism; immediately prior to development of the syndrome, psychotic symptoms and severe agitation as well as choreiform movements are common. The accompanying vegetative symptoms are often less marked than in the neuroleptic malignant syndrome. Therapy for pernicious catatonia consists of a high dosage of an antipsychotic agent or electroconvulsive therapy.

Prolactin Increase

Inhibition of dopamine D_2 receptors in the tuberoinfundibular system (see Sect. 1.3.2.1) – particularly during therapy with first-generation antipsychotics – can lead to **hormonal disorders**, particularly hyperprolactinemia. Loss of libido together with menstrual cycle abnormalities, tightness in the breast, and galactorrhea in female patients or gynecomastia and potency problems in male patients are characteristic.

It is recommended to regularly examine patients for clinical signs of hyperprolactinemia and to assess prolactin levels if indicated. At the same time, hypothyroidism, renal disorders (serum creatinine), and, in girls, pregnancy or contraceptive effects upon prolactin levels need to be excluded. Where these levels are below 200 ng/mL, moderate dosage reduction accompanied by further clinical and laboratory monitoring may be adequate; alternatively, switching to aripiprazole, quetiapine or clozapine can be considered. At levels greater than 200 ng/mL, these measures are urgently indicated; should the high levels persist, imaging of the sella turcica should be undertaken to exclude hypophyseal adenoma and parasellar tumor (Correll and Carlson 2006).

All first-generation antipsychotics acutely raise prolactin, but serum levels frequently normalize spontaneously over time, during chronic therapy (Madaan et al. 2008). Second- and third-generation antipsychotics, on the other hand, have varied affinities for the dopamine D_2 receptor (Tables 5.2. and 5.3) and also vary in their ability to induce hyperprolactinemia. Only a few studies have prospectively compared the effects of second- and third-generation antipsychotic treatment on prolactin levels in children and adolescents.

Fraguas et al. (2011) carried out a systematic review on 34 short-term studies, in which 2,719 children and adolescents with schizophrenia and bipolar I disorder were included. This study found that the **increase** in prolactin levels is **highest** in subjects treated with **risperidone** (with mean increases ranging from 8.3 to 49.6 ng/mL), followed by olanzapine (with mean changes ranging from −1.5 to +13.7 ng/mL). On the other hand, treatment with aripiprazole was associated with decreased prolactin levels, while clozapine, quetiapine, and ziprasidone were found to be mostly neutral. Regarding **head-to-head comparisons** of the effects of second- and third-generation antipsychotics on prolactin increases, Fraguas et al. (2011) found three studies showing that risperidone causes significantly greater prolactin increases than olanzapine, three studies showing that risperidone causes significantly greater prolactin increases than quetiapine, two studies showing no difference between risperidone and olanzapine, one study showing no difference between olanzapine and clozapine, and one study showing no difference between quetiapine and olanzapine.

Hematologic Changes

Hematologic changes have been described during antipsychotic therapy, particularly with **clozapine**. For this reason, **special conditions** apply **to the use** of clozapine, including a written explanation of the risks involved and regular monitoring of leukocyte and neutrophil granulocyte counts in particular.

Leukocytopenia develops at the beginning of therapy in as many as 30 % of patients treated with antipsychotics and requires no special intervention, apart from close monitoring of the blood count, if numbers do not drop beneath 3,000/mm^3. **Agranulocytosis** in the stricter sense describes the situation when granulocyte numbers fall below 1,000/mm^3. These hemato-

logic changes appear to result from an allergic-toxic disposition with respect to antipsychotic medication. Eosinophilia can develop as expression of a possible allergic complication (usually transiently in the second to fourth week of therapy; modification of the treatment regimen is usually not necessary). Changes in leukocyte numbers (agranulocytosis and neutropenia) are most common in connection with clozapine, but, depending upon their severity, a change in therapy is not always required. According to Grohmann et al. (2001), the **risk of pathological leukocyte changes** varies as follows: clozapine >risperidone >olanzapine >haloperidol (0.01 %). Because of the higher risk of agranulocytosis associated with clozapine (around 1 %), strict monitoring guidelines must be observed during treatment (see also Sect. 5.6).

Cardiovascular ADRs

Cardiovascular ADRs during treatment with antipsychotics have been reported less frequently in children and adolescents than in adult patients (Masi and Liboni 2011). All antipsychotics may cause a prolongation in the electrocardiogram (ECG) corrected QT (QTc) interval (Amor 2012; Madaan et al. 2008; Masi and Liboni 2011; Zuddas et al. 2011). Further possible cardiac ADRs include ST-segment depression, flattened T waves, and arrhythmias (caution: sudden cardiac death).

QTc interval prolongation, resulting from antipsychotic-induced blockade of ion channels, is medically significant because it can be associated with an increased risk for potentially fatal ventricular arrhythmias (called "torsades de pointes"). These changes are particularly frequent during therapy with first-generation antipsychotics of the phenothiazine class and some of the second- and third-generation antipsychotics; the risk is lower for haloperidol and olanzapine (Glassman and Bigger 2001). Two antipsychotic agents, ziprasidone and thioridazine, are mostly associated with QTc prolongation. QTc prolongation with ziprasidone was nonetheless found to be only 10 ms longer than with risperidone, quetiapine, or olanzapine (Madaan et al. 2008).

According to Glassman and Bigger (2001), the following **ranking** regarding average **QTc interval changes** applies: thioridazine (+35.6 ms) ≫sertindole (up to +30 ms) >ziprasidone (+20.3 ms) >quetiapine (+14.5 ms) >risperidone (up to +11.6 ms) >olanzapine (up to +6.8 ms) >haloperidol (+4.7 ms).

Weight Gain and Metabolic ADRs

Increased appetite associated with the atypical antipsychotics is thought to be related to the antagonism of histamine H_1 and serotonin 5-HT_{2c}-receptors (Tables 5.3 and 5.6). This antagonism is most marked with clozapine and olanzapine.

Weight gain is an important ADR observed with treatment with second- and third-generation antipsychotics in children and adolescents (Amor 2012; Correll 2008; Masi and Liboni 2011; Pringsheim et al. 2011). It is a complication that affects physical and mental health as well as psychosocial functioning. Weight gain is specifically associated with the development of medical comorbidities, depression, and eating disorders, which may negatively affect patients' life spans (Correll 2008).

A study by Fleischhaker et al. (2008) evaluated weight gain in children treated for 45 weeks with either olanzapine (10.2 ± 3.5 mg/day; $N = 15$), clozapine (311.7 ± 137.5 mg/day; $N = 8$), or risperidone (2.6 ± 1.7 mg/day; $N = 10$). The **highest increase** in weight was observed in the **olanzapine** group (16.8 ± 8.8 kg, 30.1 ± 18.8 %), compared with clozapine (9.5 ± 10.4 kg, 14.8 ± 15.8 %) and risperidone (7.2 ± 5.3 kg, 11.5 ± 6.0 %). While a weight plateau was reached after 12 weeks of risperidone therapy, this was reached only after 40 weeks of clozapine treatment; with olanzapine, weight continued to increase even after 45 weeks.

Different results have been reported for quetiapine at dosages between 400 and 800 mg/day, and the dose seems to play a role. Even within the first month of therapy at a daily dosage of less than 800 mg/day, an average weight gain of 1.5 kg has been measured; at 225 mg, however, no increase occurred, not even after 16 weeks (see Stigler et al. 2004 for review). During low

dosage therapy with ziprasidone (20–60 mg), no weight change or even a slight reduction was observed (see Stigler et al. 2004 for review).

More recently, Fraguas et al. (2011) assessed the effects of second- and third-generation antipsychotics on weight gain in a systematic review in which 34 short-term studies with 2,719 children and adolescents with schizophrenia and bipolar I disorder were included. Across the reviewed studies, mean **weight gain** ranged from 3.8 to 16.2 kg in patients treated with **olanzapine** ($N=353$), from 0.9 to 9.5 kg in subjects receiving **clozapine** ($N=97$), from 1.9 to 7.2 kg in those on **risperidone** ($N=610$), from 2.3 to 6.1 kg among patients on **quetiapine** ($N=142$), and from 0 to 4.4 kg in those treated with **aripiprazole** ($N=451$). Among subjects receiving placebo ($N=321$), the mean weight change ranged from 0.8 kg weight loss to 2.5 kg weight gain.

Head-to-head studies of second- and third-generation antipsychotics compared weight gain between olanzapine and risperidone in 13 studies (Fraguas et al. 2011). Seven showed that olanzapine caused significantly more weight gain than risperidone, while six studies found no significant differences. Five studies compared olanzapine with quetiapine: four studies showed that olanzapine caused more weight gain than quetiapine, while one found no differences. Five studies compared risperidone and quetiapine: all found no differences. Four studies compared clozapine and olanzapine: two demonstrated that olanzapine caused more weight gain than clozapine, while two found no differences. Three studies compared risperidone and clozapine and showed no differences. Other comparisons included one study showing that olanzapine caused more weight gain than aripiprazole, one study showing that risperidone caused more weight gain than aripiprazole, and one study showing that quetiapine caused more weight gain than aripiprazole.

Thus, the data summarized above show that, in general, treatment with second- and third-generation antipsychotics is associated with significant weight gain, but that the magnitude of that weight gain differs. Olanzapine is the antipsychotic agent causing the most significant weight gains (Fraguas et al. 2011), but there are no studies directly comparing second- and third-generation antipsychotics that cause less weight gain, such as aripiprazole and ziprasidone, with first-generation antipsychotics in children and adolescents. There are no in-depth studies on dose effect either, only one study showing that antipsychotic dose correlates with weight gain in patients on risperidone, the antipsychotic with the largest sample and power to show an effect (Correll et al. 2011).

Weight gain is associated with important negative effects that include medical morbidity (such as diabetes, hypertension, dyslipidemia, and osteoarthritis), social withdrawal, noncompliance, and lowered self-esteem. In addition, weight gain is considered to be an important precursor of **metabolic effects**, including obesity, hypertension, hyperglycemia, abnormal low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels, and hypertriglyceridemia (Correll 2008; Masi and Liboni 2011). There is only limited data on the metabolic effects of antipsychotic treatment in children and adolescents, and among the available studies, patient follow-up was often 12 months or less (Fraguas et al. 2011).

Antipsychotic treatment, in particular with clozapine and olanzapine, is associated with increased glucose levels and higher lipid levels (Correll 2008; Masi and Liboni 2011). Aripiprazole and ziprasidone exert only a minor effect upon glucose metabolism (Baptista et al. 2002). Risperidone and ziprasidone occasionally reduce triglyceride levels; amisulpride and aripiprazole appear to be neutral with respect to lipid metabolism (Baptista et al. 2002; DeNayer et al. 2007). It should be noted that those abnormalities are not always associated with weight gain or metabolic effects, as they are also related to other factors, such as insulin resistance or genetic predisposition (Masi and Liboni 2011). For example, polymorphisms of the 5-HT_{2C}-receptor gene have been discussed to be associated with metabolic syndromes in antipsychotic therapy. The antagonism of the 5-HT_{1A}-receptor by some antipsychotics possibly also causes reduced insulin release by the β-cells of the pancreas.

An etiological connection between antipsychotic therapy and lipid metabolism disorders has not yet been established. With regard to **diabetic conditions**, however, such a connection cannot be excluded: in a seven-year American follow-up study, 18.4 % of adult patients treated with second- and third-generation antipsychotics developed diabetes mellitus, compared with only 6.6 % in the general clinical population (Henderson et al. 2007). A review of 32 cases of diabetes in adolescents receiving antipsychotics (clozapine, olanzapine, or risperidone), reported to the FDA MedWatch drug surveillance system, showed that 78 % of these cases had new onset diabetes, while the remaining 22 % experienced a worsening of existing diabetes (Koller et al. 2001; 2004a, b). The time of onset of diabetes was six weeks in 28 % of the cases and within six months in 72 % of patients (Koller et al. 2001, 2004a, b). Another review report of 15 patients, aged seven to 19 years, treated with olanzapine, quetiapine, or risperidone, revealed that 87 % had new onset diabetes, and the average time for detection of diabetes was four months after the start of antipsychotic treatment (Cohen and Huinink 2007).

The diabetogenic effect of antipsychotics might be partly attributable to the antipsychotic-induced increase in fat tissue. It has also been shown that serum concentrations of the adipocyte-derived, insulin-sensitive cytokine adiponectin are significantly lower in olanzapine-treated patients (Ayanthi et al. 2006). Further factors include elevated plasma levels of clozapine, in particular, and high hemoglobin A1c levels (an indicator of latent diabetes mellitus).

Miscellaneous ADRs

Patients treated with antipsychotics (no more than 1 %) may experience **cerebral seizures** as the result of lowered seizure threshold (exception: melperone is anticonvulsive). This applies especially to phenothiazines with aliphatic side chains (such as levomepromazine) and clozapine. General EEG alterations are relatively frequent during antipsychotic therapy but require nothing more than regular monitoring; clozapine, in particular, is associated with intermittent generalized, high amplitude, slower-frequency groups, with general lability of frequency and amplitude. Should an antipsychotic-induced cerebral seizure occur, dosage reduction or change of medication is recommended. Should the antipsychotic agent have proved effective in treating the psychopathology, combination with an antiepileptic (e.g., phenytoin or valproic acid) might be considered in order to avoid the change of the antipsychotic agent (regular TDM is advisable).

Hepatotoxicity, although rare, has also been associated with antipsychotic drugs during long-term treatment, and it is sometimes related to weight gain, with liver enzyme abnormalities and fatty infiltration based on abdominal ultrasound data (reviewed in Amor 2012). Kumra et al. (1997) analyzed the charts of pediatric populations with psychosis being admitted to the National Institute of Mental Health from December 1993 to April 1996. The authors identified 13 children who were treated with **risperidone** (6–8 mg/day) and who presented evidence of hepatotoxicity and weight gain. Two patients had obesity and liver enzyme abnormalities and showed evidence of a fatty liver, which was reversed after discontinuation of risperidone and related weight loss. Szigethy et al. (1999) reviewed the data from 38 children and adolescents aged seven to 17 years with various psychiatric diagnoses who received risperidone (average of 2.5 mg/day) for a mean time of 15.2 months. Of the 38 patients included in the study, only one patient showed a mild increase of alanine transaminase, clinically not relevant, however.

Intoxication can occur if the dosage is increased too rapidly or if medication is combined with anticholinergics and other drugs that increase the effective therapeutic levels (see Sect. 5.4.5). Further factors that increase the risk of intoxication include organic brain damage and very young age. Toxication is expressed – depending upon agent type – as delirium (confusion, agitation, possibly hallucinations, particularly at night!) and also as anticholinergic-related cardiac rhythm disturbances and hypotonia.

Treatment of intoxication involves discontinuation of the antipsychotic agent and possibly gastric lavage with activated charcoal. Benzodiazepines can be employed, as required, for sedation, acetylcholine esterase inhibitors and parasympathomimetics (physostigmine, carbachol, neostigmine) as well as antiarrhythmics for treatment of cardiovascular symptoms. Catecholamine treatment of shock is obsolete because of the exacerbation of cardiac arrhythmia; volume substitution is instead recommended.

5.4.5 Drug Interactions

As mentioned above in the discussion about recommended dosages, it is normal in clinical practice to combine high- and low-potency antipsychotics, particularly in the early stages of therapy, in order to achieve sedation or reduction of tension. Depending upon the specific receptor profile of a particular antipsychotic agent, an elevation of antipsychotic potency and change in ADR spectrum can result.

Pharmacokinetic interactions occur when absorption, distribution, metabolism, or excretion of a drug is influenced; **pharmacodynamic interactions** occur when two drugs interact at the same neuroreceptor resulting in additive, synergistic, or antagonistic effects.

Most of the interactions observed with antipsychotics can be associated with metabolism, which is mediated by CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) or uridine diphosphate glucuronosyltransferases (see Sect. 2.2.1), whereby effective antipsychotic levels are either decreased or increased, as a result of which antipsychotic efficacy is reduced or ADRs aggravated and the risk of intoxication increased. In order to maintain dosage within the therapeutic range under these circumstances and to avoid an untimely change of medication, TDM is advisable (see also Sect. 5.6). Specific interactions are described for each antipsychotic separately in Sect. 5.7. However, a short overview of the most important co-administered drugs, foodstuffs, and recreational drugs, which might cause interactions, is summarized in Table 5.9.

Antidepressants in combination with antipsychotics are commonly used in patients with concomitant psychotic and depressive symptoms, for treatment of negative symptoms of schizophrenia, or in patients with refractory obsessive-compulsive disorder. Especially the SSRIs may cause a relevant inhibition of CYP enzymes (see Table 4.7).

Antipsychotics are often used in conjunction with benzodiazepines, with potentiation of

Table 5.9 Interactions between antipsychotics and other medications, foodstuffs, and recreational drugs relevant to children and adolescent psychiatry

Interaction with	Effect	Recommendation
ACE inhibitors (such as captopril, enalapril)	Drop in blood pressure	Monitoring of blood pressure
α-Adrenoceptor agonists (such as noradrenaline, adrenaline, clonidine)	Synergism (hypotonia, reflex tachycardia)	Blood pressure monitoring
Alcohol	Sedation	Moderate alcohol consumption
Antacids, adsorbents	Complex formation with reduced resorption of antipsychotics	Avoid simultaneous administration (at least an hour between medications)
Antiarrhythmics (such as quinidine)	Intensification of cardiac effects (QT prolongation)	ECG monitoring
Antibiotics		
Doxycycline, griseofulvin, rifampicin, chloramphenicol, clarithromycin, erythromycin	More rapid antipsychotic metabolism Inhibition of hepatic metabolism with elevation of blood levels	Choose an alternative antibiotic Monitoring of blood levels

(continued)

Table 5.9 (continued)

Interaction with	Effect	Recommendation
Anticholinergics	Synergistic intensification of anticholinergic ADRs	Caution, particularly with low-potency antipsychotics
	Dubious: reduction of antipsychotic potency	
Anticoagulants (warfarin, phenprocoumon)	Increased bleeding time	Partial thromboplastin time monitoring
Antidepressants	Elevated antipsychotic plasma levels with greater risk of ADRs Synergism, particularly with tricyclic antidepressants. **Caution**: QT prolongation (tricyclic antidepressants) Maprotiline reduces seizure threshold (especially in combination with clozapine) Avoid combination of mianserin with clozapine (additive leukocyte and granulocytopenia risks)	SSRIs are to be preferred; lowest CYP2D6 inhibition: citalopram Where levels are elevated: adjust dosage Unfavorable: fluvoxamine or fluoxetine + clozapine (ten- and twofold increase in clozapine levels, respectively) **NB**: good antidepressive effects per se reported for clozapine, flupentixol, risperidone, sulpiride, and thioridazine
Antidopaminergics (such as metoclopramide)	Increased risks of extrapyramidal motor ADRs	Selection of less centrally active medications (such as domperidone)
Antihistamines (such as diphenhydramine)	Arrhythmias, QTc prolongation, sedation, delirium	ECG monitoring
Benzodiazepines	Sedation	Synergism is often desirable
		Caution: clozapine + benzodiazepines (respiratory depression)
β-Adrenoceptor antagonists (β-blockers)	Higher antipsychotic plasma levels	Possibly dosage reduction
Carbamazepine	Reduced antipsychotic plasma levels	Dosage adjustment
	Caution: combination with clozapine (blood count changes)	
Clozapine	Increased ADRs, delirium, seizures	Avoid combination with tricyclic, low-potency, and depot antipsychotics (e.g., olanzapine, quetiapine
		TDM
Coffee, **tea**	Antipsychotic precipitation in stomach and loss of efficacy	Moderate consumption
	Anxiety states	
Diuretics	Hypotonia	Blood pressure monitoring
Grapefruit juice	Inhibition of hepatic metabolism and increase in antipsychotic level	Avoid!
Insulin	Reduce blood sugar levels	Blood glucose monitoring
Histamine H2-receptor antagonists	Cimetidine increases levels of antipsychotics	Better: ranitidine, famotidine
		Close medical monitoring, especially with clozapine
Lithium salts	Increased risk of ADRs for both medications	
	Caution: extrapyramidal motor disturbances, neurotoxicity, neuroleptic malignant syndrome	
Milk	Antipsychotic precipitation in stomach and loss of efficacy	Reduced milk consumption Antipsychotics not to be taken with milk

Table 5.9 (continued)

Interaction with	Effect	Recommendation
Opioid analgesics	Sedation	Monitoring
	Increased ADRs of antipsychotics	
Ovulation inhibitors, estrogens	Reduced hepatic metabolism of antipsychotics, with increased ADRs	Monitoring Gynecological counseling
	Caution: impaired contraceptive efficacy	
Phenytoin	Reduced antipsychotic levels as the result of CYP induction	TDM Dosage adjustment
Smoking	Reduced plasma levels of some antipsychotics as the result of CYP1A2 induction	Avoid! Smokers can require up to twice the normal antipsychotic dosage
Valproic acid	Higher valproic acid levels with phenothiazine antipsychotics (e.g., chlorpromazine, levomepromazine), with increased risk of ADRs	TDM Dosage adjustment

ACE angiotensin converting enzyme, *ADRs* adverse drug reactions, *CYP* cytochrome P-450, *SSRI* selective serotonin reuptake inhibitor, *TDM* therapeutic drug monitoring

sedative effects. Apart from clozapine, this combination is well tolerated. Antipsychotics are also frequently combined with antiepileptics, particularly those with mood-stabilizing properties. Carbamazepine, phenytoin, and phenobarbital can cause relevant interactions.

5.4.6 Contraindications

Limitations on usage apply in cases of:

- Intoxication with centrally depressant psychopharmacological agents and alcohol
- Epilepsy
- Hematologic disorders
- Cardiovascular disorders
- Endocrine disorders
- Hepatic and renal dysfunction

Table 5.10 summarizes these and other contraindications as well as the recommended therapeutic measures.

Caution is advised:

- During **pregnancy** and **nursing**. Antipsychotic drugs have not been associated with teratogenic effects, but the possibility of such effects, particularly during the first trimester, cannot be excluded. The risk of malformations (particularly microcephalia, dysmelia) appears to be somewhat higher for phenothiazines with aliphatic side chains (such as chlorpromazine). Information regarding the effects of antipsychotics on the fetus, however, is largely restricted to individual case reports, so that general conclusions cannot be drawn. A connection between the use of tricyclic antipsychotics (e.g., chlorpromazine, clozapine, flupentixol, fluphenazine, levomepromazine, olanzapine, promethazine, quetiapine, thioridazine, zotepine) during pregnancy and the increased incidence of infant retinopathy nevertheless seems likely. Transitory parkinsonian symptoms can occur in the child following use of first-generation antipsychotics during the final trimester of pregnancy. Data regarding antipsychotic concentrations in breast milk are contradictory (varying by up to 85 %), but weaning as early as possible seems advisable as a precaution.
- In **combination** therapy involving **clozapine**. Combination of clozapine with first-generation tricyclic depot antipsychotics (e.g., chlorpromazine, flupentixol, fluphenazine, levomepromazine, promethazine, thioridazine), olanzapine, carbamazepine, oxcarbazepine, lamotrigine, or mianserin increases the risk of **hematologic changes**. In combination

Table 5.10 Absolute and relative contraindications of therapy with antipsychotics in child and adolescent psychiatry

Contraindication	Recommendation
Cardiovascular disorders (arrhythmias, long QT syndrome, conduction disorders, hypotonia)	Cautious gradual increase in dosage with close ECG monitoring; QTc prolongation particularly problematic with some second- and third-generation antipsychotics
Disorders aggravated by anticholinergic effects (urinary retention, close-angle glaucoma, pyloric stenosis)	Avoid low-potency antipsychotics in particular (higher affinity for acetylcholine receptors)
Endocrine disorders	
Increased prolactin levels, including pheochromocytoma	Quetiapine and clozapine are not currently associated with elevated prolactin levels (see Sect. 5.4.4)
Diabetes mellitus type 2	Regular monitoring of blood glucose
Epileptic seizures	Avoid icterogenic antipsychotics (particularly low-potency first-generation and sedative second-generation antipsychotics; exception: melperone); monotherapy with a high-potency first- or second-/third- generation antipsychotic agent to be preferred, **not clozapine**!
Hematologic disorders (particularly leukopenia)	Changes in leukocyte count, haloperidol much less frequently (see Sect. 5.4.4) **Avoid** tricyclic antidepressants!
Hepatic and renal dysfunction	Select antipsychotics according to metabolic characteristics, Regular therapeutic drug monitoring
Hypersensitivity to particular drug components	Switch to a better tolerated antipsychotic agent
Pregnancy and nursing	See Sect. 5.4.6.

with low-potency antipsychotics, anticholinergic ADRs and the risk of seizures can be increased. Tricyclic antidepressants (especially maprotiline) further lower the seizure threshold and prolong the QTc interval. SSRIs, such as citalopram, are thus to be preferred. Parallel medication with benzodiazepines requires close monitoring because of the risk of respiratory depression. The following medications can influence effective clozapine levels: fluvoxamine, fluoxetine, paroxetine, erythromycin, ketoconazole, cimetidine, ethinylestradiol, and ritonavir increase plasma levels; and carbamazepine, phenytoin, and rifampicin lower plasma concentrations (Hiemke et al. 2011). **Caution**: **lithium**-induced leukopoiesis can conceal clozapine-related granulocytopenia.

Driving ability and capacity to attend school or pursue an occupation are improved compared to the situation prior to the beginning of therapy or even restored. The question of driving availability must be addressed on a case-by-case basis, and the same applies to certain activities in the workplace (e.g., the operation of machinery). What is far more problematic are combinations with alcohol or recreational drugs, with some co-medications (Table 5.9), as well as during changes of medication.

With regard to **driving ability**, it is recommended that patients treated with antipsychotics should be assessed with standardized (sustained) attention, reaction, and concentration tests, similar to those used in the diagnosis of ADHD. A printed summary of the findings can be given to the patients to be presented to authorities, as required. An overall assessment of driving or work capacity, however, should be avoided for legal reasons and be left to the judgment of the appropriate responsible bodies.

5.5 Duration of Treatment

When treating the initial manifestations of schizophrenic-type disorder, it is advisable to employ the prescribed antipsychotic medication

for at least one year. If complete recovery ensues more rapidly and if it seems probable that the treated symptoms were only part of a brief psychotic episode (e.g., a drug-induced episode), the dosage can be carefully reduced and discontinued at an earlier stage. In case of a **relapse**, treatment should be continued for a period of five years. Trial discontinuation of medication should in no circumstances be abrupt, and the dosage be reduced by small steps over a period of at least six months (see also Chap. 25).

For **other indications**, where medium- and low-potency antipsychotics or low dosages of second- and third-generation antipsychotics are generally employed with the aim, for instance, of sedation, tension reduction, facilitation of mental distancing, or diminution of impulsivity (see Table 5.5), the medication can be retained for several years, if the vegetative tolerance allows. This is of particular importance for severe (auto) aggressive behavioral disorders in the context, for example, of autism or intellectual deficit. In such cases, lifelong antipsychotic treatment can sometimes be necessary in order to ensure improved quality of life. High-potency first-generation antipsychotics should always be the last choice because of the risks of late dyskinesias during long-term therapy. The recommended monitoring procedures (see below) should be undertaken regularly.

5.6 Therapeutic Monitoring

As described above, studies comparing rates of antipsychotic ADRs in children and adolescents with those in similar studies of adults indicated that children and adolescents were at higher risk for developing a number of antipsychotic-induced ADRs (Correll 2008). Antipsychotics' safety profile is thus crucial for the treatment strategy in children and adolescents with schizophrenia or bipolar disorder, because of the long-term course of pharmacological therapy. Second- and third-generation antipsychotics are considered safer than the first-generation agents, but they are frequently associated with ADRs, including weight gain and metabolic complications, elevation in prolactin levels, extrapyramidal motor ADRs, sedation, and cardiac effects that require careful monitoring (Amor 2012; Fraguas et al. 2011; Masi and Liboni 2011). A **monitoring strategy** suggested by Correll (2011) is summarized in Table 5.11.

Since weight gain is associated with important negative effects that include medical morbidity (such as diabetes, hypertension, dyslipidemia, and osteoarthritis), social withdrawal, noncompliance, and lowered self-esteem, careful monitoring of weight gain in children and adolescents treated with antipsychotics is highly recommendable (Correll 2008; Correll and Carlson 2006), yet the need for guidelines or recommendations about monitoring and management of these ADRs has not been fully met.

Dietary recommendations and educational counseling are needed at the beginning of the treatment with second- and third-generation antipsychotics. Correll and Carlson (2006) have outlined **potential strategies** for predicting, preventing, and **managing weight gain** in this patient population. Monitoring patients on second- and third-generation antipsychotic agents should include measurements of body height and weight at each visit and the BMI percentile should be calculated. Specific preventive and interventional strategies aimed at minimizing weight gain and related health problems associated with psychotropic medications are discussed by Correll and Carlson (2006). These strategies include educating and monitoring as well as reinforcing healthy lifestyle behaviors; the choice of an antipsychotic agent with a lower likelihood of adverse effects on body composition and metabolic status, ideally, at the beginning of treatment or when marked initial weight gain becomes apparent; the initiation of a formalized, non-pharmacological weight loss treatment (e.g., special diet, Weight Watchers, behavioral weight management program) or a pharmacological intervention if the first and second steps insufficiently addressed weight gain and metabolic complications. Body exercises are promising and should be part of therapy already at the beginning for prevention.

Therapies that have had some success in **producing weight loss** in children and adolescents

Table 5.11 Monitoring strategies in children and adolescents following treatment with antipsychotics

Assessment	Baseline	Each visit	During titration and at target dose	At 3 months	3-monthly	6-monthly	Annually
Personal and family medical history[a]	Yes	No	No	No	No	No	Yes
Lifestyle behaviors[b]	Yes	Yes	No	No	No	No	No
Sedation/somnolence	Yes	Yes	No	No	No	No	No
Height, weight (calculate BMI percentile, BMI z score)	Yes	Yes	No	No	No	No	No
Sexual/reproductive dysfunction	Yes	No	Yes	Yes	Yes	No	No
Parkinsonism (SAS or ESRS), **akathisia** (AIMS or ESRS)	Yes	No	Yes	Yes	No	No	Yes
Tardive dyskinesia	Yes	No	No	Yes	No	No	Yes
Fasting blood, glucose and lipids[c]	Yes	No	No	Yes	No	Yes	No
Liver function tests	Yes	No	No	Yes	No	No	Yes
Electrolytes, full blood count, renal function	Yes	No	No	No	No	No	Yes, more frequent blood counts if on clozapine
Prolactin	Only if symptomatic[d]		Only if symptomatic[d]	Only if symptomatic[d]	Only if symptomatic[d]	Only if symptomatic[d]	Only if symptomatic[d]
Blood pressure and pulse	Yes	No	No	Yes	No	No	Yes
EKG	Only if symptomatic$_e$		Only if symptomatic[e]	Only if symptomatic[e]	Only if symptomatic[e]	Only if symptomatic[e]	Only if symptomatic[e]

According to Correll (2011)

AIMS Abnormal Involuntary Movement Scale, *ESRS* Extrapyramidal Symptom Rating Scale, *SAS* Simpson Angus Rating Scale

[a]Including components of the metabolic syndrome (obesity, arterial hypertension, diabetes, dyslipidemia); past medical history of coronary heart disease or coronary heart disease equivalent disorders (i.e., diabetes mellitus, peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease); history of premature coronary heart disease or in first-degree relatives (males <55 years, females <65 years); history of premature sudden cardiac death in first-degree relatives (males <50 years, females <55 years); personal history of heart murmur, irregular heartbeat, tachycardia at rest, or dizziness or syncope upon exertion; and past efficacy and adverse drug reaction experiences in patients and/or family members

[b]Lifestyle behaviors: diet, exercise, smoking, substance use, and sleep hygiene

[c]More frequent assessment may be necessary in high-risk patients (e.g., family history of diabetes, non-Caucasian ethnicity, BMI ≥95th percentile, weight gain ≥7 % over 3 months or less, or weight gain ≥0.5 BMI z score at any time point)

[d]In case of symptoms or signs of sexual dysfunction, draw fasting in the morning and approximately 12 h after the last antipsychotic dose

[e]In case of family history of sudden cardiac death in first-degree relatives (males <50 years, females <55 years); prolonged QTc syndrome; or personal history of heart murmur, irregular heartbeat, tachycardia at rest, or dizziness or syncope upon exertion; or in case of co-treatment with another QTc-prolonging medication (http://azcert.org/medical-pros/drug-list/bycategory.cfm#)

receiving antipsychotics include metformin, topiramate, amantadine, and orlistat. Lessig et al. (2001) reported that the combination of 50 mg topiramate with 75 mg quetiapine reverses weight gain that had already occurred in a 14-year-old girl with major depression and psychotic symptoms. An open study showed that 200–300 mg/day amantadine stabilized weight increase associated with different second- and third-generation antipsychotics in nine- to 16-year-old patients (Gracious et al. 2002). In nineteen ten- to 18-year-old patients, the addition of 500 mg metformin three times a day to valproic acid, olanzapine, or risperidone ended the rapid weight gain (Morrison et al. 2002).

In view of data indicating that abdominal obesity is most closely related to the metabolic syndrome in adults treated with antipsychotics, quarterly measurements of waist circumference may also be helpful (Correll and Carlson 2006). Children and adolescents are still growing, so these data are only useful in conjunction with the use of age- and sex-adjusted waist circumference percentiles.

Monitoring for diabetes should include a baseline fasting blood glucose measurement before a drug is instituted, if possible; follow-up blood glucose determinations should be performed three months after starting medication and every six months thereafter (Correll and Carlson 2006). High-risk patients should have fasting blood glucose measurements performed at least quarterly. Patients should be asked at each visit about unintended weight loss, polyuria, and polydipsia, which, if present, could indicate the onset of hyperglycemia. In conjunction with fasting blood sugar measurements, a fasting serum lipid panel should be obtained at baseline before drug therapy is begun, at three months after starting the drug, and every six to 12 months thereafter, if results are within normal limits and BMI percentile values are stable.

Although diabetes mellitus is a temporally more distant but serious potential ADR of antipsychotic medications associated with weight gain, an earlier indicator of increased risk for diabetes consists of increasing insulin resistance that can be assessed by calculating the fasting triglycerides to HDL-c cholesterol ratio in adults (reviewed in Correll and Carlson 2006). However, this use of the triglyceride-HDL cholesterol ratio has yet to be replicated in other adult populations and to be validated in children and adolescents.

In addition to and as a potential result of significant weight gain, treatment with second- and third-generation antipsychotics has been associated with lipid abnormalities, such as elevated triglyceride, total cholesterol and LDL cholesterol levels, and/or decreased HDL cholesterol levels (Correll 2008; Masi and Liboni 2011). Moreover, weight gain and obesity are also associated with the **metabolic syndrome**, a constellation of physical and laboratory features that is more common in obese patients and predisposes adults to atherosclerotic cardiovascular disease. The features of the metabolic syndrome are abdominal obesity, dyslipidemia (principally elevated serum triglycerides and low HDL cholesterol), glucose intolerance, and hypertension. A common cause for all features of the metabolic syndrome appears to be insulin resistance, which can result from weight gain.

Dyslipidemia should **be treated** initially with dietary measures; if this is not sufficient, drug therapy could be given with a fibric acid derivative (gemfibrozil or fenofibrate), a statin, fish oil, or niacin, if appropriate (Correll and Carlson 2006). **Diabetes** may **be treated** with diet, oral hypoglycemic agents, or insulin, as needed, but it should also be remembered that diabetes induced by second- and third-generation antipsychotic agents may sometimes disappear when the drug is stopped or changed (Correll and Carlson 2006).

General assessment of blood levels during therapy (TDM, see Sect. 2.3) is of increasing importance as an instrument to optimize dosage and to prevent ADRs, although the lack of age-specific therapeutic ranges for children and adolescents means that the clinical course should remain the key guide for dosage adjustment. Because of the special features of psychopharmacological agent therapy in children and adolescents (see Chap. 2), **TDM** is nevertheless **generally indicated** and useful as supplementary screening (Egberts et al. 2011):

- To check dubious compliance with regard to the medication schedule.
- To maintain dosage within the therapeutic range and to avoid premature changes of

medication, where response to an antipsychotic agent is unsatisfactory.
- For smokers (depending upon level of consumption, plasma levels can be up to 50 % lower than in nonsmokers on the same dosage).
- With clozapine, in order to avoid overdosage and increased risk of severe ADRs.
- With combination therapies, to facilitate dose adjustment according to changes in level. Most interactions observed with antipsychotics can be associated with metabolism, which is mediated by CYP isoenzymes, whereby effective antipsychotic levels are either decreased or increased, as a result of which antipsychotic efficacy is reduced or ADRs aggravated and the risk of intoxication increased.

The recommended **therapeutic reference ranges** for the treatment of adult schizophrenia and schizoaffective disorders (in alphabetical order) are as follows: amisulpride 100–320 ng/ml, clozapine 350–600 ng/ml, haloperidol 1–10 ng/ml, levomepromazine 30–160 ng/ml, melperone 30–100 ng/ml, olanzapine 20–80 ng/ml, perphenazine 0.6–2.4 ng/ml, pimozide 15–20 ng/ml, quetiapine 100–500 ng/ml, risperidone plus 9-hydroxyrisperidone (active moiety) 20–60 ng/ml, sulpiride 200–1,000 ng/ml, ziprasidone 50–200 ng/ml, and zotepine 10–150 ng/ml (Hiemke et al. 2011).

There are currently no corresponding age-specific **ranges for children and adolescents**. In one prospective naturalistic study, the relationship between dosage, serum concentration, treatment response, and ARDs was assessed in 21 adolescent schizophrenic patients (mean age 15.9 ± 1.5 years) treated with **quetiapine** (Gerlach et al. 2007). There was a marked variability of the serum concentrations, ranging from 19 to 877 ng/ml; 40.8 % of the determined values were below and 24.5 % above the previous therapeutic range (70–170 ng/ml) recommended for adults. Interestingly, none of the patients had severe ADRs. These results suggest a different therapeutic window for children and adolescents.

The relationship between the dosage, the serum concentration, and the clinical outcome for **risperidone** has been investigated in 103 children and adolescents (mean age 12.3 ± 3.1 years) with impulsive-aggressive symptoms (Klampfl et al. 2010). Based on the serum concentrations at the therapeutically effective dose range (0.25–1.5 mg/day), a therapeutic range of serum concentrations of the active moiety of risperidone for the treatment of children and adolescents with impulsive-aggressive symptoms (8–26 ng/ml) was suggested. The suggested range is much lower than that for the treatment of adult schizophrenia (20–60 ng/ml).

5.7 Clinical Pharmacology of Selected Antipsychotics: Overview

The following summaries are based upon information included in the Summary of Product Characteristics (SPCs) and the Prescribing Information (PI), respectively, depending whether the drug is approved in the EU and the USA. In addition, information is included from a recent review on the pharmacokinetic and pharmacodynamic characteristics, metabolism, and drug interactions on common antipsychotics (Patteet et al. 2012). Issues concerning the preparation of SPCs and PI and their limitations were discussed in detail in Sect. 4.7. The most important pharmacological features of the selected antipsychotics are presented as an orientation aid in clinical use.

The following is a list of abbreviations used in the tables: ADR, adverse drug reactions; AUC, area under the curve, b.i.d. 2× day; c_{max} maximal plasma concentration after oral dosing; CNS, central nervous system; CYP, cytochrome P_{450}; $D_{1–5}$, molecular dopamine receptor subtype of the D_2-receptor family; EMA, European Medicines Agency; i.m., intramuscular; K_i, the amount of the antipsychotic needed to block 50% of the receptors in vitro (therefore, a lower number denotes stronger affinity and binding to the respective receptor); q.i.d., 4× day; t.i.d., 3× day; t_{max}, time required to reach peak plasma concentration (c_{max}); $t_{1/2}$, elimination half-life; TDM, therapeutic drug monitoring

5.7.1 Amisulpride

Pharmacodynamic characteristics	Second-generation antipsychotic; high-affinity D_2 (K_i 2.8 nM) and D_3-dopamine (K_i 3.3 nM) receptor antagonist. No inhibition of dopamine D_1, D_4, and D_5 receptors or other receptors In the rodent, it preferentially blocks postsynaptic D_2-receptors located in the limbic structures as compared to those in the striatum as indicated by its reversal of D-amphetamine induced hyperactivity without affecting stereotypes. In addition, it does not induce catalepsy and it does not produce D_2-receptor hypersensitivity after repeated treatment. Moreover, it preferentially blocks presynaptic D_2-/D_3-dopamine receptors, producing dopamine release responsible for its disinhibitory effects This pharmacological profile may explain its antipsychotic effect at higher doses through postsynaptic dopamine receptor blockade located in the limbic areas and its efficacy against negative symptoms, at lower doses, through presynaptic dopamine receptor blockade. In addition, the reduced tendency to produce extrapyramidal ADRs may be related to its preferential limbic activity
Pharmacokinetic characteristics	Biphasic absorption profile: t_{max} 1 and 3–4 h, $t_{1/2}$ 12–20 h, protein binding 17 %, bioavailability 43–48 % No hepatic metabolism, no activity on main human CYP isoenzymes, renal elimination
Indications	**Approved** by the FDA in the **USA** and in **Europe** for the treatment of: Acute and chronic schizophrenic disorders, in which positive symptoms and/or negative symptoms are prominent, including patients characterized by predominant negative symptoms Amisulpride is contraindicated in children under 15 years of age as its safety has not yet been established (FDA) The efficacy and safety of amisulpride from puberty to the age of 18 years have not been established. There are limited data available on the use in adolescents in schizophrenia. Therefore, the use from puberty to the age of 18 years is not recommended (Europe)
Dosage	Amisulpride can be administered once daily at oral doses up to 300 mg, higher doses should be administered b.i.d For acute adult psychotic episodes: oral doses between 400 and 800 mg/day. In individual cases, the daily dose may be increased up to 1,200 mg/day For patients characterized by predominant negative symptoms: oral doses between 50 and 300 mg/day. Doses should be adjusted individually
ADRs	The following ADRs have been observed in controlled clinical trials: **Very common** (≥1/10): extrapyramidal symptoms may occur including tremor, rigidity, hypokinesia, hypersalivation, akathisia, and dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms, which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50–300 mg/day Psychiatric disorders: insomnia, anxiety, agitation, and orgasmic dysfunction Gastrointestinal disorders: constipation, nausea, vomiting, and dry mouth Endocrine disorders **Common** (≥1/100; <1/10): extrapyramidal motor symptoms: acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent Somnolence Endocrine disorder: increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhea, amenorrhea, gynecomastia, breast pain, and erectile dysfunction Cardiovascular disorders: hypotension Weight gain
Drug interactions	No interaction with other drugs and no effect on the activity of the CYP enzyme system Dose-corrected amisulpride plasma concentration can be required with co-administration of lithium salts or clozapine (competitive inhibition of active renal elimination)
Contraindications	Hypersensitivity to the active ingredient or to other ingredients of the medicinal product, children before the onset of puberty, lactation

5.7.2 Aripiprazole

Pharmacodynamic characteristics	Third-generation antipsychotic; dopamine D_2-receptor and serotonin 5-HT_{1A}-partial agonist, serotonin 5-HT_{2A}-receptor antagonist Modest activity for α_1-adrenergic, histamine H_1, serotonin 5-HT_6, and 5-HT_7-receptors
Pharmacokinetic characteristics	t_{max} 3–5 h, $t_{1/2}$ 60–80 h; protein binding > 99 %, bioavailability 87 % Metabolism primarily in the liver via CYP3A4 and CYP2D6 Its major metabolite that represents 40 % of the plasma aripiprazole concentration is dehydroaripiprazole, with a similar affinity for dopamine D_2-receptors as aripiprazole
Indications	**Oral formulations** Schizophrenia, for adults and adolescents aged 13–17 years (FDA, in Europe aged 15 years and older) Acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy (FDA) As adjunct to lithium or valproate for children and adolescents aged 10–17 years (FDA) Treatment of irritability associated with autistic disorder for children and adolescents aged 6–17 years (FDA) Moderate to severe manic episodes in bipolar I disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (EMA) Treatment up to 12 weeks of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 years and older (EMA) **I.m. injection** Agitation associated with schizophrenia of bipolar I disorder for adults (FDA)
Dosage	**Oral formulations**: once daily without regard to meal Schizophrenia (adolescents): initial dose 2 mg/day, recommended dose 10 mg/day, maximum 30 mg/day Bipolar I disorder (children and adolescents): initial dose 2 mg/day, recommended dose 10 mg/day, maximum 30 mg/day Irritability associated with autistic disorder (children and adolescents): initial dose 2 mg/day, recommended dose 5–10 mg/day, maximum 15 mg/day **I.m. injection** Wait at least 2 h between doses. initial dose 9.75 mg/1.3 mL, maximum daily dose 30 mg
ADRs	Commonly observed ADRs (incidence ≥5 % and at least twice that for placebo in children and adolescents) **Schizophrenia**: extrapyramidal motor ADRs, somnolence, and tremor **Bipolar I disorder**: somnolence, extrapyramidal motor ADRs, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, and dizziness **Irritability associated with autistic disorder**: sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal motor ADRs, and lethargy Adult patients with **agitation** associated with schizophrenia of bipolar I disorder: nausea
Drug interactions	Strong CYP3A4 (e.g., ketoconazole) or CYP2D6 inhibitors (e.g., **fluoxetine**) increase the drug concentration of aripiprazole; reduce the dose of aripiprazole to one-half of the usual dose when used concomitantly, except when used as adjunctive treatment with antidepressants. If a strong CYP3A4 and a strong CYP2D6 inhibitor are co-administered or a known CYP2D6 poor metabolizer is receiving a concomitant strong CYP3A4 inhibitor, the dose should be reduced to one-quarter of the usual dose CYP3A4 inducers (e.g., **carbamazepine**) decrease the dose of aripiprazole: double its dose when used concomitantly
Contraindications	Hypersensitivity to the active substance or to any of the excipients

5.7.3 Asenapine

Pharmacodynamic characteristics	First-generation antipsychotic; the efficacy is suggested to be mediated through a combination of antagonist activity at dopamine D_2 and serotonin 5-HT_{2A}-receptors High affinity for serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_5, 5-HT_6, and 5-HT_7-receptors (K_i values of 2.5, 4.0, 0.06, 0.16, 0.03, 1.6, 0.25, and 0.13 nM), dopamine D_2, D_3, D_4, and D_1-receptors (K_i values of 1.3, 0.42, 1.1, and 1.4 nM), α_1 and α_2-adrenergic receptors (K_i values of 1.2 and 1.2 nM), and histamine H_1-receptors (K_i value 1.0 nM) and moderate affinity for H_2-receptors (K_i value of 6.2 nM). In in vitro assays asenapine acts as an antagonist at these receptors. It has no appreciable affinity for muscarinic cholinergic receptors (e.g., K_i value of 8128 nM for M_1)
Pharmacokinetic characteristics	Following sublingual administration of 5 mg: t_{max} 0.5–1.5 h, $t_{1/2}$ 24 h; protein binding >95 %, bioavailability 35 % Metabolism primarily in the liver through direct glucuronidation by UGT1A4 and oxidative metabolism by CYP isoenzymes (predominantly CYP1A2)
Indications	As sublingual formulation for: Schizophrenia, acute treatment for adults (FDA) Manic or mixed episodes associated with bipolar I disorder, acute treatment for adults (FDA and EMA) The safety and effectiveness in pediatric patients have not been established
Dosage	The sublingual tablets should be placed under the tongue and left to dissolve completely. The tablet will dissolve in saliva within seconds. Eating and drinking should be avoided for 10 min after administration **Schizophrenia**: recommended starting and target dose in adults 5 mg twice daily **Bipolar I disorder**: recommended starting dose in adults 10 mg twice daily. The dose can be decreased to 5 mg twice daily if there are adverse effects
ADRs	Commonly observed ADRs (incidence ≥5 % and at least twice that for placebo) were for Schizophrenic patients: akathisia, oral hypoesthesia, and somnolence Bipolar disorder: somnolence, dizziness, extrapyramidal ADRs other than akathisia, and weight increased
Drug interactions	With **fluvoxamine** (strong CYP1A2 inhibitor) and **paroxetine** (CYP2D6 substrate and inhibitor): cautiously approach co-administration with asenapine. The risks of using asenapine in combination with other drugs have not been extensively evaluated. Given its primary CNS effects, caution should be used when it is taken in combination with other centrally acting drugs or alcohol
Contraindications	Hypersensitivity to the active substance or to any of the excipients

5.7.4 Chlorpromazine

Pharmacodynamic characteristics	First-generation antipsychotic; high-affinity dopamine D_2 (K_i value 2.0 nM), α_1-adrenergic (K_i value 2.6 nM), and histamine H_1-receptor (K_i value 0.2 nM) antagonist. Moderate and low affinity for other receptors Its pharmacological profile of activity includes pronounced sedative and hypotensive properties, with fairly marked anticholinergic and antiemetic activity and a moderate tendency to cause extrapyramidal motor ADRs
Pharmacokinetic characteristics	t_{max} 2–4 h, $t_{1/2}$ 20–40 h; protein binding 95–98 %, bioavailability 32 ± 19 % Main route of metabolism is by oxidation, this is mediated by hepatic microsomal and other enzymes. Conjugation with glucuronic acid is prominent. Hydrophilic metabolites are excreted in urine and to some extent in the bile

Indications	**US FDA-approved** Management of manifestations of psychotic disorders Treatment of schizophrenia Control of manifestations of the manic type of manic-depressive illness Treatment of severe behavioral problems in children (1–12 years of age) marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations) and in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance Chlorpromazine should generally not be used in pediatric patients under 6 months of age except where potentially lifesaving. It should not be used in conditions for which specific pediatric dosages have not been established **Europe** Schizophrenia, other psychoses (especially paranoid), mania, and hypomania In anxiety psychomotor agitation excitement, violent or dangerously impulsive behavior. Chlorpromazine is used as an adjunct in the short-term management of these conditions Childhood schizophrenia
Dosage	Oral administration for **pediatric patients with severe behavioral problems** (6 months to 12 years of age) Outpatients: select route of administration according to severity of patient's condition and increase dosage gradually as required. Oral: ¼ mg/lb-mass body weight every 4–6 h, when necessary (e.g., for 40 lb-mass child 10 mg every 4–6 h) Hospitalized patients: as with outpatients, start with low doses and increase dosage gradually. In severe behavior disorders higher dosages (50–100 mg daily and in older children, 200 mg daily or more) may be necessary. There is little evidence that behavior improvement in severely disturbed mentally retarded patients is further enhanced by doses beyond 500 mg/day Oral administration of **patients with schizophrenia**, other psychoses, mania, hypomania, anxiety, psychomotor agitation, excitement, and violent or dangerously impulsive behavior Adults: initially 25 mg 3 times daily or 75 mg at bedtime increasing daily by 25 mg to an effective maintenance dose. This maintenance dose is usually 70–300 mg daily but may be up to 1 g daily in some patients Children 6–12 years: one-third to half the adult dose to a maximum recommended dose of 75 mg daily

ADRs	ADRs include insomnia, nightmares, depression, agitation, dry mouth, nasal stuffiness, apathy, pallor, convulsions, and hypothermia
	Hypotension, usually postural, is a common ADR. **Cardiac arrhythmias**, possibly dose related, have been reported with antipsychotic therapy and include atrial arrhythmia, A-V block, ventricular tachycardia (rare), and fibrillation. ECG changes have been reported, including prolongation of the QT interval, ST depression, T wave changes, torsades de pointes, and appearance of U waves
	In a small percentage of patients taking chlorpromazine, **jaundice**, which is usually transient, occurs and may be preceded by the sudden onset of fever after 1–3 weeks of treatment. Liver function may also be affected
	Extrapyramidal motor ADRs may occur. Acute dystonias or dyskinesias, which are usually transient, are more common in children and young adults. They usually occur within the first 4 days of treatment or after increase in dosage. Parkinsonism is more common in adults and elderly patients and usually develops after weeks or months of treatment. One or more of the characteristics of Parkinsonism may be apparent (e.g., tremor, rigidity, akinesia). Tremor is common. Akathisia characteristically occurs after administration of large initial doses. Tardive dyskinesia may occur
	Patients may develop skin rashes of various kinds. Ocular changes including corneal and lens opacities and development of a metallic grayish-mauve coloration of exposed skin, the cornea, the retina, and conjunctiva have been reported in long-term therapy
	Antipsychotic agents including chlorpromazine may cause **hyperprolactinemia**, resulting in galactorrhea, gynecomastia and oligomenorrhea or amenorrhea. Impotence and weight gain may occur. Phenothiazines have been reported to cause hyperglycemia, hypercholesterolemia, fecal impaction, severe paralytic ileus, and megacolon
	Neuroleptic malignant syndrome characterized by hyperthermia, rigidity, autonomic dysfunction, and altered consciousness may occur with any antipsychotic agent
Drug interactions	Chlorpromazine diminishes the effect of oral anticoagulants
	Chlorpromazine may **lower the convulsive threshold**; dosage adjustments of anticonvulsants may be necessary. Potentiation of anticonvulsant effects does not occur. However, it has been reported that it may interfere with the metabolism of phenytoin and thus precipitate phenytoin toxicity
	Concomitant administration with propranolol results in increased plasma levels of both drugs
	Concomitant use with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsades de pointes. Therefore, concomitant use of these products is **not recommended**. Examples include certain **tricyclic antidepressants** (such as amitriptyline), certain tetracyclic antidepressants (such as **maprotiline**), and **antipsychotics** (e.g., phenothiazines, pimozide, sertindole, and haloperidol)
Contraindications	In cases of coma due to direct CNS depressants, such as alcohol, barbiturates, and opiates, and hypersensitivity to phenothiazines such as chlorpromazine

5.7.5 Clozapine

Pharmacodynamic characteristics	Second-generation antipsychotic; high-affinity serotonin 5-HT_{2A} and 5-HT_{2c} (K_i values 2.59 and 4.8, respectively), α_1-adrenergic (K_i value 6.8 nM), histamine H_1- (K_i value 3.1 nM), and acetylcholine M_1-receptor (K_i value 1.4 nM) antagonist; moderate-affinity dopamine $D_{1–4}$ (K_i values 50–170 nM), α_2-adrenergic (K_i value 158 nM), and serotonin 5-HT_{1A}-receptor (K_i value 160 nM) antagonist Its greater antagonistic activity on cortical and limbic dopamine D_4 than D_2-receptors is believed to be responsible for the low risk of extrapyramidal motor ADRs
Pharmacokinetic characteristics	t_{max} 1–4 h, $t_{1/2}$ 4–12 h; protein binding around 97 %, bioavailability 24–50 % Metabolism in the liver chiefly via CYP1A2; CYP2C19, CYP3A4, CYP2CP, and CYP2D6 also contribute moderately
Indications	Approved by the FDA (**USA**) and in **European countries** for: Treatment-resistant schizophrenia Because of the significant risk of agranulocytosis and seizure associated with its use, it should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments for schizophrenia, either because of insufficient effectiveness or because of the inability to achieve an effective dose due to intolerable from those drugs ADRs Safety and effectiveness in pediatric patients have not been established
Dosage	Initial treatment in adults: it is recommended that treatment begins with one-half of a 25-mg tablet once or twice daily and then to be continued with daily dosage increments of 25–50 mg/day, if well tolerated, to achieve a target dose of 300–450 mg/day by the end of 2 weeks Subsequent dosage increments should be made no more than once or twice weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation Therapeutic dose adjustment: daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300 and 600 mg/day, it may be necessary to raise the dose to the 600–900 mg/day range to obtain an acceptable response. Dosing should not exceed 900 mg/day
ADRs	ADRs observed in clinical trials at an incidence of greater than 5 % were as follows: CNS complaints, including drowsiness/sedation, dizziness/vertigo, headache, and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth, and visual disturbances; cardiovascular findings, including tachycardia, hypotension, and syncope; gastrointestinal complaints, including constipation and nausea; and fever Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction Salivation may be profuse, especially during sleep, but may be diminished with dose reduction **Caution**: **agranulocytosis** (1 %, mostly between weeks 6 and 14 of treatment), EEG changes, cerebral seizures (1 %), hypersalivation, hypotonia, tachycardia, ECG changes, anticholinergic effects, hepatic dysfunction, hyperglycemia, ketoacidosis, cutaneous reactions, and weight gain
Drug interactions	**Pharmacokinetic interactions** Carbamazepine and phenytoin, both inducers of CYP1A2 and CYP3A4, are known to decrease levels of clozapine Combined with fluoxetine and paroxetine, CYP2D6 inhibitors, it causes higher levels of clozapine **Pharmacodynamic interactions** Combination therapy with benzodiazepines can cause in the first 24–46 h after clozapine initiation lethargy, ataxia, loss of consciousness, and respiratory arrest Combination with other drugs inducing bone marrow suppression (carbamazepine, co-trimoxazole, chloramphenicol, penicillamine, sulfonamide, antineoplastics, and pyrazolone analgesics) should be avoided
Contraindications	Patients with a previous hypersensitivity to clozapine or any other component of this drug and patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, or a history of clozapine-induced agranulocytosis or severe granulocytopenia It should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The mechanism of clozapine-induced agranulocytosis is unknown; nonetheless, it is possible that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression

5.7.6 Fluphenazine

Pharmacodynamic characteristics	High-potency first-generation antipsychotic; high-affinity dopamine D_1- and D_2-receptor antagonist, low affinity for dopamine D_3, D_4, serotonin 5-HT_2, α_1-adrenergic, and histamine H_1-receptors
Pharmacokinetic characteristics	t_{max} 3 h, $t_{1/2}$ 20 h; protein binding around 91–92 %, bioavailability 20 % Metabolism chiefly via CYP3A4
Indications	**Oral application** Management of manifestation of psychotic disorders in adults (FDA) **I.m. injection** (USA and Europe) As long-acting parenteral antipsychotic drug intended for use in the management of patients requiring prolonged parenteral antipsychotic therapy (e.g., chronic schizophrenics) It has not been shown effective in the management of behavioral complications in patients with mental retardation Fluphenazine injection is not intended for use in children under 12 years of age
Dosage	**Oral application** Initial treatment in adults: 2.5–10 mg divided and given at 6- to 8-h intervals. Therapeutic effect is often achieved with doses under 20 mg daily. Patients remaining severely disturbed or inadequately controlled may require upward titration of dosage. Daily doses up to 40 mg may be necessary Maintenance treatment: when symptoms are controlled, dosage can generally be reduced gradually to daily maintenance doses of 1–5 mg, often given as a single daily dose. Continued treatment is needed to achieve maximum therapeutic benefits; further adjustments in dosage may be necessary during the course of therapy to meet the patient's requirements **I.m. injection** In general, the oral dose has been found to be approximately 2–3 times the parenteral dose Initial treatment: for most patients, a dose of 12.5–25 (0.5–1.0 mL) may be given to initiate therapy. The onset of action generally appears between 24 and 72 h after injection, and the effects of the drug on psychotic symptoms become significant within 48–96 h Maintenance treatment: a single injection may be effective in controlling schizophrenic symptoms up to 4 weeks or longer. The response to a single dose has been found to last as long as 6 weeks in a few patients on maintenance therapy
ADRs	As for other first-generation antipsychotics The most frequently reported ADRs are **extrapyramidal motor symptoms** including parkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Muscle rigidity sometimes accompanied by hyperthermia has been reported. Most often these extrapyramidal symptoms are reversible; however, they may be persistent. These reactions can usually be controlled by administration of antiparkinsonian drugs such as benztropine and by subsequent reduction in dosage Occurrences of **neuroleptic malignant syndrome** have been reported in patients on antipsychotic therapy; leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur. Drowsiness or lethargy, if they occur, may necessitate a reduction in dosage; the induction of a catatonic-like state has been known to occur with dosages far in excess of the recommended amounts Phenothiazine derivatives have been known to cause, in some patients, restlessness, excitement, or bizarre dreams. Hypertension and fluctuations in blood pressure have been reported
Drug interactions	Not known Because of added anticholinergic effects, the combination with psychotropic drugs affecting the cholinergic system should be avoided
Contraindications	Patients with suspected or established subcortical brain damage, in patients who have shown hypersensitivity to fluphenazine (cross-sensitivity to phenothiazine derivatives may occur), and in patients receiving large doses of hypnotics. The presence of blood dyscrasia or liver damage

5.7.7 Haloperidol

Pharmacodynamic characteristics	High-potency first-generation antipsychotic; high-affinity dopamine D_{2-}-receptor antagonist, moderate-affinity adrenergic α_1-receptor and serotonin 5-HT_{2A}-receptor antagonist, no affinity for muscarinic acetylcholine receptors (see Tables 5.2 and 5.3)
Pharmacokinetic characteristics	t_{max} 2–6 h (oral), t_{max} 20 min (i.m. injection of the lactate form), t_{max} 14–28 days (i.m. injection of the long-acting decanoate form); $t_{1/2}$ 14–41 h (oral and i.m. injection of the lactate form), $t_{1/2}$ 14–28 h (i.m. injection of the decanoate form); protein binding ca. 90 %, bioavailability 60–70 % Metabolism via CYP3A4 plays an important role. CYP2D6 is also involved but to a lesser degree, and influence of CYP1A2 is probably negligible
Indications	**FDA approved (USA)** Management of manifestations of psychotic disorders Control of tics and vocal utterances of Tourette's disorder in children and adults Treatment of severe behavior problems in children of combative, explosive hyperexcitability (which cannot be accounted for by immediate provocation) Short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance Haloperidol should be reserved for these two groups of children only after failure to respond to psychotherapy or medications other than antipsychotics Safety and effectiveness in pediatric patients have not been established Haloperidol is not intended for children under 3 years old **Europe** *Adults* Schizophrenia: treatment of symptoms and prevention of relapse Other psychoses: especially paranoid Mania and hypomania Mental or behavioral problems such as aggression, hyperactivity, and self-mutilation in the mentally retarded and in patients with organic brain damage As an adjunct to short-term management of moderate to severe psychomotor agitation, excitement, violent or dangerously impulsive behavior Restlessness and agitation in the elderly Gilles de la Tourette's syndrome and severe tics *Children* Childhood behavioral disorders, especially when associated with hyperactivity and aggression Gilles de la Tourette's syndrome Childhood schizophrenia

Dosage	**Oral application** Children (ages of 3–12 years, weight range 15–40 kg): therapy should begin at the lowest dose possible (0.5 mg/day). If required, the dose should be increased by an increment of 0.5 mg at 5–7-day intervals until the desired therapeutic effect is obtained. The total dose may be divided, to be given b.i.d. or t.i.d Upon achieving a satisfactory therapeutic response, dosage should then be gradually reduced to the lowest effective maintenance level Adults: initial dose range 0.5–2 mg b.i.d. or t.i.d. (moderate symptomatology), 3–5 mg b.i.d. or t.i.d (severe symptomatology) **I.m. injection** Doses of 2–5 mg are utilized for prompt control of the acutely agitated schizophrenic patient with moderately severe to very severe symptoms. Depending on the response of the patient, subsequent doses may be given, administered as often as every h although 4–8 h intervals may be satisfactory
ADRs	As for other first-generation antipsychotics Frequently extrapyramidal motor symptoms, tiredness, and hyperprolactinemia; rarely anticholinergic and antiadrenergic effects; very rarely cerebral seizures, hematologic changes, cholestatic hepatitis, leg and pelvic venous thromboses, peripheral edema, body temperature variations, cognitive impairment, alopecia, and respiratory distress
Drug interactions	**Pharmacodynamic interactions** Since QT prolongation has been observed, caution is advised when prescribing to patient with **QT-prolongation conditions** (long QT syndrome, hypokalemia, electrolyte imbalance) or to patients receiving medications known to prolong the QT interval or known to cause electrolyte imbalance As with other antipsychotic agents, haloperidol may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol **Pharmacokinetic interactions** Co-administration of inhibitors or inducers of CYP3A4 and to a lesser extent CYP2D6 are known to cause increased plasma concentrations, respectively. Haloperidol itself is a moderate inhibitor of both CYP2D6 and CPY3A4. Co-administration of **phenytoin** or **carbamazepine**, inducers of CYP3A4, can cause a rebound increase in haloperidol concentrations to toxic levels when these antiepileptics are removed from the therapeutic regimen In pharmacokinetic studies, mild to moderately increased haloperidol concentrations have been reported when it was given concomitantly with drugs characterized as substrates or inhibitors of CYP3A4 or CYP2D6 isoenzymes, such as, itraconazole, nefazodone, buspirone, venlafaxine, alprazolam, fluvoxamine, quinidine, fluoxetine, sertraline, chlorpromazine, and promethazine In a study of 11 schizophrenic patients co-administered haloperidol and increasing doses of **carbamazepine**, haloperidol plasma concentrations decreased linearly with increasing carbamazepine concentrations
Contraindications	In severe toxic CNS depression or comatose states from any cause and in individuals who are hypersensitive to this drug

5.7.8 Iloperidone

Pharmacodynamic characteristics	Second-generation antipsychotic; strong antagonist of dopamine D_2 and D_3, α_1- and α_2-adrenergic, and serotonin 5-HT_{2A}-receptors (see Table 5.3). Moderate affinity to 5-HT_{1A}, 5-HT_{2c}, and histamine H_1-receptors A strong inhibition of adrenergic receptors implicates a high risk for orthostatic hypotension and syncope but also positive effects on cognition. The low affinity for histamine H_1-receptors is believed to explain the lower risk for weight gain and sedation
Pharmacokinetic characteristics	t_{max} 2–4 h, $t_{1/2}$ 18 h (extensive metabolizers), 33 h (poor metabolizers); protein binding 95 %, bioavailability 96 % Metabolism extensively in the liver via CYP3A4 and CYP2D6. It is only partly metabolized by CYP1A2 and CYP2E1. One of the main major metabolites, reduced iloperidone, has a comparable efficacy than the parent drug and passes the blood-brain barrier
Indications	**US FDA approved** for the acute treatment of schizophrenia in adults of at least 18 years of age The safety and efficacy in pediatric and adolescent patients have not been established It is **not approved in Europe**, because the Committee for Medicinal Products for Human considered by consensus that the safety and efficacy are not sufficiently demonstrated and therefore recommended the refusal of the granting of the Marketing Authorization (EMA/177796/2013)
Dosage	The recommended starting dose in adults is 1 mg twice daily and should be increased to reach the target dosage range of 6–12 mg twice daily by increasing the daily dose to 2 mg twice daily on day 2, 4 mg twice daily on day 3, 6 mg twice daily on day 4, 8 mg twice daily on day 5, 10 mg twice daily on day 6, and 12 mg twice daily on day 7 The drug must be titrated from a low starting dose to avoid the orthostatic hypotension. The maximum recommended dose is 12 mg twice daily (24 mg/day)
ADRs	On the basis of the published clinical trials, the most commonly reported ADR was **dizziness** in approximately 12.1 % of patients taking iloperidone 4–8 mg/day, in 10.3 % of those taking 10–16 mg/day, and in 23.2 % of those given 20–24 mg/day, compared with 6.8 % of those receiving placebo In one study, **insomnia** was the major ADR, affecting between 18.1 and 21.1 % of patients receiving a mean dose of 11.8 mg/day, compared with 25.1 % of patients receiving a mean haloperidol dose of 13.2 mg/day. Somnolence, dry mouth, and dyspepsia were also reported at all dosage ranges, but extrapyramidal motor symptoms were reported with the same frequency as placebo in trials The **dosage range with the lowest rate** of ADRs is 10–16 mg/day. The highest incidence of ADRs was in patients taking 20–24 mg/day. ADRs occurring in at least 5 % of patients were akathisia, dizziness, dry mouth, dyspepsia, dystonia, fatigue, somnolence, extrapyramidal motor disorders, nasal congestion, and tremors. Akathisia, dizziness, flatulence, and tremor were noted at the lowest rates in patients receiving 10–16 mg. Dyspepsia and dystonia, however, were observed with the lowest frequency in the 20–24 mg group The incidence of corrected QT (QTc) prolongation with iloperidone was equal to that observed with ziprasidone. The mean increase reported in a clinical study was 7.2 ms with iloperidone and 6.1 ms with ziprasidone
Drug interactions	Because it is metabolized via CYP2D6 and CYP3A4, caution is advised when it is given together with strong CYP inhibitors. The dose should be reduced by half when it is co-administered with these strong CYP inhibitors Given that iloperidone displays primarily CNS effects, alcohol and other centrally acting drugs should be used with caution. In addition, considering the antagonism of adrenoceptors, the effect of antihypertensive agents would be potentiated when administered concomitantly
Contraindications	Known hypersensitivity to the drug or any of the components in the formulation. Pruritus and urticaria have been reported as symptoms of hypersensitivity

5.7.9 Levomepromazine

Pharmacodynamic characteristics	Low-potency first-generation antipsychotic; low-affinity D_2-receptor antagonist; high affinity for histamine H_1 (anti-pruriginous effect!), serotonin 5-HT_2, and adrenergic α_1-receptors; low affinity for acetylcholine receptors It resembles chlorpromazine and promethazine in the pattern of its pharmacology. It possesses antiemetic, antihistamine, and anti-adrenaline activity and exhibits a strong sedative effect
Pharmacokinetic characteristics	t_{max} 2–3 h, $t_{1/2}$ 30 h; protein binding not known, bioavailability 50 % Levomepromazine and its non-hydroxylated metabolites are reported to be potent inhibitors of CYP2D6
Indications	**Europe** As an alternative to chlorpromazine in schizophrenia especially when it is desirable to reduce psychomotor activity According to the manufacturer, no age restrictions Currently, it is **not registered in the USA**
Dosage	**Children** are very susceptible to its hypotensive and soporific effects. It is advised that a total daily oral dosage of 37.5 mg should not be exceeded. The average effective daily intake for a 10-year-old is 12.5–25 mg **Adults**: initially the total daily oral dose in ambulant patients should not exceed 25–50 mg usually divided into 3 doses; a larger portion of the dosage may be taken at bedtime to minimize diurnal sedation. The dosage is then gradually increased to the most effective level compatible with sedation and other side effects In **bed patients** the initial total daily oral dosage may be 100–200 mg, usually divided into 3 doses, gradually increased to 1 g daily if necessary. When the patient is stable, attempts should be made to reduce the dosage to an adequate maintenance level
ADRs	Tiredness and other ADRs characteristic for low-potency antipsychotics
Drug interactions	**Pharmacokinetic interactions** Co-administration of drugs primarily metabolized by CYP2D6 may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic or ADRs of those drugs **Pharmacodynamic interactions** There is an increased risk of arrhythmias when antipsychotics are used with **drugs that prolong the QT interval** such as certain class 1A and III antiarrhythmics (such as quinidine, disopyramide, procainamide, amiodarone, sotalol, and dofetilide), certain antimicrobials (such as sparfloxacin, moxifloxacin and erythromycin IV), **tricyclic antidepressants** (e.g., amitriptyline), tetracyclic antidepressants (e.g., **maprotiline**), other **antipsychotics** (e.g., phenothiazines, pimozide and sertindole), antihistamines (e.g., terfenadine), cisapride, bretylium, and antimalarials (e.g., quinine and mefloquine) The anticholinergic effect of antipsychotics may be enhanced by other anticholinergic drugs. Avoid concomitant antipsychotics and any other drugs that may cause electrolyte imbalance. **Diuretics**, in particular those causing hypokalemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred Simultaneous administration of desferrioxamine and prochlorperazine has been observed to induce a transient metabolic encephalopathy, characterized by loss of consciousness for 48–72 h. It is possible that this may occur with levomepromazine since it shares many of the pharmacological activities of prochlorperazine Adrenaline (epinephrine) must not be used in patients overdosed with antipsychotics. Alcohol should be avoided
Contraindications	There are no absolute contraindications. Safety in pregnancy has not been established

5.7.10 Melperone

Pharmacodynamic characteristics	Low-potency second-generation antipsychotic; high-affinity serotonin 5-HT_2-receptor antagonist, moderate affinity dopamine D_4-receptor antagonist, low-affinity dopamine D_2, D_3, adrenergic α_1, and histamine H_1-receptor antagonist. Only antipsychotic agent with anticonvulsive effect (can therefore be used in children with epilepsy)
Pharmacokinetic characteristics	t_{max} 1,5 h, $t_{1/2}$ 3–4 h; protein binding ca. 50 %, bioavailability 60 % CYP-metabolism not known
Indications	Restlessness and agitation states, sleep disorders, neuroses, from 12 years
	Melperone is **not licensed** in the **USA** and in the UK, but is **approved** for the above indications in **several European countries**.
Dosage	3–4 × 12.5–25 mg/day, incremental dosage increase, max. 200 mg/day; no recommendations for children
ADRs	Tiredness; other characteristic ADRs of second- and third-generation antipsychotics
Drug interactions	No alcohol and drugs also dampening any further soothing or the brain (other psychotropic drugs, sleep aid, opioid pain relievers, antihistamines) should be used in addition to melperone. In combination with tricyclic antidepressants there may be mutual efficiency gain to sudden toxic effects When simultaneous taking of blood pressure devices, there may also be an excessive lowering of blood pressure. Melperone reduces the effects of sympathomimetics such as phenylephrine (in nose drops). With adrenaline, an emergency drug that is administered in a shock, in combination with melperone there will be a fall in blood pressure (so-called adrenaline reverse)
	Tri- and tetracyclic antidepressants and melperone mutually reinforcing in their effects and ADRs
Contraindications	Known hypersensitivity to the drug or any of the components in the formulation, severe liver disease or acute poisoning by alcohol, sleep medications, opioid painkillers, or other medicinal damping of the brain

5.7.11 Olanzapine

Pharmacodynamic characteristics	Second-generation antipsychotic; high-affinity serotonin 5-HT_{2A} and 5-HT_{2C}, histamine H_1, and muscarinic M_1-receptor antagonist (Table 5.3); moderate-affinity dopamine D_2-family (Table 5.2) and serotonin 5-HT_2-receptor antagonist
Pharmacokinetic characteristics	t_{max} 5–8 h (oral), t_{max} 15–45 min (i.m.); $t_{1/2}$ 30–60 h, $t_{1/2}$ about 30 days (depot form: olanzapine pamoate); men show an increased clearance compared with women, and smokers have a 20 % shorter $t_{1/2}$ compared to nonsmokers; protein binding 93 %, bioavailability 60 % Metabolism via CYP1A2, CYP2D6 is only a minor pathway
Indications	**Oral formulation** **US FDA approval** for: Treatment of schizophrenia in adults and adolescents (ages 13–17 years) Acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder in adults and adolescents (ages 13–17 years) Adjunct to valproate or lithium in the treatment of manic or mixed episodes associated with bipolar I disorder in adults Safety and effectiveness in children <13 years of age have not been established. Medication therapy for pediatric patients with schizophrenia or bipolar I disorder should be undertaken only after a thorough diagnostic evaluation and with careful consideration of the potential risks. The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents Approved in **European countries** (coated tablets) for: Treatment of schizophrenia Maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response Treatment of moderate to severe manic episode Prevention of recurrence in patients with bipolar disorder whose manic episode has responded to olanzapine treatment It is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid, and prolactin alterations has been reported in short-term studies of adolescent patients than in studies of adult patients **I.m. injection** (USA and Europe) Treatment of acute agitation associated with schizophrenia and bipolar I mania in adults There is no experience in children

Dosage	**Oral formulation** (immediate-release formulations) Schizophrenia and bipolar I disorder in adolescents: start at 2.5–5 mg once daily; target 10 mg/day within several days Schizophrenia in adults: start at 5–10 mg once daily; target 10 mg/day within several days Bipolar I disorder in adults (mono- and adjunct therapy: start at 10 mg once daily **I.m. injection** Adults: 10 mg (5 or 7.5 mg when clinically warranted). Assess for orthostatic hypotension prior to subsequent dosing (max. 3 doses 2–4 h apart)
ADRs	Most common ADRs (≥5 % and at least twice that for placebo) associated with **oral monotherapy**: Schizophrenia (adults): postural hypotension, constipation, weight gain, dizziness, personality disorder, and akathisia Schizophrenia (adolescents): sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, and dry mouth Manic or mixed episodes, bipolar I disorder (adults): asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, and tremor Manic or mixed episodes, bipolar I disorder (adolescents): sedation, weight increased, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain, and pain in the extremity **Combination with lithium or valproate** Dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, and paresthesia
Drug interactions	**Oral formulations** *Olanzapine monotherapy* Diazepam and alcohol: may potentiate orthostatic hypotension Carbamazepine: increased clearance of olanzapine Fluvoxamine (a CYP1A2 inhibitor): may increase olanzapine levels There may be a risk for QT prolongation when olanzapine and other drugs known to cause this effect are combined *Combination with lithium or valproate* CNS-acting drugs: caution should be used when taken in combination with other centrally acting drugs and alcohol Antihypertensive agents: enhanced antihypertensive effect Combination with valproate can induce neutropenia, and combination with valproate or lithium is associated with an increased incidence of tremor, dry mouth, increased appetite, and weight gain **I.m. injection** Lorazepam (i.m.): increased somnolence with i.m. olanzapine
Contraindications	Hypersensitivity to the active substance or to any of the excipients

5.7.12 Paliperidone

Pharmacodynamic characteristics	Second-generation antipsychotic; major active metabolite of risperidone (9-OH-risperidone); high affinity for dopamine D_2, serotonin 5-HT_{2A}, and histamine H_1-receptors (see Tables 5.2 and 5.3); moderate affinity for adrenergic α_1 receptors, low affinity for histamine and adrenergic α_2-receptors, no affinity for muscarinic acetylcholine receptors
Pharmacokinetic characteristics	Extended-release formulation: t_{max} 24 h, $t_{1/2}$ 24 h (25–49 h after i.m. injection); protein binding ca. 74 %, bioavailability 28 % Excretion primarily renal, minor metabolism via CYP2D6 and CYP3A4
Indications	**US FDA approved** Treatment of schizophrenia in adults and adolescents (ages 12–17 years) Treatment of schizoaffective disorder as monotherapy and as adjunct to mood stabilizers and/or antidepressants in adults **EMA approved** Treatment of schizophrenia in adults Treatment of psychotic or manic symptoms of schizoaffective disorder in adults. Effect on depressive symptoms has not been demonstrated There is no relevant use in children aged less than 12 years. The safety and efficacy in children aged 12–17 years have not been established
Dosage	**Schizophrenia** Adolescents (<51 kg): initial dose 3 mg/day, recommended dose 3–6 mg/day, maximum dose 6 mg/day Adolescents (≥51 kg): initial dose 3 mg/day, recommended dose 3–12 mg/day, maximum dose 12 mg/day Adults: initial dose 6 mg/day, recommended dose 3–12 mg/day, maximum dose 12 mg/day **Schizoaffective disorder in adults** Initial dose 6 mg/day, recommended dose 3–12 mg/day, maximum dose 12 mg/day
ADRs	Commonly observed ADRs (incidence ≥5 % and at least twice that for placebo) were for Adults with schizophrenia: extrapyramidal symptoms, tachycardia, and akathisia Adolescents with schizophrenia: somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight increased, and tachycardia Adults with schizoaffective disorder: extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis In a short-term study with prolonged-release tablets conducted in children 12–17 years of age with schizophrenia, the safety profile was similar to that seen in adults
Drug interactions	Centrally acting drugs: due to CNS effects, use caution in combination Drugs that may cause orthostatic hypotension: an additive effect may be observed when co-administered Co-administration with carbamazepine decreased mean steady-state c_{max} and AUC of paliperidone by approximately 37 %. Adjust dose paliperidone if necessary based on clinical assessment Co-administration of divalproex sodium increased c_{max} and AUC of paliperidone by approximately 50 %. Adjust dose of paliperidone if necessary based on clinical assessment
Contraindications	Known hypersensitivity to paliperidone, to risperidone, or to any components in the formulation

5.7.13 Perphenazine

Pharmacodynamic characteristics	High-potency first-generation antipsychotic; high-affinity dopamine D_2 and serotonin 5-HT_{2A}-receptor antagonist (see Table 5.3), moderate-affinity histamine H_1-receptor agonist and adrenergic α_1-receptor antagonist
Pharmacokinetic characteristics	t_{max} 1–3 h, $t_{1/2}$ 9–12 h (dose independent); protein binding ca. 90 %, bioavailability 20 % Extensively metabolized in the liver chiefly via CYP2D6
Indications	**US FDA approved** for the treatment of schizophrenia in adults Not effective for the management of behavioral complications in patients with mental retardation It is not recommended for pediatric patients under 12 years of age **Europe** As an adjunct to the short-term management of anxiety, severe psychomotor agitation, excitement, and violent or dangerously impulsive behavior Schizophrenia, treatment of symptoms and prevention of relapse, other psychoses especially paranoid, mania and hypomania, and nausea and vomiting It should not be given to children under the age of 14 years
Dosage	Moderately disturbed nonhospitalized patients with schizophrenia: 4–8 mg t.i.d. initially, reduce as soon as possible to minimum effective dosage Hospitalized patients with schizophrenia: 8–16 mg b.i.d. to q.i.d., avoid dosages in excess of 64 mg daily
ADRs	As for other typical first-generation antipsychotics
Drug interactions	**Poor metabolizers** demonstrate higher plasma concentrations of antipsychotic drugs at usual doses, which may correlate with emergence of ADRs The concomitant administration of other drugs that inhibit the activity of CYP2D6 may acutely increase plasma concentrations of antipsychotics. Among these are **tricyclic antidepressants** and **SSRIs**, e.g., fluoxetine, sertraline, and paroxetine. When prescribing these drugs to patients already receiving antipsychotic therapy, close monitoring is essential and dose reduction may become necessary to avoid toxicity. Lower doses than usually prescribed for either the antipsychotic or the other drug may be required
Contraindications	Patients with leukopenia, or in association with drugs liable to cause bone marrow depression, patients in comatose states, patients with a known hypersensitivity to perphenazine or any of the other excipients Patients with suspected or established **subcortical brain damage**, with or without hypothalamic damage, since a hyperthermic reaction with temperatures in excess of 104 °F may occur in such patients, sometimes not until 14–16 h after drug administration. Total body ice-packing is recommended for such a reaction; antipyretics may also be useful

5.7.14 Pimozide

Pharmacodynamic characteristics	High-potency first-generation antipsychotic; high-affinity dopamine D_2 and D_3-receptor antagonist, low affinity for dopamine D_4, serotonin 5-HT_2, and adrenergic α_1-receptors
Pharmacokinetic characteristics	t_{max} 4–12 h, $t_{1/2}$ 55 h; protein binding unknown, bioavailability unknown Extensively metabolized in the liver chiefly via CYP3A4 and to a lesser extent by CYP2D6 and CYP1A2
Indications	**US FDA approved** Suppression of motor and phonic tics in patients with Tourette's disorder who have failed to respond satisfactorily to standard treatment for adolescent and adults (12 years and older) It should be reserved for use in Tourette's disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics. Although Tourette's disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy in patients less than 12 years of age is limited **Europe** Chronic schizophrenia, for the treatment of symptoms and prevention of relapse Other psychoses, especially paranoid and monosymptomatic hypochondriacal psychoses (e.g., delusional parasitosis) Intended for once daily oral administration in adults and children over 12 years of age
Dosage	Because use implicates a high risk for **cardiotoxic and neurological ADRs**, **dosing** has to be performed **carefully**. TDM would be valuable; however, a clear quantitative relationship between plasma concentrations, efficacy, or ADRs are not yet described **Tourette's disorder** Children and adolescents (≥12 years): initial dose 0.05 mg/kg preferably taken once at bedtime. The dose may be increased every third day to a maximum of 0.2 mg/kg not to exceed 10 mg/day At doses above 0.05 mg/kg/day, CYP2D6 genotyping should be performed. In poor CYP2D6 metabolizers, doses should not exceed 0.05 mg/kg per day, and doses should not be increased earlier than 14 days Adults: in general, treatment should be initiated with a dose of 1–2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg per day or 10 mg/day are not recommended At doses above 4 mg/day, CYP2D6 genotyping should be performed. In **poor CYP2D6 metabolizers**, doses should **not exceed 4 mg/day**, and doses should not be increased earlier than 14 days **Chronic schizophrenia** (≥12 years) The dose ranges between 2 and 20 mg daily, with 2 mg as a starting dose. This may be increased according to response and tolerance to achieve an optimum response **Other psychoses** (≥12 years) An initial dose of 4 mg daily which may then be gradually increased, if necessary, according to response, to a maximum of 16 mg daily
ADRs	As for other first-generation antipsychotics Extrapyramidal motor symptoms, cerebral seizures, anxiety, tiredness. In addition, cardiac arrest and sudden unexplained death have been reported

Drug interactions	Combination with macrolide antibiotics (clarithromycin, erythromycin, azithromycin, dirithromycin, and troleandomycin), antifungal agents (itraconazole and ketoconazole), and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir) that are inhibitors of CYP3A4 Combination with **SSRIs** that are inhibitors of CYP3A4 and CYP2D6 (fluvoxamine, sertraline). Because pimozide is metabolized partly by these CPY isoenzymes, these combinations could potentially impede pimozide metabolism
Contraindications	Parallel use of CYP3A4 and CYP2D6 inhibitors such as macrolide antibiotics, antifungal agents, protease inhibitors, and SSRIs such as fluvoxamine and sertraline Because pimozide prolongs the QT interval, it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, patients taking other drugs which prolong the QT interval, or patients with known hypokalemia or hypomagnesemia Patients with severe toxic CNS depression or comatose states from any cause and patients with hypersensitivity to it

5.7.15 Quetiapine

Pharmacodynamic characteristics	Second-generation antipsychotic; low-affinity dopamine D_2-receptor family antagonist and moderate affinity for serotonin 5-HT_{2A}, adrenergic $\alpha_{1/2}$, and histamine H_1-receptor (see Tables 5.2. and 5.3)
Pharmacokinetic characteristics	t_{max} 1–1.5 h (retard form: 6 h), $t_{1/2}$ 7 h (also with retard form), $t_{1/2}$ 12 h (active metabolite *N*-desalkylquetiapine); protein binding ca. 83 %, bioavailability 70 % Extensively metabolism in the liver chiefly via CYP3A4; CYP2D6 and CYP2A5 only play a minor role Two metabolites, 7-OH-quetiapine and 7-OH-*N*-desalkylquetiapine, are found active. Because of their low plasma concentrations, they are not considered important for the overall activity of quetiapine. In contrary, *N*-desalkylquetiapine (norquetiapine) is believed to have antidepressant activities
Indications	**US FDA approved** *Immediate-release tablets* Treatment of schizophrenia in adults and adolescents (ages 13–17 years) Acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy in children and adolescents (ages 10–17 years) Acute treatment of manic or mixed episodes associated with bipolar I disorder both as monotherapy and as an adjunct to lithium or divalproex in adults Acute treatment of depressive episodes associated with bipolar disorder in adults Maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex in adults *Extended-release (ER) tablets* Treatment of schizophrenia in adults Acute treatment of manic or mixed episodes associated with bipolar I disorder both as monotherapy and as an adjunct to lithium or divalproex in adults Acute treatment of depressive episodes associated with bipolar disorder in adults Maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex in adults Adjunctive treatment of major depressive disorder Safety and effectiveness have not been established for children and adolescent **EMA approved in the EU** *Immediate- and prolonged-release tablets (XR)* Treatment of schizophrenia including preventing relapses in stable schizophrenic patients who have been maintained on quetiapine XR Treatment of moderate to severe manic episodes in bipolar disorder Treatment of major depressive episodes in bipolar disorder Prevention of recurrence in patients with bipolar disorders, in patients whose maniac or depressive episode has responded to quetiapine treatment Add-on treatment (XR) of major depressive episodes in patients with major depressive disorder, who have had suboptimal response to initial antidepressant monotherapy It is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group

Dosage	**Immediate-release tablets** *Schizophrenic adolescents*: initial dose 25 mg twice daily; day 2, twice daily dosing totaling 100 mg; day 3, twice daily dosing totaling 200 mg; day 4, twice daily dosing totaling 300 mg; day 5, twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400–800 mg/day *Schizophrenic adults*: initial dose 25 mg twice daily. Increase in increments of 25–50 mg divided 2 or 3 times on days 2 and 3 to range of 300–400 mg by day 4. Further adjustments can be made in increments of 25–50 mg twice a day, in intervals of not less than 2 days. Recommended dose 150–750 mg/day *Bipolar mania in children and adolescents*: initial dose 25 mg twice daily, titration day 2–5 as for schizophrenic adolescents. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400–600 mg/day *Bipolar mania in adults*: initial dose 100 mg twice daily; day 2, twice daily dosing totaling 200 mg; day 3, twice daily dosing totaling 300 mg; day 4, twice daily dosing totaling 400 mg; further dosage adjustments up to 800 mg/day by day 6 should be increments of no greater than 200 mg/day within the recommended dose range of 400–800 mg/day *Bipolar depression in adults*: administer once daily at bedtime; day 1, 50 mg; day 2, 100 mg; day 3, 200 mg; day, 300 mg *Bipolar I disorder maintenance therapy in adults*. Administer twice daily totaling 400–800 mg/day as adjunct to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized **ER tablets** *Schizophrenia in adults*: day 1, 300 mg/day. Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day. Recommended dose 400–800 mg/day *Schizophrenia maintenance (monotherapy) in adults*: 400–800 mg/day *Bipolar manias as acute monotherapy or as an adjunct to lithium or divalproex in adults*: day 1, 300 mg; day 2, 600 mg; day 3, between 400 and 800 mg/day *Depressive episodes associated with bipolar disorder in adults*: day 1, 50 mg; day 2, 100 mg; day 3, 200 mg; day 4, 300 mg *Bipolar I disorder maintenance treatment as an adjunct to lithium or divalproex in adults*: 400–800 mg/day *Major depressive disorder, adjunctive therapy with antidepressants in adults*: days 1 and 2, 50 mg; days 3 and 4, 150 mg; recommended dose, 150–300 mg/kg
ADRs	As for other second- and third-generation agents Most common ADRs (incidence ≥5 % and twice placebo) for Adults: somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, ALT increased, and dyspepsia Children and adolescents: somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, and weight increased

Drug interactions	**Pharmacokinetic interactions** Hepatic enzyme inducers may increase the clearance of quetiapine. Higher doses may be required with phenytoin or other inducers Co-medication with inducers of CYP3A4 (mainly **antiepileptic drugs**) which can cause a clinically relevant decrease in quetiapine concentrations. However, erythromycin, an inhibitor of CYP3A4, can increase the $t_{1/2}$ of quetiapine with 92 % and decrease the clearance with 55 % Thioridazine, an antipsychotic agent, can increase the oral clearance of quetiapine, probably due to influence on the absorption process of quetiapine **Pharmacodynamic interactions** Centrally acting drugs: caution should be used when quetiapine is used in combination with other CNS-acting drugs Antihypertensive agents: quetiapine may add to the hypotensive effects of these agents Drugs known to cause electrolyte imbalance or increase QT interval: caution should be used when quetiapine is used concomitantly with these drugs Interference with urine drug screens: false-positive urine drug screens using immunoassays for methadone or tricyclic antidepressants in patients taking quetiapine have been reported
Contraindications	Hypersensitivity to the active substance or to any of the excipients. Concomitant administration of CYP3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin, and nefazodone

5.7.16 Risperidone

Pharmacodynamic characteristics	Second-generation antipsychotic; high-affinity dopamine D_2, serotonin 5-HT_2, and adrenergic α_1-receptor antagonist (see Tables 5.2 and 5.3). Its affinity for D_3 and D_4-receptors is 5 times lower. The drug also shows a strong antagonism for α_2-adrenergic and for histamine H_1-receptors, which increases the risk for orthostatic hypotension and sedation especially with initiation of therapy
Pharmacokinetic characteristics	t_{max} about 1 h, $t_{1/2}$ 3 h (parent substance for extensive metabolizers) or 20 h (poor metabolizers); $t_{1/2}$ 20 h (9-OH-risperidone); protein binding 89 and 74 % for risperidone and 9-OH-risperidone, respectively; bioavailability 70 % (alone), 100 % (risperidone and 9-OH-risperidone) Metabolism chiefly via CYP2D6 (to lesser extent: CYP3A4) The main metabolite formed after hydroxylation is 9-OH-risperidone (commercially available as paliperidone as described in 5.7.12), with an activity which is equipotent to the parent compound, and its plasma concentration is 22-fold higher than those of risperidone in extensive metabolizers
Indications	**US FDA approved** Treatment of schizophrenia in adults and adolescents (ages 13–17 years) Treatment of acute manic or mixed episodes associated with bipolar I disorder as monotherapy in adults and adolescents (ages 10–17 years) Treatment of acute manic or mixed episodes associated with bipolar I disorder as adjunctive therapy with lithium or valproate in adults Treatment of irritability associated with autistic disorder including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods in children and adolescents (ages 10–17 years) **EMA approved in the EU** (film-coated tablets, orodispersible tablets, and oral solutions) Treatment of schizophrenia in adults Treatment of moderate to severe manic episodes associated with bipolar disorders in adults Short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others Short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors require pharmacological treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment program, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents Risperidone is not recommended for use in children below age 18 with schizophrenia and bipolar mania due to a lack of data on efficacy

Dosage	Available as tablets, for oral use; as oral solution; and as orally disintegrating tablets The oral solution can be administered directly from calibrated pipette or mixed with beverage (water, coffee, orange juice, or low-fat milk) Orally disintegrating tablets: open the blister only when ready to administer, and immediately place tablet under tongue. Can be swallowed with or without liquid **Schizophrenia** Adolescents: initial dose 0.5 mg/day, titration (increments) 0.5–1 mg, target dose 3 mg/day, effective dose range 1–6 mg/day Adults: initial dose 2 mg/day, titration (increments) 1–2 mg, target dose 4–8 mg/day, effective dose range 4–16 mg/day **Bipolar mania** Children and adolescents: initial dose 0.5 mg/day, titration (increments) 0.5–1 mg, target dose 1–2.5 mg/day, effective dose range 1–6 mg/day Adults: initial dose 2–3 mg/day, titration (increments) 1 mg, target dose 1–6 mg/day, effective dose range 1–6 mg/day **Irritability associated with autistic disorder** Weight <20 kg: initial dose 0.25 mg/day, titration (increments) after day 4, at intervals of >2 weeks, 0.25 mg; target dose 0.5 mg/day, effective dose range 0.5–3 mg/day Weight ≥20 kg: initial dose 0.5 mg/day, titration (increments) 0.5 mg; target dose 1 mg/day, effective dose range 0.5–3 mg/day
ADRs	The most common ADRs in clinical trials (>5 % and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain
Drug interactions	**Carbamazepine** and other enzyme inducers decrease plasma concentrations of risperidone. Increase its dose up to double the patient's usual dose, titrate slowly **Fluoxetine**, **paroxetine**, and other CYP2D6 enzyme inhibitors increase plasma concentrations of risperidone. Reduce the initial dose. Do not exceed a final dose of 8 mg/day The risk of QT interval prolongation is increased with co-administration of drugs that are known to cause this effect Co-administration of drugs with high protein binding can increase the unbound portion of risperidone
Contraindications	Known hypersensitivity to the drug or any of the components in the formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed

5.7.17 Thioridazine

Pharmacodynamic characteristics	First-generation antipsychotic with tricyclic structure (phenothiazine derivative); dopamine D_2-receptor family antagonist
	The basic pharmacological activity is similar to that of other phenothiazines, but is associated with minimal extrapyramidal stimulation
Pharmacokinetic characteristics	t_{max} 2 h, $t_{1/2}$ 21–24 h; protein binding > 99 %, bioavailability not known Metabolism chiefly via CYP2D6
Indications	**Approved by the US FDA and in Europe**
	Management of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs
	Due to the risk of significant, **potentially life-threatening, pro-arrhythmic effects** with thioridazine treatment, thioridazine should be used only in patients who have failed to respond adequately to treatment with appropriate courses of other antipsychotic drugs, either because of insufficient effectiveness or because of the inability to achieve an effective dose due to intolerable ADRs from those drugs. Consequently, before initiating treatment with thioridazine, it is strongly recommended that a patient be given at least two trials, each with a different antipsychotic drug product, at an adequate dose and for an adequate duration
	However, the prescriber should be aware that **thioridazine has not been systematically evaluated in controlled trials** in treatment refractory schizophrenic patients and its efficacy in such patients is unknown
Dosage	Pediatric patients: recommended initial dose is 0.5 mg/kg/day given in divided doses Dosage may be increased gradually until optimum therapeutic effect is obtained or the maximum dose of 3 mg/kg/day has been reached
	Adults: the usual starting dose is 50–100 mg three times a day, with a gradual increment to a maximum of 800 mg daily if necessary
	Once effective control of symptoms has been achieved, the dosage may be reduced gradually to determine the minimum maintenance dose. The total daily dosage ranges from 200 to 800 mg, divided into 2–4 doses
ADRs	As for other typical first-generation antipsychotics
	In the recommended dosage ranges, most ADRs are mild and transient

Drug interactions	**Pharmacokinetic interactions** Drugs which inhibit CYP2D6 activity (e.g., **fluoxetine** and **paroxetine**) and certain other drugs (e.g., **fluvoxamine**, propranolol, and pindolol) appear to appreciably inhibit the metabolism of thioridazine. The resulting elevated levels would be expected to **augment the prolongation of the QTc** interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsades de pointes-type arrhythmias Higher c_{max} and a 4.5-fold higher AUC for thioridazine in slow compared to rapid metabolizers **Drugs that reduce the clearance** of thioridazine through other mechanisms Fluvoxamine: the effect (25 mg b.i.d. for 1 week) on thioridazine's steady-state concentration was evaluated in ten male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites increased threefold Propranolol: concurrent administration (100–800 mg/day) has been reported to produce increases in plasma levels of thioridazine (approximately 50–400 %) and its metabolites (approximately 80–300 %) Pindolol: concurrent administration has resulted in moderate, dose-related increases in the serum levels of thioridazine and two of its metabolites, as well as higher than expected serum pindolol levels **Pharmacodynamic interactions** As in the case of other phenothiazines, thioridazine is capable of potentiating CNS depressants (e.g., alcohol, anesthetics, barbiturates, narcotics, opiates, other psychoactive drugs) as well as atropine and phosphorus insecticides. Severe respiratory depression and respiratory arrest have been reported when a patient was given a phenothiazine and a concomitant high dose of a barbiturate An increased risk of serious, potentially fatal, cardiac arrhythmias, such as torsades de pointes-type arrhythmias may result from the additive effect of co-administering thioridazine with other agents that prolong the QTc interval
Contraindications	Thioridazine use should be avoided in combination with other drugs that are known to prolong the QTc interval and in patients with congenital long QT syndrome or a history of cardiac arrhythmias Combination with drugs that inhibits CYP2D6 (see above) as well as in patients, comprising about 7 % of the normal population, who are known to have a genetic defect leading to reduced levels of activity of CYP2D6 In common with other phenothiazines, in severe CNS depression or comatose states from any cause including drug-induced CNS depression. It should also be noted that hypertensive or hypotensive heart disease of extreme degree is a contraindication of phenothiazine administration

5.7.18 Ziprasidone

Pharmacodynamic characteristics	Second-generation antipsychotic; high in vitro binding affinity for the dopamine D_2 and D_3, the serotonin 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1A}, α_1-adrenergic, and histamine H_1-receptors (Tables 5.2 and 5.3). Antagonist at the D_2, 5-HT_{2A}, and 5-HT_{1D}-receptors, agonist at the 5-HT_{1A}-receptor. Inhibition of serotonin and adrenaline reuptake The antagonism of histamine H1-receptors may explain the somnolence observed with this drug. The antagonism of α_1-adrenergic receptors may explain the orthostatic hypotension observed with this drug
Pharmacokinetic characteristics	Oral application: t_{max} 6–8 h, $t_{1/2}$ about 7 h; protein binding >99 %, bioavailability 60 % under fed conditions I.m. injection: t_{max} 60 min, $t_{1/2}$ 2–5 h; protein binding >99 %, bioavailability 100 % In vitro studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism. CYP1A2 may contribute to a much lesser extent. Based on in vivo abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by CYP-catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase
Indications	**US FDA approval** Treatment of schizophrenia in adults Acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder in adults Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate in adult patients Safety and effectiveness for pediatric patients have not been established **Approved in Europe** Treatment of schizophrenia in adults Treatment of manic or mixed episodes of moderate severity in bipolar disorder in adults and children and adolescents aged 10–17 years (prevention of episodes of bipolar disorder has not been established) The safety and efficacy of ziprasidone in pediatric patients with schizophrenia have not been established
Dosage	Give oral doses with food **Adult schizophrenia**: initiate at 20 mg twice daily. Daily dosage may be adjusted up to 80 mg twice daily. Dose adjustments should occur at intervals of not less than 2 days. Safety and efficacy have been demonstrated in doses up to 100 mg twice daily **Bipolar mania in children and adolescents**: the recommended dose, in acute treatment of bipolar mania, is a single dose of 20 mg on day 1. It should subsequently be administered in 2 daily divided doses and should be titrated over 1–2 weeks to a target range of 120–160 mg/day for patients weighing ≥45 kg or to a target range of 60–80 mg/day for patients weighing <45 kg. Subsequent dosing should be adjusted on the basis of individual clinical status within the range of 80–160 mg/day for patients weighing ≥45 kg or 40–80 mg/day for patients weighing <45 kg It is of particular importance **not** to **exceed** the weight-based **maximum dose** as the safety profile above the maximum dose (160 mg/day for children ≥45 kg and 80 mg/day for children <45 kg) has not been confirmed and ziprasidone is associated with dose-related prolongation of the QT interval **Bipolar mania in adults**: initiate at 40 mg twice daily. Increase to 60 or 80 mg twice daily on day 2 of treatment. Subsequent dose adjustments should be based on tolerability and efficacy within the range of 40–80 mg twice daily Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate: continue treatment at the same dose on which the patient was initially stabilized, within the range of 40–80 mg twice daily

ADRs	Commonly observed ADRs (incidence ≥5 % and at least twice the incidence for placebo): Schizophrenia: somnolence and respiratory tract infection Manic and mixed episodes associated with bipolar disorder: somnolence, extrapyramidal motor symptoms, dizziness, akathisia, abnormal vision, asthenia, and vomiting Bipolar I disorder in children and adolescents: in a placebo-controlled study, the most frequent ADRs (reported with a frequency >10 %) were sedation, somnolence, headache, fatigue, nausea, and dizziness. The frequency, type, and severity of ADRs in these subjects were generally similar to those in adults with bipolar disorder Ziprasidone was associated with a similar mild to moderate dose-related prolongation of the QT interval in the pediatric bipolar clinical trial to those seen in the adult population Tonic-clonic seizures and hypotension were not reported in the placebo-controlled pediatric bipolar clinical trials
Drug interactions	**Pharmacodynamic interactions** Combination with other drugs that have demonstrated QT prolongation Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents **Pharmacokinetic interactions** Carbamazepine is an inducer of CYP3A4; administration of 200 mg twice daily for 21 days resulted in a decrease of approximately 35 % in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg q.i.d. for 5 days, increased the AUC and c_{max} of ziprasidone by about 35–40 %. Other inhibitors of CYP3A4 would be expected to have similar effects The absorption of ziprasidone is increased up to twofold in the presence of food
Contraindications	Patients with a known history of QT prolongation, patients with uncompensated heart failure, combination with other drugs that have demonstrated QT prolongation, and patients with known hypersensitivity to ziprasidone

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Anxiolytics and Sedative-Hypnotics

6

Manfred Gerlach and Andreas Warnke

Contents

M. Gerlach, PhD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Laboratory for Clinical Neurobiology and Therapeutic Drug Monitoring, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: manfred.gerlach@uni-wuerzburg.de

A. Warnke, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: warnke@kjp.uni-wuerzburg.de

6.1 Definition

Anxiolytics (synonym, tranquillizers) are anti-anxiety drugs that are used in the pharmacological treatment of anxiety disorders. Anxiety is rather untypical for psychiatric disorders in that it may occur as both a normal emotional and a pathological state. During early human history, anxiety was probably adaptive and thus a criterion for selection. This may explain the high lifetime prevalence for anxiety states (≥15 % of population; Nutt 2003). Anxiety disorders often first emerge during childhood and adolescence and represent one of the most common forms of psychopathology among children and adolescents. Anxiety disorders include seven major

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debilitating subtype disorders: separation anxiety disorder, generalized anxiety disorder, social phobia, panic disorder (with and without agoraphobia), agoraphobia without panic disorder, post-traumatic stress disorder, and obsessive-compulsive disorder (OCD).

Anxiolytics encompasses a number of psychopharmacological agents that:

- have a predominantly depressant effect upon the CNS,
- reduce anxiety,
- exert a relaxant effect upon the emotions,
- ameliorate agitation states as well as accompanying somatic signs and symptoms.

Sedative-hypnotics are agents that are used in the pharmacological treatment of sleep disorders. Sleep disorders are characterized by difficulties with the initiation and maintenance of sleep. Duration, quality, and timing of sleep are abnormal, causing distress (insomnias, dyssomnias). There are also abnormal experiences and behaviors that occur during sleep, perceived as annoying by the affected person or by those around them (parasomnias). Insomnia is the most prevalent sleep disorder in the general population and is commonly encountered in medical practices. Insomnia is defined as the subjective perception of difficulty with sleep initiation, duration, consolidation, or quality, occurring despite adequate opportunity for sleep, and results in some form of daytime impairment (Schutte-Rodin et al. 2008).

Sedative drugs moderate excitement, decrease activity, and induce calmness, whereas hypnotic drugs produce drowsiness and facilitate the onset and maintenance of a state resembling normal sleep in its electroencephalographic characteristics.

6.2 Classification

Ideal, classic anxiolytics are exclusively relaxant and calmative across a broad dose range without eliciting hypnotic adverse drug reactions (ADRs; Fig. 6.1).

Hypnotics differ from ideal anxiolytics in regard to their steep dose-response curves (Fig. 6.1): their anxiolytic character shifts quickly to hypnotic and (at higher doses) narcotic effects.

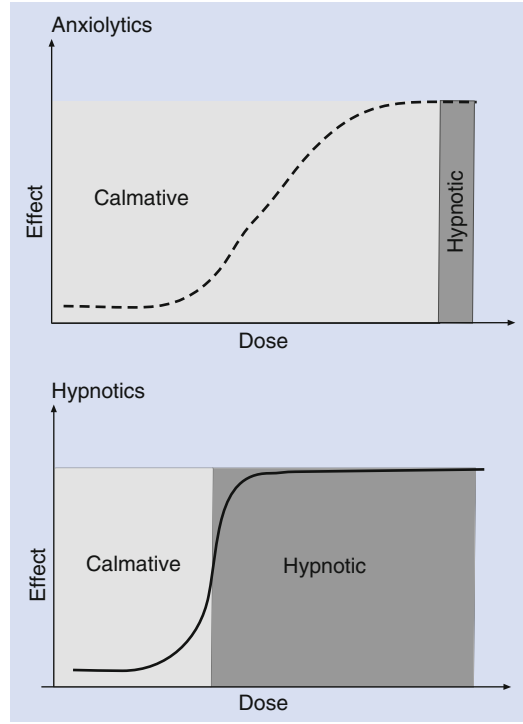

Fig. 6.1 Dose-response curves for anxiolytics and hypnotics

Anxiolysis, sleep induction, and narcosis are therefore regarded as different stages of a response continuum to these medications, characterized by different intensity levels of a centrally depressant, vigilance-reducing effect. The evaluation of ADRs is thus chiefly determined by the specific therapeutic goals of each case. The substance- and dosage-related hypnotic effects are particularly undesirable where anxiety and tension are the target symptoms. In certain cases, however, a sleep-promoting effect might, in fact, be convenient.

Examples of the "**hypnotics**" include the barbiturates as well as the non-medication ethanol (alcohol). **Barbiturates** are not discussed in this chapter as their narrower therapeutic range (compared with benzodiazepines) and the associated higher risk of a lethal outcome in cases of intoxication (respiratory depression) as well as the development of tolerance have effectively rendered them **obsolete** in clinical practice. **Chloral hydrate** is currently labeled by the US Food and

Table 6.1 Pharmacodynamic effects of anxiolytics and sedative-hypnotics

Substance group	Primary pharmacodynamic effects
Benzodiazepines	Agonists of the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex Enhancement of the inhibitory function of central GABAergic neurons
Antidepressants with serotonergic and/or antihistaminergic effects	Serotonin reuptake inhibitor, monoamine oxidase type A (MAO-A) inhibitor, and/or antagonists of histamine $H_{1,2}$-receptors Enhancement of the effects of central serotonergic neurons Blockade of the effects of histamine on histaminergic neurons
Low-potency antipsychotics	Dopamine D_2-receptor antagonists, inhibit binding of dopamine to the corresponding neuroreceptors and thereby the CNS effects of dopamine Additional substance-specific effects at adrenergic, histamine, and/or serotonin receptors
Buspirone	Partial agonist at postsynaptic serotonin 5-HT_{1A}-receptors, full agonist at presynaptic serotonin 5-HT_{1A}-receptors; no sedative, muscle-relaxant, and anticonvulsive properties
β-Adrenoceptor antagonists (β-blockers)	Antagonists of β-adrenergic receptors, inhibition of vegetative nervous system
Antihistamines	Antagonists of peripheral and/or central histamine H_1-receptors

GABA γ-aminobutyric acid

Drug Administration (FDA) and is still employed as a sleep-inducing medication (see Chap. 26).

Melatonin, a nutritional substance and over-the-counter medication, and **ramelteon** with an entirely new mechanism of action that is different from classic hypnotics are not considered in this chapter. Ramelteon is a US FDA-approved melatonin receptor agonist (MT_1 and MT_2) for the treatment of insomnia characterized by difficulty with sleep onset. Melatonin is a hormone endogenously produced by the pineal gland, which plays a key role in the regulation of the sleep-wake cycle. The efficacy of melatonin supplementation has been tested in a large number of clinical trials. Meta-analyses have demonstrated that melatonin has only little effects on sleep latency as well as on wake time after sleep onset or total sleep time. Therefore, it is not recommended for the treatment of chronic insomnia (Schutte-Rodin et al. 2008). Melatonin and ramelteon are reviewed in the chapter on the treatment of sleep disorders (see Chap. 26).

In discussing anxiolytics and sedative-hypnotics, many psychopharmacology handbooks almost exclusively treat barbiturates and benzodiazepines. This conceptual classification, however, does not accurately reflect the current state of clinical knowledge. In fact, certain "antidepressants" are employed in place of the "classic" sedative-hypnotics as first choice medications in the treatment of sleep disorders; and even certain "antipsychotics" are now used in particular disorders as first choice "anxiolytics and sedative-hypnotics." This **chapter reviews**, according to the current state of knowledge, the **substance groups clinically relevant** to the pharmacotherapy of target symptoms such as "agitation," "anxiety," and "sleep disorders" in child and adolescent psychiatry.

Anxiolytics and sedative-hypnotics are **chemically and pharmacologically** a **heterogeneous group** of psychopharmacological agents (Table 6.1). Apart from the barbiturates, this group includes:

- Benzodiazepines, the classic representatives of this class of psychopharmacological agents. They are internationally among the most frequently prescribed medications in almost all medical disciplines.

  However, this particular class also includes:
- Antidepressants that include serotonergic and/or antihistaminergic components among their mechanisms of action.
- Low-potency antipsychotics (for definition, see Sect. 5.2) with sedative effects.
- Buspirone, with a differing mechanism of action that is different from classic hypnotics.
- β-Adrenoceptor antagonists (β-blockers)

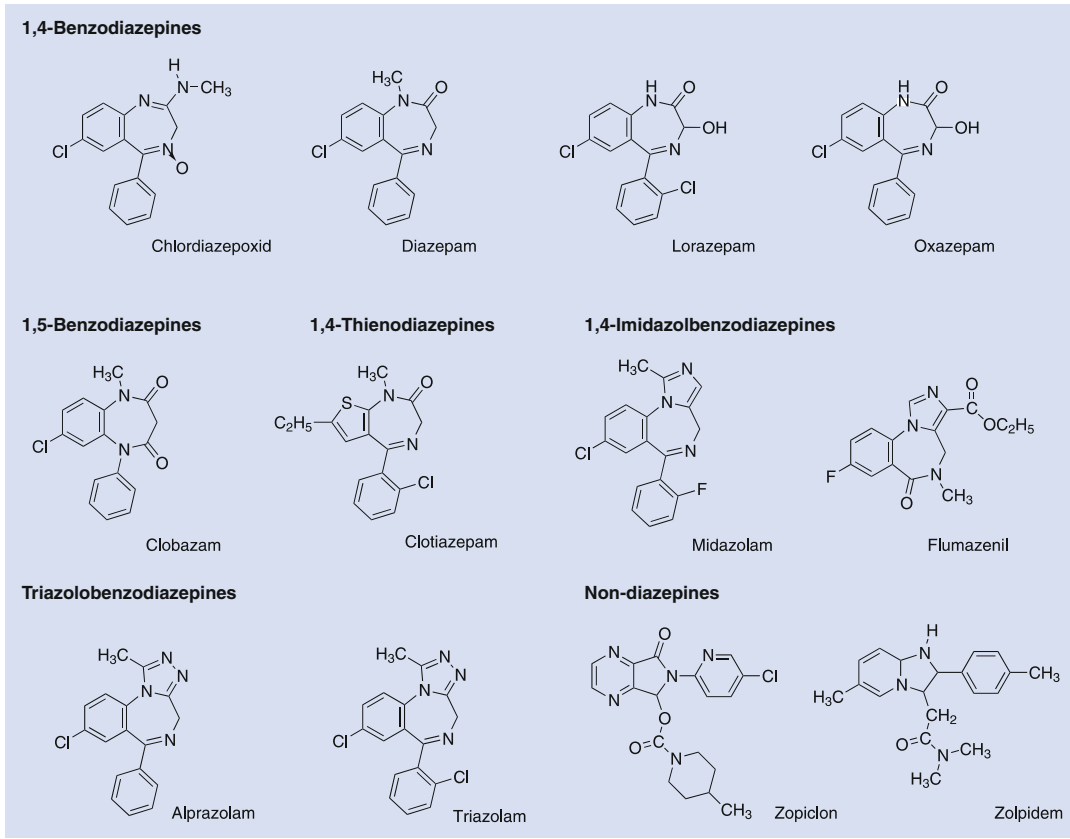

Fig. 6.2 Structural formulas of pharmacologically defined benzodiazepines

- Antihistamines
- Certain phytopharmacological agents
- Certain antiepileptics with mood-stabilizing properties including carbamazepine, valproate, lamotrigine, topiramate, and gabapentin.

The term **benzodiazepine** originally referred to a chemical class of medications derived from 1,4-benzodiazepine structure (Fig. 6.2). Typical examples include chlordiazepoxide (the first benzodiazepine introduced into clinical practice), diazepam, lorazepam, and oxazepam. Their action as agonists of the benzodiazepine binding site of the $GABA_A$-receptor-Cl^- channel complex (Table 6.1; see also Sect. 1.3.3.2) later led to the adoption of the term "benzodiazepine" in pharmacological textbook, thus denoting a **pharmacological substance group** that includes not only substituted 1,4-benzodiazepines but also 1,5-benzodiazepines 1,4-thienodiazepines 1,4-imidazolebenzodiazepine, 1,4-triazolobenzodiazepine, as well as non-diazepines, the structures of which are unrelated to the original benzodiazepines (Fig. 6.2). Accordingly, "benzodiazepines" in this chapter refer to the pharmacologically defined group of substances.

Botanical preparations of different origins (valerian, hops, lemon balm, and others) employed in herbal medicine for their sedative and calmative properties in the treatment of anxiety and sleep disorders will not be discussed. There is no sufficient proof of efficacy for these preparations (Bandelow et al. 2008; Neubauer 2007): on the contrary, effect-size analyses of available trials in anxiety disorders even indicate a worsening of symptoms (Hidalgo et al. 2007). Valerian will be considered in the chapter on sleep disorders (Chap. 26). Extracts of the kava root (*Piper methysticum*) exhibit efficacy in the

treatment of stress states, but have been taken from the market due to hepatotoxicity. The current guidelines for the diagnosis and therapy of anxiety and sleep disorders in children, adolescents, and adults (AACAP Official Action 2007; Bandelow et al. 2008; Schutte-Rodin et al. 2008) do not recommend botanic extracts for the treatment.

Antiepileptics, which can also be employed as anxiolytics and sedative-hypnotics, are similarly not considered here, as the few trials investigating their efficacy in this respect have almost exclusively involved adult patients, and, finally, they are also not recommended for the treatment of anxiety disorders and phobias.

6.3 Mechanisms of Action

The mechanisms of action of the anxiolytics and sedative-hypnotics are only incompletely known, as the pathophysiological correlates of the target symptoms – sleep, fatigue, agitation, and anxiety – are only incompletely understood. The **etiology of anxiety disorders** differs according to the specific disorder but is essentially multifactorial, whereby the interplay of biological, personality, and family factors, together with life experience, could be unfavorable (Möhler 2012; Strawn et al. 2012b). Data from brain imaging studies in patients with anxiety disorders as well as findings from experimental investigations in animals (e.g., auditory anxiety conditioning) suggest that the corpus amygdaloideum (**amygdala**), the ventrolateral prefrontal cortex, the anterior cingulate cortex, and the impossibility of impaired connectivity among these brain regions play a central role in the origins of anxiety and fear. The amygdala is the site for formation and storage of fear and extinction memories, which is located immediately before the hippocampus, the central coordination center of the limbic system. Both brain regions have a high density of **$GABA_A$ receptors** that are the targets for barbiturates and benzodiazepines (see Sect. 1.3.3.2). The basolateral portion of the amygdala receives input from all sensory systems; the corticomedial part sends projection neurons to the hypothalamus, thereby modulating the release of stress hormones as well as the vegetative nervous system. Their effects, in the form of feelings, act in turn upon the brain.

Insomnia may present with a variety of specific complaints and etiologies. Consistent risk factors include increasing age, female sex, comorbid (medical, psychiatric, sleep, and substance abuse) disorders, shift work, and possibly unemployment and lower socioeconomic status. Patients with comorbid medical and psychiatry conditions are at particularly increased risk, with psychiatric and chronic pain disorders having insomnia rates as high as 50–75 % (Schutte-Rodin et al. 2008). The risk relationship between insomnia and psychiatric disorders appears to be bidirectional; several studies have demonstrated an increased risk of psychiatric disorders among individuals with prior insomnia.

The anxiolytic and sedative-hypnotic efficacy of benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) suggests that **dysfunction of GABAergic and serotonergic neurotransmission** plays a decisive role in the pathogenesis of anxiety and sleep disorders. For example, in panic disorder, a pathophysiological $GABA_A$ receptor was demonstrated through a globally reduced benzodiazepine binding, observed in a [^{11}C]-flumazenil positron emission tomography (PET) study, with strongest decrease in cortical areas in particular in the orbitofrontal cortex, in the insula, and in the ventrolateral prefrontal cortex, with the severity of anxiety symptoms correlating with the deficit in $GABA_A$ receptors (Möhler 2012).

The **biological targets** of benzodiazepines, antidepressants, and antipsychotics are discussed in detail in Sects. 1.3.4.2, 1.4.2, and 1.4.3; Table 6.1 briefly summarizes the major points. Studies in mouse lines in which each of the benzodiazepine-sensitive $GABA_A$ receptors (containing α_1, α_2, α_3, or α_5 subunits) was rendered insensitive to diazepam by a point mutation in the benzodiazepine binding site showed that α_1 $GABA_A$-receptors mediate the sedative action of classical benzodiazepines and are implicated in their dependence liability, while α_2

$GABA_A$-receptors mediate their tranquilizing activity (Möhler 2012). Based on these findings, **novel anxiolytics**, which are devoid of the deficits of classical benzodiazepines, were developed. However, only few compounds with selective efficacy at α_2 and α_3 $GABA_A$-receptors have been validated in human proof of concept studies. They include TPA023, eszopiclone, ocinaplon, and the indirect-acting XBD173, a TSPO ligand (Möhler 2012).

In the following, the clinical psychopharmacology of anxiolytics and sedative-hypnotics that are used in child and adolescent psychiatry will be discussed.

6.4 Clinical Psychopharmacology

6.4.1 Benzodiazepines

Indications

Because of their multiple pharmacological actions, benzodiazepines have been found useful in many areas of medical practice such as induction of anesthesia, use of muscle relaxant, and seizure control. It is beyond the scope of this chapter to elaborate on all these different uses.

In psychiatry, the areas of application of benzodiazepines are:

- Restlessness, anxiety, and stress states
- Psychosomatic symptoms
- In combination with antidepressants, the initial treatment of anxious-agitated depression
- In combination with antipsychotics, the acute treatment of schizophrenic psychoses and mania
- Crisis intervention in acute suicidality
- Functional sleep disorders
- Epileptic seizures

Long-term use, however, is not generally recommended because of the potential to develop physical tolerance as well as their ability to interfere with memory and learning.

Alprazolam was the first benzodiazepine to be approved by the US FDA for the treatment of panic disorder in adults. Since then, clonazepam has also received approval from the FDA for the treatment of panic disorder. Current FDA-approved benzodiazepines for pharmacological treatments of insomnia in adults include estazolam, eszopiclone, flurazepam, lorazepam, quazepam, temazepam, triazolam, zaleplon, and zolpidem.

In **children and adolescence**, benzodiazepines have an FDA-approved indication for preanesthesia only. However, because of their quick onset of action, their favorable safety profile, and long history of use, benzodiazepines are chiefly employed in:

- The acute therapy of schizophrenic psychoses (in combination with antipsychotics)
- Acute suicidality
- Anxiety disorders
- Epilepsies
- Functional sleep disorders

The current **guidelines** for the diagnosis and therapy of children and adolescents with **anxiety disorders** (AACAP Official Action 2007) recommend benzodiazepines as an adjunct short-term treatment with SSRIs to achieve rapid reduction in severe anxiety symptoms permitting initiation of the exposure phase of cognitive behavioral therapy (CBT; e.g., panic disorder, school refusal behavior).

According to the clinical **guideline** for the evaluation and management of chronic **insomnia** in adults, which are reported to be generally appropriate also for younger adults (Schutte-Rodin et al. 2008), the first-choice pharmacological treatment for primary insomnia is the short-term use of short-/intermediate-acting benzodiazepines: examples of these medications include eszopiclone, temazepam, triazolam, zaleplon, and zolpidem. No specific agent within this group is recommended as preferable to the others in a general sense. In addition, benzodiazepines not specifically approved for insomnia (e.g., clonazepam, lorazepam) might also be considered if the duration of action is appropriate for the patient's presentation or if the patient has a comorbid condition that might improve through these drugs.

Table 6.2 Benzodiazepines with their affinity for the benzodiazepine binding site on the $GABA_A$ receptor-Cl^- channel complex and their elimination half-life ($t_{1/2}$)

Benzodiazepines	IC_{50} (nM)	$t_{1/2}$ (h)
Alprazolam	20	10–18
Bromazepam	18	12–24
Brotizolam	1	4–8
Chlordiazepoxide	350	10–18[a]
Clobazam	130	10–30[a]
Clonazepam	2	24–56
Clorazepate	59	2–3[a]
Clotiazepam	2	3–15
Desmethyldiazepam	9	50–80
Diazepam	8	30–45[a]
Flunitrazepam	4	10–25[a]
Flurazepam	15	2[a]
Loprazolam	6	7–8
Lorazepam	4	10–18
Lormetazepam	4	9–15
Medazepam	870	2[a]
Metaclazepam	930	18–20[a]
Midazolam	5	1–3
Nitrazepam	10	20–50
Oxazepam	18	5–18
Prazepam	110	1–3
Temazepam	16	6–16
Tetrazepam	34	12
Triazolam	4	2–4

From Müller and Hartmann (1995)
The affinity is given as the half-maximal inhibitory concentration of specific binding to the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex in vitro (IC_{50}). The smaller the value, the greater the affinity of the drug for the binding site
[a]Active metabolites with long $t_{1/2}$ values are produced in vivo

Clinical Effects and Efficacy

Various benzodiazepines differ primarily according to their effect at the $GABA_A$ receptor-Cl^- channel complex in the CNS and their pharmacokinetics (Table 6.2); they differ less, however, with respect to their clinical effects profile (Table 6.3). In many cases, it is only the dosage that determines which effect is most prominent.

Benzodiazepines have **not shown efficacy in anxiety disorders** in double-blind placebo-controlled trials in children and adolescents (AACAP Official Action 2007; Strawn et al. 2012a), despite established benefit in the treatment of panic disorder and agoraphobia (alprazolam, clonazepam, diazepam, lorazepam), generalized anxiety disorder (diazepam, lorazepam), and social anxiety disorder (clonazepam) in adult trials (Bandelow et al. 2008). The studies in adults showed that the anxiolytic effect starts within 30–60 min after oral or parenteral application. In contrast to antidepressants, they do not lead to initially increased nervousness.

The short-term **efficacy** of benzodiazepines in the treatment of chronic **insomnia** (estazolam, eszopiclone, flurazepam, quazepam, temazepam, triazolam, zaleplon, and zolpidem) has been shown in a large number of randomized controlled clinical trials in adults (Schutte-Rodin et al. 2008). A smaller number of controlled trials have demonstrated continued efficacy for eszopiclone and zolpidem without significant complications for 6 months, and in open-label extension studies for 12 months or longer. Each benzodiazepine has been demonstrated to have positive effects on sleep latency, total sleep time, and/or waking after sleep onset.

Dosing

There are no specific dosing guidelines for children and adolescents with anxiety and sleep disorders. The dosing of benzodiazepines employed in the treatment of anxiety and sleep disorders is summarized in Table 6.4. See product labeling and tables in Sect. 6.7 for detailed information on dosing of specific drugs.

Frequency of administration of benzodiazepines for the treatment of sleep disorders depends on the specific clinical presentation; empirical data support both nightly and intermittent (two to five times per week) administration (Schutte-Rodin et al. 2008). Many clinicians recommend scheduled non-nightly dosing at bedtime as a means to prevent tolerance, dependence, and abuse, although these complications may be less likely with newer benzodiazepines.

When pharmacotherapy with a benzodiazepine is indicated, benzodiazepine doses should be as low as possible, but as high as necessary.

Table 6.3 Activity profile of benzodiazepines according to their elimination half-life ($t_{1/2}$)

Benzodiazepines	Hypnotic	Anxiolytic	Anticonvulsive
Short-acting benzodiazepines ($t_{1/2}$ <6 h)			
Midazolam	+++	+	
Triazolam	+++	+	
Medium-acting benzodiazepines ($t_{1/2}$ 6–24 h)			
Alprazolam	+	++	+
Bromazepam		++	
Brotizolam	++	++	
Clotiazepam	++	++	?
Flunitrazepam	+++	++	+
Loprazolam	+	+	
Lorazepam	++	+++	+
Lormetazepam	++	+	+
Oxazepam	+	++	?
Temazepam	+++	+	+
Long-acting benzodiazepines ($t_{1/2}$>24 h)			
Chlordiazepoxide	?	++	?
Clobazam	++	+	?
Clonazepam	+	++	+++
Diazepam	++	+++	+
Clorazepate	+	++	?
Flurazepam	+++	+	
Medazepam	+	++	?
Nitrazepam	+++	+	++
Nordazepam	++	+	
Prazepam		++	

From Bezchlibnyk-Butler and Virani (2007)
+ weak, ++ moderate, +++ strong, ? no data

Table 6.4 Recommended oral dosing for non-retarded benzodiazepines in the treatment of anxiety disorders and chronic insomnia

Benzodiazepines	Anxiety disorders (p.o)	Insomnia (mg at bedtime p.o.)
Alprazolam	Initial 0.25–0.5 mg t.i.d., max 4 mg in divided doses	
Clonazepam	Initial 0.25 mg b.i.d., max 1–4 mg	
Diazepam	Usually 2 t.i.d., max 30 mg in divided doses	
Estazolam		1–2
Eszopiclone		2–3
Flurazepam		15–30
Lorazepam	Initial 2–3 mg b.i.d or t.i.d., max 10 mg	
Quazepam		7.5–15
Temazepam		7.5–15, max. 30
Triazolam		0.25, max. 0.5
Zaleplon		10, max. 20
Zolpidem		5–10

The table is partially constructed from individual drug prescribing information labeling and from guidelines for the therapy of insomnia (Schutte-Rodin et al. 2008). See product labeling for complete prescribing information
Special precaution is advised because safety and effectiveness are not established in patients <18 years
b.i.d., 2 × day, *p.o.* per orally, *t.i.d.*, 3 × day

Adverse Drug Reactions (ADRs)

In general, benzodiazepines have a good record of safety. The most important ADR associated with the use of benzodiazepines is the frequent **habituation**, in which the usual dosage is not increased (so-called **low-dose dependency**). This involves the fact that sudden withdrawal of the medication, particularly after chronic use of the agent, can cause increased anxiety or sleeplessness, so that the patient again resorts to the medication. In order to avoid the rebound effect, patients who have benefited from their anxiolytic effect of a benzodiazepine must be gradually weaned from the medication. Physical dependence with increasing dosage (dependency syndrome; see Sect. 8.4.1.4) is rare.

Benzodiazepines are among the best-tolerated medications. The great majority of ADRs are dose dependent, due to excessive effects of the agent, and occur mostly at the commencement of therapy. The most important ADRs are sleepiness or daytime somnolence, disturbed concentration, and reduced attention. In rare cases, headaches, diplopia, articulation disorders, increased appetite (with or without weight gain), hypotension, ataxia, myasthenia, exanthemata, and allergic reactions may occur. Paradoxical reactions in the form of sleep disorders, restlessness, agitation, acute anxiety and agitation states, aggressive outbursts, hallucinations, and nightmares may be experienced. Impairment of driving ability is possible. In rare cases, menstruation disorders and reduced libido may also develop.

The **US FDA** recently recommended that a **warning** be issued regarding ADRs associated with benzodiazepines' hypnotics. These medications have been associated with reports of disruptive sleep-related behaviors including sleepwalking, eating, driving, and sexual behavior. Patients should be informed about the potential for these ADRs, about the importance of allowing appropriate sleep time, to use prescribed doses only, and to avoid the combination of benzodiazepines' hypnotics with alcohol, other sedatives, and sleep restriction.

Drugs Interactions

Important interactions with other medications are summarized in Table 6.5. Antidepressants that inhibit the cytochrome P450 enzymes (see Table 4.7), such as fluoxetine, inhibit the metabolism of benzodiazepines such as alprazolam and triazolam, and thus increase plasma concentrations, causing increased psychomotor effects.

Contraindications

Restrictions on use apply in the following situations:

- Intoxication with centrally depressant drugs and alcohol
- Hypersensitivity to benzodiazepines
- Marked respiratory insufficiency (hypercapnia)

Caution is advised

- in their use:
  - because effectiveness is not established in patients <18 years. In order to avoid abuse and low-dose dependency, the need for their employment should be carefully considered, and the prescribed dosage and the duration of therapy should be kept to a minimum.
- With regard to driving, at school, in the workplace, and during recreational activities, as driving skills and the ability to operate vehicles and machinery as well as the capacity for learning and performance may be impaired.
- During adjuvant therapy of sleep disorders, because of the risk of low-dose dependency. The etiology of the sleep disorder should be elucidated as early as possible, in order to enable a more directed therapy, such as treatment with antidepressants or behavioral therapeutic measures.

6.4.2 Antidepressants with Serotonergic and/or Antihistaminergic Effects

Indications

Areas of application for these antidepressants are:

- Anxiety disorders (panic disorder, phobias, OCD)
- Sedation and sleep induction

Table 6.5 Interactions of anxiolytics and sedative-hypnotics with prescription and recreational drugs, and foodstuffs of relevance for children and adolescents

Interaction with substance class or substance	Effect
Allopurinol	Decreased catabolism and increased $t_{1/2}$ of benzodiazepines that are oxidatively metabolized, leading to increased efficacy
Amiodarone	Reduced catabolism and increased plasma levels of midazolam
Anesthetics	
Ketamine, inhalation anesthetics (e.g., halothane, propofol, thiopental, opiates)	Longer recovery phase following diazepam administration resulting from reduced catabolism Reduced protein binding of diazepam: enhanced diazepam effect Increased sedative effects, increased anesthesia with midazolam Increased respiratory depression and hypoventilation, especially in combination with midazolam
Antibiotics	
Erythromycin, clarithromycin, chloramphenicol, gyrase inhibitors (ciprofloxacin, enoxacin)	Reduced catabolism and consequently increased plasma levels of midazolam, triazolam (ca. 54 % increase), alprazolam (60 %), and diazepam; no interactions with azithromycin Reduced catabolism of benzodiazepines that are oxidatively metabolized Reduced catabolism of diazepam
Antidepressants	
Tricyclic antidepressants, such as: desipramine, imipramine	Elevated plasma levels of desipramine in combination with alprazolam Hypothermia reported with combination of triazolam and desipramine Reduction of appetite by desipramine can be increased by benzodiazepines
SSRIs (fluoxetine, fluvoxamine, sertraline)	Reduced catabolism, increased $t_{1/2}$ of alprazolam and diazepam in combination with fluoxetine or fluvoxamine (increased efficacy) Reduction of diazepam clearance (c. 13 %) in combination with sertraline
Antiepileptics	
For example: carbamazepine, phenobarbital, phenytoin, valproic acid	Increased catabolism and reduced plasma levels of alprazolam and clonazepam Increased catabolism of diazepam, additive CNS depressive effect Decreased plasma phenytoin levels in combination with clonazepam Elevated phenytoin levels and increased toxicity with diazepam and chlordiazepoxide Reduced midazolam plasma levels through induction of CYP3A4 Displacement of diazepam from protein binding, leading to increased plasma levels Inhibition of catabolism of clonazepam and lorazepam, leading to increased efficacy
Antimycotics	
For example: itraconazole, ketoconazole, fluconazole	Reduced catabolism and increased $t_{1/2}$ of chlordiazepoxide and midazolam Reduced catabolism of triazolam; dosage should be reduced by 50–75 %
Antipsychotics	Increased sedation, hypersalivation, hypotonia (collapse, delirium, respiratory arrest possible)

Table 6.5 (continued)

Interaction with substance class or substance	Effect
Antituberculosis agents	
For example: isoniazid, rifampicin	Inhibition of catabolism of oxidatively metabolized benzodiazepines (triazolam excretion reduced by up to 75 %)
	Increased catabolism of oxidatively metabolized benzodiazepines through induction of CYP3A4 (diazepam by 300 %, midazolam by 83 %)
β-**Adrenoceptor antagonists** (β-blockers)	
For example: oxprenolol, propranolol	Increased $t_{1/2}$ and reduced clearance of diazepam and bromazepam (no interactions with alprazolam, lorazepam, or oxazepam)
Caffeine	Can reduce sedative effects or exacerbate sleep disorders
Cimetidine	Reduced catabolism of oxidatively metabolized benzodiazepines (not, however, with ranitidine, famotidine, or nizatidine); increased c_{max} of alprazolam (86 %)
CNS depressants	
For example: barbiturates, antihistamines, alcohol	Increased CNS depression; at higher dosages, coma or respiratory insufficiency possible
	Alprazolam: increased aggression in alcoholics possible
	Brain concentrations of some benzodiazepines are altered by alcohol: triazolam concentrations are reduced, diazepam concentrations increased; no change with chlordiazepoxide
Digoxin	Reduced catabolism and elimination of digoxin
Disulfiram	Elevated plasma levels of triazolam (by 100 %) and midazolam, resulting from reduced catabolism by CYP3A4
Estrogens (oral contraceptives)	Reduced catabolism of oxidatively metabolized benzodiazepines
Grapefruit juice	Reduced catabolism of alprazolam, diazepam, midazolam, and triazolam leads to increased c_{max} and bioavailability, due to inhibition of CYP3A4
Lithium salts	Increased incidence of sexual dysfunction (by 49 %) in combination with clonazepam, increased CNS effects
Omeprazole	Increased risk of ataxia and sedation through reduced catabolism of oxidatively metabolized benzodiazepines (not with lansoprazole)
Probenecid	Reduced lorazepam clearance (by 50 %)
Protease inhibitors	Elevated plasma levels of benzodiazepines oxidatively metabolized by CYP3A4 (e.g., triazolam)
St John's wort preparations	Reduced $t_{1/2}$ of alprazolam (by up to 50 %), resulting from increased catabolism
Tobacco	Enhanced chlordiazepoxide and diazepam clearance (by up to 50 %) through enzyme induction

From Bezchlibnyk-Butler and Virani (2007)
c_{max} maximum drug concentration, $t_{1/2}$ plasma half-life, *CNS* central nervous system, *SSRIs* selective serotonin reuptake inhibitors

In child and adolescent psychiatry, SSRIs have become the agents of **first choice** for the pharmacological **treatment of anxiety disorders** and **phobias** (AACAP Official Action 2007; Strawn et al. 2012a), although only few SSRIs have thus far been approved for these indications in children and adolescents. Fluoxetine has been FDA-approved for major depression from the age of 8 years and older, and for OCD from the age of 7 and older as has been fluvoxamine from the same age. Sertraline has been FDA-approved for OCD from the age of 6 and older.

The current guidelines for the diagnosis and therapy of psychiatric disorders in children and

adolescents (AACAP Official Action 2007; Strawn et al. 2012a) recommend **tricyclic antidepressants** only as medications of **second choice** in the therapy of anxiety disorders because of the lack of positive results and the higher probability of ADRs. Their use is associated with greater success when employed in the treatment of comorbid depressive episodes. Clomipramine has been FDA-approved for OCD from the age of 10 years and older; imipramine has been FDA-approved for the use in children older than 6 years for nocturnal enuresis; and doxepin has been FDA-approved for anxiety and depression in adolescents older than 12 years.

As there is no danger of dependency, antidepressants (primarily SSRIs) are currently the first choice therapeutic alternative for anxiety disorders of severe and/or chronic-relapsing course. Combination treatment with benzodiazepines and SSRIs, particularly in the acute and short-term therapy of patients with anxiety disorders and depressive episodes, can significantly improve the prognosis in comparison with pharmacological monotherapy (Dunlop and Davis 2008).

An analysis of 2002 **prescribing practices** in the USA found that three of four medications prescribed for **insomnia** were antidepressants such as amitriptyline, mirtazapine, and trazodone (Walsh 2004). However, due to the occurrence or potentially significant ADRs (daytime residual sedation, orthostatic hypotension, cardiac arrhythmias, and anticholinergic effects), these drugs should not be used in nonpsychiatric patients. According to the clinical guidelines for the evaluation and management of chronic insomnia in adults, which are reported to be generally appropriate also for younger adults (Schutte-Rodin et al. 2008), however, sedating low-dose antidepressants may be considered only when insomnia is accompanied with comorbid depression or in the case of other treatment failures. Examples of these drugs include amitriptyline, doxepin, mirtazapine, and trazodone. From these agents, low-dose doxepin is the only FDA-approved drug for sleep maintenance in insomnia in adults.

Clinical Effects and Efficacy

Sertraline, has been shown in a randomized controlled study in children and adolescents to be superior to placebo in reducing OCD symptoms, although the remission rate was 21.4 % (Pediatric OCD Treatment Study [POTS] Team 2004). A current review of double-blind placebo-controlled clinical trials that were carried out to assess the safety and efficacy of SSRIs in child and adolescent non-OCD (e.g., generalized anxiety disorder, separation anxiety disorder, social anxiety) anxiety disorders was published by Ghalib et al. (2011). However, there is no published study in childhood-onset panic disorder and specific phobia. A trial of SSRIs in adolescents with panic disorder and chart review in adolescent with panic disorder showed improvement in panic symptoms (AACAP Official Action 2007).

All of the tested **SSRIs** (fluoxetine, fluvoxamine, paroxetine, sertraline) demonstrated **positive results**. Fluoxetine (Birmaher et al. 2003), fluvoxamine (The Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001), and sertraline (Walkup et al. 2008) were studied in children diagnosed with one or several anxiety disorders and showed efficacy in treating generalized anxiety disorder, separation anxiety disorder, and/or social anxiety disorder. Sertraline was demonstrated in a small sample with a low dose (50 mg/day) to be more effective than placebo in generalized anxiety disorder (Rynn et al. 2001). Fluoxetine (Beidel et al. 2007) and paroxetine (Wagner et al. 2004) have shown benefits for socially anxious youths; fluoxetine was compared to placebo and a behavioral treatment and was found to be more effective than placebo, but less effective than behavioral treatment. This is the only available comparative treatment trial suggesting the superiority of a behavioral monotherapy to SSRIs medications. A recently conducted Cochrane

review confirmed that antidepressants with serotonergic effects led to larger treatment responses than placebo among children and adolescents with non-OCD anxiety disorders (Ipser et al. 2009).

Two large independent trials in generalized anxiety showed conflicting results for an extended-release formulation of **venlafaxine**, a serotonin noradrenaline reuptake inhibitor (one was positive, one was negative). However, when data were combined, a significant result was observed (Rynn et al. 2007). Venlafaxine was reported to be effective also in socially anxious youths (March et al. 2007).

Five studies examining the efficacy of **tricyclic antidepressants** (clomipramine, imipramine) in treating separation anxiety disorder and school refusal offered mixed results. In one of these studies, imipramine provided benefit for a substantial proportion of subjects, but did not demonstrate superiority to placebo in separation anxiety disorder (Klein et al. 1992). Two studies with clomipramine and imipramine were carried out to treat anxiety disorders in school-refusing youths (Berney et al. 1981; Bernstein et al. 1990, 2000). In both studies also youths with depressive disorders were included. Clomipramine and imipramine compared to placebo demonstrated no effect on subjects' return to school (Bernstein et al. 1990; Berney et al. 1981). When imipramine combined with weekly CBT was compared to placebo, school attendance was improved in the imipramine plus CBT group versus the CBT plus placebo group. In addition, anxiety and depressive symptoms were reduced in both treatment groups.

Compared to benzodiazepines, there are substantially fewer studies on antidepressants in the treatment of adult **insomnia**. A meta-analysis of randomized controlled clinical trials on the efficacy and safety of drug treatments in chronic insomnia showed some evidence that antidepressants, particularly **doxepin** and **trazodone**, **may** be an **effective treatment** in patients with comorbid depression (Buscemi et al. 2007). Until now, only two relatively short-term insomnia efficacy trials with trazodone in nondepressed patients have been carried out, and these have not demonstrated continued benefits in improving sleep (Neubauer 2007).

Dosing

Currently, there are no specific dosing guidelines for children and adolescents with anxiety and sleep disorders. Detailed information regarding antidepressant dosages is found in Table 4.5.

In randomized controlled trials in adults, the **SSRIs** and **venlafaxine** show a flat response curve, i.e., approximately 75 % of patients respond to initial (low) dose (with the exception of OCD) (Bandelow et al. 2008). In some patients, treatment should be started with half the recommended dose or less to minimize ADRs, such as nausea, dizziness, and headache, and a paradoxical increase in anxiety. In particular, patients with panic disorder may be sensitive to serotonergic stimulation and may easily discontinue because of initial jitteriness and nervousness. In the studies carried out in adults, reviewed above, response to treatment was identified as early as 4 weeks posttreatment initiation, but response may not manifest itself until several weeks after a therapeutic dose is reached. To avoid overstimulation and insomnia, doses might be given in the morning or at midday, except in patients reporting daytime sedation.

For **tricyclic antidepressants**, it is recommended to initiate the drug at a low dose and to increase dose every 3–5 days until dosage levels as high as in the treatment of depression are reached. Patients should be informed that the onset of the anxiolytic effect of the drug can have a latency of 2–4 weeks (in some cases up to 6 weeks, and generally in OCD). During the first 2 weeks, ADRs may be stronger. Also, during the first days of treatment, jitteriness or increase in anxiety symptoms may occur.

The antidepressant dose should be increased to the highest recommended therapeutic level if the

initial treatment with a low or medium dose fails (Bandelow et al. 2008). For OCD, medium to high doses are recommended. Although controlled data on maintenance treatment of anxiety disorders are scarce, it is recommended to use the same dose as in the acute phase (Bandelow et al. 2008).

If a sedating antidepressant drug is used as monotherapy for a patient with comorbid depression and insomnia, the dose should be that for treatment of depression (Schutte-Rodin et al. 2008). In many cases, this dose will be higher than the typical dose to treat insomnia alone.

Adverse Drug Reactions

In general, the frequency of ADRs is higher for tricyclic antidepressants than for SSRIs and venlafaxine. ADRs are discussed in detail in Sect. 4.4.

Drug Interactions

Important drug interactions are summarized in Tables 4.8 and 4.9.

Contraindications

Contraindications of antidepressants are described in detail in Sect. 4.4. Caution is advised in the use of antidepressants in the treatment of sleep disorders because safety and effectiveness are not established in this indication.

6.4.3 Low-Potency Antipsychotics

Indications

Areas of application for low-potency antipsychotics (for definition, see Sect. 5.2) with marked sedative properties that include both first-generation (e.g., sulpiride, fluspirilene, thioridazine) and second- and third-generation antipsychotics (e.g., quetiapine) are:

- The treatment of anxiety and anxious-depressive states
- Generalized anxiety disorders and anxious-depressive syndromes
- Sleep induction

In exceptional cases, high-potency antipsychotics without significant sedative properties (e.g., clozapine, flupentixol, risperidone) can also provide a therapeutic alternative in generalized anxiety disorders and anxious-depressive syndromes as well as for sleep induction.

> Because of concerns regarding tardive dyskinesias after long-term treatment, typical first-generation antipsychotics (for definition, see Sect. 5.2) should be **only employed** in anxiety disorders during **acute therapy** or when other therapeutic options have proved ineffective or were not tolerated.

None of these antipsychotics have been approved for these indications in children and adolescents. Trifluoperazine was approved by the FDA for the short-term treatment of nonpsychotic general anxiety disorders in adults. The pediatric indications of antipsychotics approved by the FDA are summarized in Table 5.4. The current **guidelines** for the assessment and therapy of children and adolescents with **anxiety** disorders do **not recommend** low-potency antipsychotics for pharmacological treatment (AACAP Official Action 2007; Strawn et al. 2012a).

According to the clinical **guideline** for the evaluation and management of chronic **insomnia** in adults, which are reported to be generally appropriate also for younger adults (Schutte-Rodin et al. 2008), second-generation antipsychotics such as quetiapine and olanzapine may only be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect. Because all of these agents have significant risks, their use is not recommended in the treatment of chronic insomnia in the general population.

Clinical Effects and Efficacy

Some antipsychotics also possess, in addition to their antipsychotic effect, substance-specific adrenergic, histaminergic, and serotonergic effects of varying degrees, by means of which they can exert additional depressant effects upon the psyche and vegetative nervous system (see Table 5.6). For this reason, these drugs were used in the treatment of anxiety and anxious-depressive states as well as for sleep induction at lower doses than in the treatment of schizophrenia.

In adults, it was demonstrated in a double-blind placebo-controlled study that low doses of trifluoperazine were superior to treatment with placebo in generalized anxiety disorder (Gao et al. 2006). Most of the less well-designed studies showed that other first-generation antipsychotics might be **superior to placebo** or as effective as benzodiazepines in the treatment of generalized anxiety disorders and other anxiety conditions (Gao et al. 2006). In most studies, second- and third-generation antipsychotic **augmentation** (e.g., olanzapine, quetiapine, risperidone) to antidepressants was superior to placebo in treating refractory OCD and post-traumatic stress disorder (Gao et al. 2006). Both olanzapine and quetiapine significantly reduced anxiety compared to placebo in studies of bipolar depression (Gao et al. 2006). According to a more recent study, quetiapine was reported to be effective also as a monotherapy for generalized anxiety disorders (see Bandelow et al. 2008).

For children and adolescents, there have been **no clinical trials** that meet current scientific standards regarding the use of antipsychotics to treat anxiety disorders. There are no double-blind placebo-controlled clinical trials to assess the safety and efficacy of these antipsychotics in patients with insomnia.

Dosing

Currently, there are no specific dosing guidelines for children and adolescents with anxiety and sleep disorders. Where possible, the aim should be a **low dosage treatment** (less than that employed for an antipsychotic effect); the required daily dosage should be based upon clinical efficacy with respect to the target symptom. Therapy should otherwise conform with the general dosage recommendations for antipsychotics (see Sect. 5.4.3). The predominantly parenteral administration with a dosing interval of 1–2 weeks is also particularly advantageous with respect to compliance problems.

In the study carried out in adults and reviewed above, the dose of antipsychotics examined was much lower than that recommended for schizophrenia. For example, maximal dose of trifluoperazine in the generalized anxiety disorders study was 6 mg/day (2–6 mg/day), but the recommended maximal dose for psychosis is 25 mg/day (effective dose 15–20 mg/day). This nonpsychotic effective dose for anxiety may also be applied to second- and third-generation antipsychotics.

Adverse Drug Reactions

Detailed discussion of ADRs is found in Sect. 5.4.4. An overview of ADRs and recommendations regarding therapy are included in Tables 5.7 and 5.8. In the studies carried out in adults, reviewed above, the antipsychotics examined were well tolerated in patients with primary generalized anxiety disorders for up to 6 weeks. One important factor was that the dose of antipsychotics was much lower than that recommended for schizophrenia (see above).

Drug Interactions

Important drug interactions are summarized in Table 5.9.

Contraindications

Absolute and relative contraindications are summarized in Table 5.10. Caution is advised in the use of antipsychotics in the treatment of sleep disorders because safety and effectiveness are not established in this indication.

6.4.4 Buspirone

Indications

Buspirone, a partial agonist at postsynaptic 5-HT_{1A}-receptors in the limbic system and a full agonist at presynaptic serotonin 5-HT_{1A}-receptors, was originally developed with the intention of developing a better antipsychotic agent. However, clinical trials demonstrated little antipsychotic effects. Because animal models suggested some anxiolytic effects, it was developed as an anxiolytic that is on the market since 1986.

Areas of application in psychiatry are acute and chronic anxiety states. Buspirone is US FDA-approved for the treatment of short-term management of anxiety disorders and the relief of symptoms of anxiety with or without accompanying symptoms of depression in adults.

The current **guidelines** for the diagnosis and therapy of children and adolescents with **anxiety**

(AACAP Official Action 2007; Strawn et al. 2012a) suggest buspirone as an alternative to be used alone or in combination with SSRIs.

Clinical Effects and Efficacy

In adults, it has been demonstrated in some, but not all, double-blind placebo-controlled studies that buspirone is effective for symptoms of generalized anxiety disorders (Bandelow et al. 2008). When compared to benzodiazepines, the onset of anxiolytic effects is slower for buspirone but anxiolysis is equivalent at 4–6 weeks.

In contrast to adults, two double-blind placebo-controlled trials in **children and adolescents** (6–17 years of age) have shown **no effect** on symptoms of generalized anxiety disorders using similar doses, despite pharmacokinetic studies of this agent, which have revealed that plasma exposure to buspirone is equivalent or greater in pediatric patients compared to adults (Strawn et al. 2012a).

Dosing

In the studies carried out in children and adolescents, reviewed above, the dose range of buspirone examined was 15–60 mg per day. At the commencement of treatment, the dosage is 5 mg, three times a day; if required, the daily dosage can be increased to 60 mg, divided into several individual doses.

Adverse Drug Reactions

Buspirone may be well tolerated at dose of 5–30 mg twice daily in anxious adolescents and at lower doses of 5–7.5 mg twice daily in anxious children (AACAP Official Action 2007). The most common ADRs in youths were lightheadedness, headache, and dyspepsia.

Drug Interactions

Combination of buspirone with the MAO-A inhibitor moclobemide should be avoided because of the danger of a hypotonic crisis.

Contraindications

Restrictions on the use of buspirone are:

- Severe liver and kidney dysfunction
- A history of seizures
- Myasthenia gravis

6.4.5 β-Adrenoceptor Antagonists (β-Blockers)

Indications

Because β-blockers may influence the autonomic anxiety symptoms such as palpitations and tremor, they have been used in the treatment of anxiety disorders. Areas of application in psychiatry are:

- Situational anxiety
- Post-traumatic stress disorder

β-Blockers have not been approved for these indications in children and adolescents and were not considered for the pharmacological treatment of anxiety disorders in children and adolescents in the USA (AACAP Official Action 2007; Strawn et al. 2012a). This is in contrast to some other countries. For example, in Germany, β-blockers are recommended primarily for the therapy of panic disorders, generalized anxiety disorders, and separation anxiety disorder in children, in each instance to reduce concomitant vegetative symptoms (Blanz et al. 2007).

> β-Blockers have significant ADRs, cannot be used in asthmatics, and are toxic in overdose; therefore, they are **not commonly used**.

Clinical Effects and Efficacy

Available double-blind placebo-controlled studies in adults do not show efficacy in anxiety disorder (Bandelow et al. 2008). **Propranolol** has been demonstrated in a double-blind placebo-controlled study to reduce the vegetative and β-adrenergically mediated somatic components of anxiety (e.g., tachycardia, palpitations, trembling, sweating, diarrhea) in anxiety states (Granville-Grossman and Turner 1966).

Dosing

The average single oral dose for propranolol is 10–80 mg. It should preferably be used only as required and as short as possible.

Adverse Drug Reactions

Patients with anxiety disorders frequently suffer from low blood pressure or postural hypotension, and these conditions may be intensified by

β-blockers. During therapy of situational anxiety with β-blockers, particular attention should be paid to cardiovascular effects, especially aggravation of latent cardiac insufficiency, hypotension, and/or tendency to bradycardia.

Drug Interactions

A clinically relevant interaction involving β-blockers is the delayed recovery of blood sugar levels after the administration of insulin or oral antidiabetic agents, potentially raising the danger of extended hypoglycemic reactions. Furthermore, the usual warning symptoms resulting from sympathetic stimulation may not be present, particularly in patients treated with nonselective β-blockers (such as oxprenolol and propranolol) as β-blockers suppress sympathetic impulses.

Contraindication

Restrictions on use apply in the following situations:

- Obstructive bronchial disorders and bronchial asthma
- Second and third-degree AV block, sinoatrial block, and sinus node dysfunction
- Bradycardia <50/min
- Marked hypotonia
- Diabetes mellitus

Caution is advised:

- In the use of these drugs in the treatment of anxiety disorders because safety and effectiveness are not established in patients <18 years.
- During discontinuation of therapy. In order to avoid so-called rebound effects (e.g., danger of inducing angina pectoris seizures), gradual dosage reduction is necessary.
- In juvenile diabetics, as exacerbation of hypoglycemia, with a tendency to ketoacidosis, is possible.
- With regard to metabolic acidosis, for example, as a consequence of extended "fasts" or of nutritional deficits resulting from anorexia nervosa.

6.4.6 Antihistamines

Indications

The antihistamines are histamine receptor (H_1, H_2) antagonists that block or reduce the effect of histamine. First-generation antihistamines, including diphenhydramine and hydroxyzine, are H_1-receptor antagonists that cross the blood-brain barrier. In the CNS, the histamine blockade leads to a diminished alertness, slowed reaction time, and somnolence. Therefore, they are used also as anxiolytics and sedative-hypnotics.

Psychiatric areas of application are:

- Acute and chronic anxiety states
- Sleep disorders
- Acute restlessness and agitation states

Promethazine is FDA-approved for sedation in children, adolescents, and adults. In addition, it is labeled for relief of apprehension and production of light sleep from which the patient can be easily aroused.

The current **guidelines** for the diagnosis and therapy of children and adolescents with **anxiety** do **not recommend** antihistamines such as doxylamine and diphenhydramine in pharmacological treatment (AACAP Official Action 2007; Blanz et al. 2007; Strawn et al. 2012a).

Prescription data show that antihistamines are widely used in pediatric psychiatric practice mainly as a sedative in patients with insomnia (Zito et al. 2000). Most of the over-the-counter sleep medications contain doxylamine and diphenhydramine as active ingredient. However, according to the clinical **guideline** for the evaluation and management of chronic **insomnia** in adults, which are reported to be generally appropriate also for younger adults (Schutte-Rodin et al. 2008), antihistamines are **not recommended** for the long-term use.

Clinical Effects and Efficacy

The antihistamines that are used as anxiolytics and sedative-hypnotics cross the blood-brain barrier and inhibit H_1 receptors in the CNS. Brainstem histaminergic neurons are involved in the regulation of vigilance and the sleep-wake rhythm. Inhibition of these neurons achieves centrally depressant effects that are exploited in the therapy of anxiety and sleep disorders.

In comparison to genuine hypnotics, the sleep-inducing effect of antihistamines is not as strong, but their toxicity is higher than that of benzodiazepines and similar substances.

Although the efficacy of antihistamines in the therapy of anxiety disorders and phobias as well as insomnia in children and adolescents has not been investigated in controlled studies, they are widely used in pediatric psychiatric practice (Zito et al. 2000). In **adults**, however, the efficacy of **hydroxyzine** in **generalized anxiety disorder** was demonstrated in a number of double-blind placebo-controlled studies (Bandelow et al. 2008). Because of sedating effects, it should only be used when treatment with other medications has not been successful or was not tolerated. There is no antidepressant effect or effects in panic or social anxiety disorder, post-traumatic stress disorder, or OCD (Bandelow et al. 2008).

Evidence for the efficacy and safety of antihistamines in the treatment of **insomnia** is very limited, with very few available studies using contemporary study designs and outcome (Schutte-Rodin et al. 2008). In one randomized placebo-controlled clinical trial study for **diphenhydramine**, modest improvements of subjective sleep parameters were obtained, but few group differences with placebo reached statistical significance (Morin et al. 2005).

Dosing

There are no specific dosing guidelines for children and adolescents with anxiety and sleep disorders. Diphenhydramine is administered orally at doses of 25–50 mg two to three times a day. Doxylamine is administered orally at doses of 12.5 mg two to four times a day. Hydroxyzine is administered orally for anxiety disorders at doses of 25–75 mg, broken into two to three individual doses.

Adverse Drug Reactions

ADRs include sedation, anticholinergic effects at high doses, blurred vision, confusion, and delirium. **Attention** should be given to the **anticholinergic features** of centrally active antihistamines, which in individual cases can lead to an acute attack of glaucoma and urinary retention. As with other sedative-hypnotic medications, reduced patient responsiveness must be expected. Furthermore, they also have pro-convulsive properties.

In cases of **intoxication**, disturbed consciousness (as severe as coma) accompanied by hypotonia and anticholinergic symptoms, including delirium, can develop. Cholinesterase inhibitors that cross the blood-brain barrier, such as physostigmine, are suitable symptomatic antidotes, as they both suppress the delirium symptoms (if only for a relatively short time) and elicit a pro-vigilance effect.

Drug Interactions

The effects of analgesics, hypnotics, narcotics, and alcohol can be amplified by the centrally active H_1 antihistamines discussed above. The concomitant antimuscarinic effects also increase the anticholinergic effect of parasympatholytics and some antidepressants.

Contraindications

Restrictions on use apply in the following situations:

- Intestinal or urethral obstructions (urinary retention)
- Intoxications with alcohol or other centrally depressant agents

Relative contraindications are cerebral seizure disorders and bronchial asthma. Combination of hydroxyzine with the MAO-A inhibitor moclobemide should be avoided because of the danger of a hypotonic crisis. Caution is advised in the use of these drugs in the treatment of anxiety and sleep disorders because safety and effectiveness are very limited in patients <18 years.

6.5 Duration of Treatment

The employment of anxiolytics and sedative-hypnotics must be targeted and continually subject to critical review, as chronic application increases the danger of psychological dependence.

Where possible, the employment of benzodiazepines in anxiety disorders should be reserved for crisis intervention, and the duration of continuous therapy should not exceed 4–6 weeks.

Anxiolytic therapy with other medications should be limited to crisis situations, and their application reserved for cases involving severe symptoms with a tendency to chronification, whereby discontinuation or gradual reduction of dosage after no longer than 6 months therapy should be planned. A central goal of the psychopharmacological (supplementary) treatment of anxiety disorders is the initial **support** of the utility and increase in efficacy of **psychotherapeutic measures**.

Duration of treatment of **sleep disorders** also depends on specific clinical characteristics and patients' preferences. FDA class labeling for hypnotics prior to 2005 implicitly recommended **short treatment duration**; since 2005, hypnotic labeling does not address duration of treatment. Antidepressants and other drugs commonly used off-label for treatment of insomnia also carry no specific restrictions with regard to duration of use. For many patients with insomnia, an initial treatment period of 2–4 weeks may be appropriate, followed by reevaluation of the continued need for treatment (Schutte-Rodin et al. 2008). A subset of patients with severe chronic insomnia may be appropriate candidates for longer-term or chronic maintenance treatment, but the specific defining characteristics of these patients are unknown. There is little empirical evidence available to guide decisions regarding which drugs to apply long term, either alone or in combination with behavioral treatments.

6.6 Therapeutic Monitoring

Children with anxiety disorders are at greater risk of alcohol abuse in adolescents (Schuckit and Hesselbrock 1994). Therefore, **comorbid alcohol abuse/dependence** in adolescents should be **assessed** and considered in treatment planning with anxiety disorders.

Therapy of anxiety disorders with benzodiazepines requires no routine clinical laboratory or electrophysiological parameter monitoring. Benzodiazepine elimination may be slowed in patients with hepatic and renal disorders.

In February 2004, the US FDA issued a **black box warning** and advised clinicians to carefully monitor pediatric patients receiving treatment with **antidepressants** including SSRIs for worsening depression, agitation, or suicidality, particularly at the beginning of medication treatment or during dose changes. This warning is based on the review of studies with adolescents, whose primary diagnosis was depression, not studies of youths with anxiety (see also Sect. 4.4.1).

Prior to treatment with **β-blockers**, contraindications and application limitations in various cardiovascular, pulmonary, and metabolic disorders (see above) must be carefully considered. Depending upon the specific disease or dysfunction, the necessity for clinical laboratory and physical examinations must be established on an individual basis according to the medical criteria of the relevant comorbid disorder.

For information regarding the recommended monitoring for therapy with antidepressants and antipsychotics, the reader is referred to Sect. 4.6 and 5.6. If sedative-hypnotic medications are **used long term**, regular **follow-up visits** should be scheduled at least every 6 months in order to monitor efficacy, ADRs, tolerance, and abuse/misuse of medications (Schutte-Rodin et al. 2008). Periodic attempts to reduce the frequency and dose in order to minimize ADRs and determine the lowest effective dose may be indicated.

The general monitoring of drug blood levels during therapy (therapeutic drug monitoring, **TDM**) is assuming increasing importance as an instrument for dosage optimization and the prevention of ADRs, although lack of information regarding age-specific therapeutic ranges for children and adolescents means that the clinical course remains the most important guide for the adjustment of

dosage. Because of the special features of psychopharmacological therapy in children and adolescents (see Chap. 2), TDM is generally appropriate (Egberts et al. 2011; Hiemke et al. 2011).

For adults, the desired therapeutic plasma levels are as follows (in alphabetical order; from Hiemke et al. 2011): alprazolam 5–50 ng/ml, buspirone 1–4 ng/ml, clonazepam 4–80 ng/ml, diazepam and metabolites 200–2,500 ng/ml, lorazepam 10–15 ng/ml, temazepam 20–900 ng/ml, triazolam 2–20 ng/ml, and zolpidem 80–150 ng/ml.

6.7 Clinical Pharmacology of Selected Anxiolytics and Sedative-Hypnotics: Overview

The following summaries are based upon information included in the Summary of Product Characteristics (SPCs) and the Prescribing Information (PI), respectively, depending whether the drug is approved in the EU and the USA. Issues concerning the preparation of SPCs and PI and their limitations were discussed in detail in Sect. 4.7. The most important pharmacological features of the selected anxiolytics and sedative-hypnotics are presented as an orientation aid in clinical use. "Benzodiazepines" in these tables refer to the pharmacologically defined group of substances. Other pharmacological agents that were used as anxiolytics and sedative-hypnotics are given in Sects. 4.7 and 5.7.

Abbreviations used in the following tables are as follows: ADRs, adverse drug reactions, AUC, area under the curve; b.i.d., 2× day; c_{max}, maximal plasma concentration after oral dosing; CNS, central nervous system; CYP, cytochrome P450; EMA, European Medicines Agency; GABA, γ-aminobutyric acid; IC_{50} half-maximal inhibitory concentration of specific binding; i.v. intravenous; MAO, monoamine oxidase; q.i.d., 4 × day; t.i.d., 3 × day; t_{max}, time required to reach peak plasma concentration (c_{max}); $t_{1/2}$, elimination half-life.

6.7.1 Alprazolam

Pharmacodynamic properties	Anxiolytic. Agonist of the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex (IC_{50} 20 nM; see Table 6.2); amplification of the inhibitory function of GABAergic neurons
Pharmacokinetic properties	t_{max} 1–2 h, $t_{1/2}$ 12–15 h, protein binding 80 %, bioavailability 80 % Metabolized by CYP 3A4
Indications	**US FDA approval** Treatment of generalized anxiety disorder in adults Treatment of panic disorder, with or without agoraphobia Safety and efficacy of alprazolam have not been established in children and adolescents below the age of 18 years; therefore, use of alprazolam is not recommended **Europe** Short-term treatment of moderate or severe anxiety states and anxiety associated with depression in adults. It is only indicated when the disorder is severe, disabling, or subjecting the individual to extreme distress Should not be used to treat short-term mild anxiety, such as anxiety or tension associated with the stress of everyday life. As the efficacy in depression and in phobic or obsessional states has yet to be established, specific treatment may have to be considered
Dosage	Anxiety disorder in adults: initial 0.25–0.5 mg given 3 times daily; max. 4 mg/day given in divided doses Panic disorder in adults: initial 0.5 mg given 3 times daily; max. doses up to 10 mg/day may be required to achieve successful response

ADRs	If they occur, they are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage Very common (≥1/10) ADRs include sedation and somnolence Common (≥1/100 to <1/10) ADRs include decreased appetite, psychiatric disorders (confusional state, depression, disorientation, decreased libido), nervous system disorders (ataxia, balance disorder, abnormal coordination, memory impairment, dysarthria, disturbance in attention, hypersomnia**,** lethargy**,** dizziness, headache), blurred vision, constipation, dry mouth, nausea, fatigue, and irritability As with all benzodiazepines, amnesia, paradoxical reactions (e.g., excitement, agitation), and other adverse behavioral effects may occur unpredictably
Drug interactions	Benzodiazepines produce an additive effect when coadministered with alcohol or other CNS depressants Compounds that inhibit certain hepatic enzymes (particularly CYP3A4) may increase the concentration of alprazolam and enhance its activity. The coadministration of nefazodone or fluvoxamine increases the AUC of alprazolam by approximately twofold
Contraindications	In patients with known hypersensitivity to benzodiazepines, alprazolam, or to any component of the product's formulation, patients with myasthenia gravis, severe respiratory insufficiency, sleep apnea syndrome, severe hepatic insufficiency

6.7.2 Buspirone

Pharmacodynamic properties	Anxiolytic with a different mechanism of actions as benzodiazepines. Partial agonist at postsynaptic serotonin 5-HT_{1A}-receptors and full agonist at presynaptic serotonin 5-HT_{1A}-receptor The exact mechanism of buspirone anxiolytic action is not fully known. It does not act on benzodiazepine receptor sites. In animal studies, it interacts with serotonin, noradrenaline, acetylcholine, and dopamine systems of the brain
Pharmacokinetic properties	t_{max} 40–90 min, $t_{1/2}$ 2–4 h, protein binding ca. 95 %, bioavailability 4 % Metabolized by CYP 3A4 Plasma concentrations of buspirone and its active metabolite were higher in pediatric patients, compared to adults given equivalent doses (7.5 mg b.i.d., 2.9-fold; 15 mg b.i.d., 2.1-fold)
Indications	**Approval in the USA (FDA) and in Europe** Treatment of short-term management of anxiety disorders and the relief of symptoms of anxiety with or without accompanying symptoms of depression Placebo-controlled trials, in which 334 patients were treated with buspirone for up to 6 weeks, have not shown buspirone at doses recommended for adults to be an effective treatment for generalized anxiety disorder in patients less than 18 years
Dosage	No official dosage advice for children and adolescents Adult dosage: the recommended initial dose is 15 mg daily (7.5 mg b.i.d.). To achieve an optimal therapeutic response, at intervals of 2–3 days, the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20–30 mg per day were commonly employed
ADRs	If they occur, they are generally observed at the beginning of drug therapy and usually subside with use of the medication and/or decreased dosage When patients receiving buspirone were compared with patients receiving placebo, dizziness, headache, nervousness, light-headedness, nausea, excitement, and sweating/clamminess were the only ADRs occurring with significantly greater frequency ($P<0.10$) in the buspirone group than in the placebo group

Drug interactions	The concomitant use of buspirone with other CNS-active drugs should be approached with caution The coadministration with nonselective MAO inhibitors, erythromycin, and itraconazole is not recommended
Contraindications	Patients with known hypersensitivity to buspirone or any ingredient in the tablet, patients with epilepsy, severe renal or hepatic impairment

6.7.3 Clonazepam

Pharmacodynamic properties	Anxiolytic. Agonist of the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex (IC_{50} 2 nM; see Table 6.2); amplification of the inhibitory function of GABAergic neurons Pharmacodynamic properties include anticonvulsive, sedative, muscle relaxing, and anxiolytic effects. Animal data and EEG investigations in man have shown that clonazepam rapidly suppresses many types of paroxysmal activity including the spike and wave discharge in absence seizures (petit mal), slow spike wave, generalized spike wave, spikes with temporal or other locations, as well as irregular spikes and waves
Pharmacokinetic properties	t_{max} 1–4 h, $t_{1/2}$ 20–60 h; protein binding ca. 85, bioavailability 90 % Clonazepam pharmacokinetics is dose independent throughout the dosing range. Clonazepam is highly metabolized, with less than 2 % unchanged clonazepam being excreted in the urine Biotransformation occurs mainly by reduction of the 7-nitro group to the 4-amino derivative. This derivative can be acetylated, hydroxylated, and glucuronidated. CYP, including CYP3A, may play an important role in clonazepam reduction and oxidation There is no evidence that clonazepam induces its own metabolism or that of other drugs in humans
Indications	**US FDA approval** Alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures Treatment of panic disorder, with or without agoraphobia Because of the possibility that adverse effects on physical or mental development could become apparent only after many years, a benefit-risk consideration of the long-term use of clonazepam is important in pediatric patients being treated for seizure disorder Safety and effectiveness in pediatric patients with panic disorder below the age of 18 have not been established **Europe** All clinical forms of epileptic disease and seizures in infants, children, and adults, especially absence seizures (petit mal) including atypical absence; primary or secondarily generalized tonic-clonic (grand mal), tonic, or clonic seizures; partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus, and associated abnormal movements

Dosage	**Seizure disorders** Pediatric patients: (up to 10 years of age or 30 kg of body weight) in order to minimize drowsiness, the initial dose should be 0.01–0.03 mg/kg but not to exceed 0.05 mg/kg daily given in 2 or 3 divided doses. Dosage should be increased by no more than 0.25–0.5 mg every third day until a daily maintenance dose of 0.1–0.2 mg/kg of body weight has been reached, unless seizures are controlled or side effects preclude further increase. Whenever possible, the daily dose should be divided into 3 equal doses. If doses are not equally divided, the largest dose should be given before retiring **Panic disorder** The initial dose for adults is 0.25 mg b.i.d. An increase to the target dose for most patients of 1 mg/day may be made after 3 days. It is possible that some individual patients may benefit from doses of up to a maximum dose of 4 mg/day, and in those instances, the dose may be increased in increments of 0.125–0.25 mg b.i.d. every 3 days until panic disorder is controlled or until ADRs make further increases undesired. To reduce the inconvenience of somnolence, administration of one dose at bedtime may be desirable
ADRs	As for all benzodiazepines (see Sect. 6.7.1)
Drug interactions	Enhanced effects on sedation, respiration, and hemodynamics may occur when clonazepam is coadministered with any centrally acting depressants, e.g., alcohol, and other anticonvulsant (antiepileptic) agents, anesthetics, hypnotics, psychoactive drugs, and some analgesics as well as muscle relaxants and may result in mutual potentiation of drug effects
Contraindications	Patients with known sensitivity to benzodiazepines or any of the drug excipients, acute pulmonary insufficiency, severe respiratory insufficiency, sleep apnea syndrome, myasthenia gravis, severe hepatic insufficiency

6.7.4 Diazepam

Pharmacodynamic properties	Anxiolytic. Agonist of the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex (IC_{50} 8 nM, see Table 6.2); amplification of the inhibitory function of GABAergic neurons Little autonomic activity
Pharmacokinetic properties	t_{max} 30–90 min, $t_{1/2}$ 24–48 h, protein binding 98 %, bioavailability 80 % Metabolized by CYP3A and CYP2C19 It is *N*-demethylated by CYP3A4 and CYP2 2C19 to the active metabolite *N*-desmethyldiazepam and is hydroxylated by CYP3A4 to the active metabolite temazepam. *N*-desmethyldiazepam and temazepam are both further metabolized to oxazepam. Temazepam and oxazepam are largely eliminated by glucuronidation

Indications	**US FDA approval** Management of anxiety disorders or for the short-term relief of the symptoms of anxiety In acute alcohol withdrawal, it may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens, and hallucinosis Adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma), spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia), athetosis, and stiff-man syndrome May be used adjunctively in convulsive disorders, although it has not proved useful as the sole therapy Safety and effectiveness in pediatric patients below the age of 6 months have not been established **Approval in Europe** *Adults* The short-term relief (2–4 weeks) only of anxiety which is severe, disabling, or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness Cerebral palsy, muscle spasm, as an adjunct to certain types of epilepsy (e.g., myoclonus) Symptomatic treatment of acute alcohol withdrawal As oral premedication for the nervous dental patient, for premedication before surgery *Children* Control of tension and irritability in cerebral spasticity in selected cases As an adjunct to the control of muscle spasm in tetanus Oral premedication
Dosage	Diazepam can be administered orally, parenterally (i.v. and i.m.), or rectally. With oral administration, it has the most rapid onset of action of all benzodiazepines For optimal effect, the dosage should be carefully individualized. Treatment should begin at the lowest effective dose appropriate to the particular condition In anxiety states for adults, the usual oral dose is 2 mg 3 times/day maximum dose up to 30 mg daily in divided doses, adjusted on an individual basis i.v. administration must be quite slow (**N.B.**, possibility of respiratory depression) Rectal administration as micro-enema 5–10 mg for rapid relief of seizures
ADRs	As for all benzodiazepines (see Sect. 6.7.1). The most commonly reported ADRs are fatigue, drowsiness, and muscle weakness; they are usually dose related. These phenomena occur predominantly at the start of therapy and usually disappear with prolonged administration As with all benzodiazepines, amnesia, paradoxical reactions (e.g., excitement, agitation), and other adverse behavioral effects may occur unpredictably
Drugs interactions	The concomitant use with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase its clinical effects possibly including severe sedation and clinically relevant respiratory and/or cardiovascular depression Substrates, which are modulators of CYP3A and/or of CYP2C19, may potentially alter the pharmacokinetics of diazepam. Drugs like cimetidine, ketoconazole, fluvoxamine, fluoxetine, and omeprazole which are CYP3A or CYP2C19 inhibitors may lead to increased and prolonged sedation There have also been reports that the metabolic elimination of phenytoin is affected by diazepam
Contraindications	Myasthenia gravis, hypersensitivity to benzodiazepines or any of the drug's excipients, severe respiratory insufficiency, sleep apnea syndrome, severe hepatic insufficiency, phobic or obsessional state, chronic psychoses

6.7.5 Diphenhydramine

Pharmacodynamic properties	Sedative-hypnotic. First-generation histamine H_1-receptor antagonist, thus inhibiting H_1-receptor mediated reactions, such as vasodilation, flare and itch reactions, and sneezing It easily crosses the blood-brain barrier, consequently producing well-documented sedative and anticholinergic effects. First-generation antihistamines also have affinity for serotonin 5-HT-receptors, α-adrenoceptors, and muscarinic acetylcholine receptors. They also reduce cyclic GMP concentrations, increase atrioventricular nodal conduction, and inhibit activation of airway vagal afferent nerves
Pharmacokinetic properties	t_{max} 1–4 h, $t_{1/2}$ 2.4–9.3 h, protein binding 80–85 %, bioavailability 40–60 % Metabolized by CYP2D6 (ca 80 %) and CYP3A4 (ca 10 %)
Indications	**US FDA approval** Antihistaminic: for allergic conjunctivitis due to foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; amelioration of allergic reactions to blood or plasma; dermatographism; as therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled Motion sickness: for active and prophylactic treatment of motion sickness Antiparkinsonism: for parkinsonism (including drug induced) in the elderly unable to tolerate more potent agents; mild cases of parkinsonism (including drug induced) in other age groups; in other cases of parkinsonism (including drug induced) in combination with centrally acting anticholinergic agents Nighttime sleep aid **Approval in Europe** An aid to the relief of temporary sleep disturbance Should not be used in children under 16 years
Dosage	25–50 mg t.i.d. or q.i.d. The nighttime sleep-aid dosage is 50 mg at bedtime
ADRs	ADRs which have been observed in clinical trials and which are considered to be common (occurring in >1/100 to <1/10) or very common (occurring in >1/10) are fatigue, sedation, drowsiness, disturbance in attention, unsteadiness, dizziness, and dry mouth
	In pediatric patients, especially, antihistamines in overdosage may cause hallucinations, convulsions, or death. As in adults, antihistamines may diminish mental alertness in pediatric patients. In the young pediatric patient, particularly, they may produce excitation
Drug interactions	It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines) MAO inhibitors prolong and intensify the anticholinergic effects of diphenhydramine. It should be used with caution with MAO inhibitors or within 2 weeks of stopping an MAO inhibitor As diphenhydramine has some antimuscarinic activity, the effects of some anticholinergic drugs (e.g., atropine, tricyclic antidepressants) may be potentiated; therefore, medical advice should be sought before taking diphenhydramine with such medicines Diphenhydramine is an inhibitor of CYP2D6. Therefore, there may be a potential for interaction with drugs which are primarily metabolized by CYP2D6, such as metoprolol and venlafaxine
Contraindications	Patients who are hypersensitive to diphenhydramine or any of the excipients and in those with the following conditions: stenosing peptic ulcer and pyloroduodenal obstruction

6.7.6 Doxylamine

Pharmacodynamic properties	Sedative-hypnotic. First-generation histamine H_1-receptor antagonist, thus inhibiting H_1-mediated reactions, such as vasodilation, flare and itch reactions, and sneezing It easily crosses the blood-brain barrier, consequently producing well-documented sedative and anticholinergic effects. First-generation antihistamines also have affinity for serotonin 5-HT-receptors, α-adrenoceptors, and muscarinic acetylcholine receptors. They also reduce cyclic GMP concentrations, increase atrioventricular nodal conduction, and inhibit activation of airway vagal afferent nerves
Pharmacokinetic properties	t_{max} 2–4 h; $t_{1/2}$ 8–10 h; protein binding, no data; bioavailability, no data Induction of CYP2B, weak induction of CYP2A and CYP3A
Indications	**Approved in USA (FDA) and in Europe** Nighttime sleep aid It should not be administered to children under 12 years of age
Dosage	Adults and children 12 years of age and over: 25 mg 30 min before going to bed, once daily or as directed by a doctor
ADRs	Drowsiness or dizziness
Drug interactions	It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines)
Contraindications	A breathing problem such as asthma, emphysema, or chronic bronchitis

6.7.7 Estazolam

Pharmacodynamic properties	Sedative-hypnotic. Agonist at the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex; amplification of the inhibitory function of GABAergic neurons
Pharmacokinetic properties	t_{max} 0.5–6 h, mean $t_{1/2}$ 10–24 h, protein binding 93 %, bioavailability not reported Metabolism to the major circulating metabolite 4-hydroxy-estazolam catalyzed by CYP3A
Indications	**US FDA approval** Short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings Safety and effectiveness in pediatric patients below the age of 18 have not been established.
Dosage	The recommended initial dose for adults is 1 mg at bedtime; however, some patients may need a 2 mg dose
ADRs	The most commonly observed ADRs, not seen at an equivalent incidence among placebo-treated patients, were somnolence, hypokinesia, dizziness, and abnormal coordination. As with all benzodiazepines (see Sect. 6.7.1), amnesia, paradoxical reactions (e.g., excitement, agitation), and other adverse behavioral effects may occur unpredictably
Drug interactions	It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines) Compounds that are potent CYP3A inhibitors (such as ketoconazole, itraconazole, nefazodone, fluvoxamine, and erythromycin) would be expected to increase plasma estazolam concentrations, and CYP3A inducers (such as carbamazepine, phenytoin, rifampicin, and barbiturates) would be expected to decrease estazolam concentrations
Contraindications	Pregnant women: if there is a likelihood of the patient becoming pregnant while receiving estazolam, she should be warned of the potential risk to the fetus and instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered Adjunct therapy with ketoconazole and itraconazole, since these medications significantly impair oxidative metabolism mediated by CYP3A

6.7.8 Eszopiclone

Pharmacodynamic properties	Eszopiclone is the active S-enantiomer of R,S-zopiclone Sedative-hypnotic. Agonist at the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex; amplification of the inhibitory function of GABAergic neurons (S)-*N*-desmethyl zopiclone, one of the primary plasma metabolites, binds also to GABA receptors but with substantially lower potency than eszopiclone
Pharmacokinetic properties	t_{max} 1 h, $t_{1/2}$ 6 h, protein binding ca. 52–59 %, bioavailability 48.9 % Metabolized by CYP3A4 and CYP2E1
Indications	**US FDA approval** Treatment of insomnia It is a schedule IV-controlled substance under the Controlled Substances Act. Other substances under the same classification are classical benzodiazepines as well as zaleplon and zolpidem Safety and effectiveness in children below the age of 18 years have not been established
Dosage	The dose should be individualized. The recommended starting dose for most nonelderly adults is 2 mg immediately before bedtime. Dosing can be initiated at or raised to 3 mg if clinically indicated, since 3 mg is more effective for sleep maintenance Clinical experience in patients with concomitant illness is limited
ADRs	ADRs that suggest a dose-response relationship in adults include viral infection, dry mouth, dizziness, hallucinations, infection, rash, and unpleasant taste, with this relationship clearest for unpleasant taste Because of its long $t_{1/2}$, it may also produce residual sedation and impairment of driving performance in the initial morning waking hours As with all benzodiazepines (see Sect. 6.7.1), amnesia, paradoxical reactions (e.g., excitement, agitation), and other adverse behavioral effects may occur unpredictably
Drug interactions	It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines) There were no pharmacokinetic or pharmacodynamic interactions between eszopiclone and paroxetine, digoxin, or warfarin. When eszopiclone was coadministered with olanzapine, no pharmacokinetic interaction was detected in levels of eszopiclone or olanzapine, but a pharmacodynamic interaction was seen on a measure of psychomotor function Eszopiclone and **lorazepam** decreased each other's c_{max} by 22 % Coadministration of eszopiclone 3 mg to subjects receiving ketoconazole 400 mg. a potent inhibitor of CYP3A4, resulted in a 2.2-fold increase in exposure to eszopiclone
Contraindications	None known. Eszopiclone should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses

6.7.9 Flurazepam

Pharmacodynamic properties	Sedative-hypnotic. Agonist at the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex (IC_{50} 15 nM; see Table 6.2); amplification of the inhibitory function of GABAergic neurons
Pharmacokinetic properties	t_{max} 30–60 min, mean $t_{1/2}$ 2.3 h, protein binding and bioavailability not reported The major active metabolite in blood is N_1-desalkyl-flurazepam which reached steady-state (plateau) levels after 7–10 days of dosing, at levels approximately 5–6-fold greater than the 24-h levels observed on day 1 ($t_{1/2}$ 47–100 h) This pharmacokinetic profile may be responsible for the clinical observation that flurazepam is increasingly effective on the 2nd or 3rd night of consecutive use and that for 1 or 2 nights after the drug is discontinued, both sleep latency and total wake time may still be decreased
Indications	**Approved in the USA (FDA) and in Europe** Treatment of insomnia Clinical investigations have not been carried out in children. Therefore, the drug is not currently recommended for use in persons under 15 years of age
Dosage	Dosage should be individualized for maximal beneficial effects. The usual adult dosage is 30 mg at bedtime before retiring. In some patients, 15 mg may suffice
ADRs	Dizziness, drowsiness, light-headedness, staggering, ataxia, and falling have occurred, particularly in elderly or debilitated persons. Severe sedation, lethargy, disorientation, and coma, probably indicative of drug intolerance or overdosage, have been reported Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, gastrointestinal pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains, and genitourinary complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase As with all benzodiazepines, amnesia, paradoxical reactions (e.g., excitement, agitation), and other adverse behavioral effects may occur unpredictably
Drug interactions	It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines)
Contraindications	In patients with known hypersensitivity to the drug

6.7.10 Hydroxyzine

Pharmacodynamic properties	Anxiolytic. First-generation histamine H_1-receptor antagonist, thus inhibiting H_1-mediated reactions, such as vasodilation, flare and itch reactions, and sneezing It easily crosses the blood-brain barrier, consequently producing well-documented sedative and anticholinergic effects First-generation antihistamines also have affinity for serotonin 5-HT-receptors, α-adrenoceptors, and muscarinic acetylcholine receptors. They also reduce cyclic GMP concentrations, increase atrioventricular nodal conduction, and inhibit activation of airway vagal afferent nerves
Pharmacokinetic properties	Mean t_{max} 2.1 h; $t_{1/2}$ 14–20 h; protein binding and bioavailability, no data reported Metabolites include cetirizine, which has also antihistaminic activity The pharmacokinetics and antipruritic effects of hydroxyzine were studied in 12 children (mean age 6.1 ± 4.6 years) with severe atopic dermatitis, each given a single 0.7 mg/kg oral dose. The biological effects of hydroxyzine appear to be much more prolonged than would be predicted from the $t_{1/2}$ values
Indications	**US FDA approval** For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested Useful in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses, and in histamine-mediated pruritus As a sedative when used as premedication and following general anesthesia **Approval in Europe** To assist in the management of anxiety in adults Management of pruritus associated with acute and chronic urticaria, including cholinergic and physical types, and atopic and contact dermatitis in adults and children Efficacy has not been established in children and adolescents with anxiety disorders below the age of 18 years
Dosage	For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested: in adults, 50–100 mg q.i.d.; children under 6 years, 50 mg daily in divided doses; and over 6 years, 50–100 mg daily in divided dose
ADRs	Anticholinergic effects, reduced responsiveness, pro-convulsive properties The most common ADR of the sedating antihistamines is CNS depression. Effects vary from slight drowsiness to deep sleep and include lassitude, dizziness, and incoordination. Paradoxical stimulation may occasionally occur, especially at high doses and in children and the elderly. If sedative effects occur, they may diminish after a few days of treatment. Other common ADRs include headache, psychomotor impairment, and antimuscarinic effects Children are more susceptible to ADRs
Drug interactions	It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines) Hydroxyzine may cause drug-drug interactions with CYP2D6 substrates Cimetidine, 600 mg b.i.d., has been shown to increase the serum concentrations of hydroxyzine and to decrease t_{max} of the metabolite cetirizine
Contraindications	Patients who have shown previous hypersensitivity to hydroxyzine or any of the excipients, asthmatics who have previously experienced a serious antihistamine-induced adverse bronchopulmonary effect, porphyria, pregnancy, and breast-feeding

6.7.11 Lorazepam

Pharmacodynamic properties	Anxiolytic and sedative-hypnotic. Agonist of the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex (IC_{50} 4 nM; see Table 6.2); amplification of the inhibitory function of GABAergic neurons
Pharmacokinetic properties	t_{max} 1–2 h, $t_{1/2}$ 12 h, protein binding 85 %, bioavailability 90 % Metabolism by CYP3A4 enzymes. No major active metabolites
Indications	**US FDA approval** Management of anxiety disorders or for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms Safety and effectiveness in children of less than 12 years have not been established. **Approval in Europe** Symptomatic relief of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress occurring alone or in association with insomnia or short-term psychometric, organic, or psychotic illness As premedication (adults and children 5 years and above) before operative dentistry and general surgery Efficacy has not been established in children and adolescents with anxiety disorders below the age of 18 years
Dosage	The usual range is 2–6 mg/day given in divided doses, the largest dose being taken before bedtime, but the daily dosage may vary from 1 to 10 mg/day For **anxiety**, most patients require an initial dose of 2–3 mg/day given b.i.d. or t.i.d For **insomnia due to anxiety** or transient situational stress, a single daily dose of 2–4 mg may be given, usually at bedtime For elderly or debilitated patients, an initial dosage of 1–2 mg/day in divided doses is recommended, to be adjusted as needed and tolerated **Premedication children** (aged 5 and above): 0.5–2.5 mg at 0.05 mg/kg to the nearest 0.5 mg according to weight, not less than 1 h before operation
ADRs	ADRs, when they occur, are usually observed at the beginning of therapy and generally decrease in severity or disappear with continued use or upon decreasing the dose. Most frequently reported ADRs associated with benzodiazepines include daytime drowsiness, dizziness, muscle weakness, and ataxia As with all benzodiazepines, amnesia, paradoxical reactions (e.g., excitement, agitation), and other adverse behavioral effects may occur unpredictably. Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued In some pharmaco-epidemiological studies, it was found to possess the **highest dependence potential** of all benzodiazepines
Drug interactions	**Pharmacodynamic interactions** It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines) Concomitant use with sodium oxybate should be avoided Reports of **marked sedation**, excessive salivation, hypotension, ataxia, delirium, and respiratory arrest when **clozapine** is given concurrently with lorazepam. Other drugs enhancing the sedative effect of diazepam are cisapride, lofexidine, nabilone, disulfiram, and the muscle relaxants baclofen and tizanidine **Pharmacokinetic interactions** CYP-inhibitors (e.g., cimetidine, isoniazid, erythromycin, omeprazole, esomeprazole) reduce clearance and may potentiate the action of benzodiazepines. Itraconazole, ketoconazole, and to a lesser extent fluconazole and voriconazole are potent inhibitors of CYP3A4 and may increase plasma levels of benzodiazepines. CYP-inducers (e.g., rifampicin) may increase clearance of benzodiazepines

Contraindications	Hypersensitivity to benzodiazepines or to any of the other ingredients; acute pulmonary insufficiency, respiratory depression, sleep apnea (risk of further respiratory depression), obsessional states (inadequate evidence of safety and efficacy), severe hepatic insufficiency (may precipitate encephalopathy), planning a pregnancy, pregnancy, myasthenia gravis Benzodiazepines should not be used alone in depression or anxiety with depression (may precipitate suicide)

6.7.12 Quazepam

Pharmacodynamic properties	Sedative-hypnotic. Agonist of the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex; amplification of the inhibitory function of GABAergic neurons Selective for type I benzodiazepine receptors containing the α_1 subunit. Type I $GABA_A$ receptors include the α_1 subunit containing $GABA_A$ receptors which are responsible for hypnotic properties of the drug
Pharmacokinetic properties	t_{max} 1.75 h, mean $t_{1/2}$ of quazepam and 2-oxoquazepam 39 h and that of *N*-desalkyl-2-oxoquazepam 73 h, protein binding <95 %, bioavailability 29–35 % Extensively metabolized in the liver; two of the plasma metabolites are 2-oxoquazepam and *N*-desalkyl-2-oxoquazepam. All three compounds show CNS depressant activity
Indications	**US FDA approval** Short-term treatment (usually 7–10 days) for insomnia Efficacy and safety have not been established in patients below the age of 18 years
Dosage	The recommended initial dose is 7.5 mg at bedtime. The dose can be increased to 15 mg if necessary for efficacy
ADRs	Quazepam has fewer ADRs than other benzodiazepines and less potential to induce tolerance and rebound effects. There is significantly less potential to induce respiratory depression or to adversely affect motor coordination than other benzodiazepines Most common ADRs (>1 %): drowsiness, headache, fatigue, dizziness, dry mouth, and dyspepsia Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur
Drug interactions	It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines) In vitro inhibition studies conducted to assess the potential of quazepam to inhibit CYP2B6, CYP2C8, and CYP2E1 at relevant clinical c_{max} concentrations (0.15 μM = 58 ng/ml) demonstrate that quazepam is a CYP2B6 mechanism-based inhibitor. However, the in vivo extrapolation of this is unknown. It may be possible that coadministration of quazepam and drugs primarily metabolized by CYP2B6 (e.g., efavirenz and **bupropion**) may result in increased plasma concentrations of these drugs resulting in an increase in ADRs (e.g., CNS toxicities associated with quazepam and precipitation of seizures with bupropion). Patients taking medications that are CYP2B6 substrates with quazepam should be monitored closely for ADRs associated with these medications
Contraindications	Hypersensitivity to quazepam or other benzodiazepines, established or suspected sleep apnea, or chronic pulmonary insufficiency

6.7.13 Temazepam

Pharmacodynamic properties	Sedative-hypnotic. Agonist of the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex (IC_{50} 16 nM; see Table 6.2); amplification of the inhibitory function of GABAergic neurons
Pharmacokinetic properties	Mean t_{max} 1.5 h, mean $t_{1/2}$ 8.8 h, protein binding 96 %, bioavailability 100 % Minimal first pass metabolism. There were no active metabolites formed and the only significant metabolite present in blood was the O-conjugate
Indications	**Approved in the USA (FDA) and in Europe** Short-term treatment of insomnia (generally 7–10 days) Efficacy and safety have not been established in patients below the age of 18 years
Dosage	While the recommended usual adult dose is 15 mg before retiring, 7.5 mg may be sufficient for some patients, and others may need 30 mg. In transient insomnia, a 7.5 mg dose may be sufficient to improve sleep latency
ADRs	The following ADRs have been reported less frequently (0.5–0.9 %): anorexia, ataxia, equilibrium loss, tremor, increased dreaming, dyspnea, palpitations, vomiting, backache, hyperhidrosis, burning eyes, amnesia, hallucinations, and horizontal nystagmus. Paradoxical reactions including restlessness, overstimulation, and agitation were rare (less than 0.5 %) Preexisting depression may be unmasked during treatment with temazepam. Blood dyscrasias and increased liver enzymes have also been reported to occur occasionally. If any of these effects do occur, treatment should be discontinued
Drug interactions	**Pharmacodynamic interactions** It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines) Concomitant use with sodium oxybate should be avoided When used concurrently with **antiepileptic drugs**, ADRs and toxicity may be more evident, particularly with hydantoins (e.g., phenytoin) and/or barbiturates. This requires extra care in adjusting dosage in the initial stages of treatment **Pharmacokinetic interactions** CYP450 inhibitors (e.g., cimetidine, ritonavir, fluvoxamine) reduce clearance and may potentiate the action of temazepam CYP450 inducers (e.g., rifampicin) may increase clearance of benzodiazepines
Contraindications	Hypersensitivity to benzodiazepines or to any of the other ingredients; acute pulmonary insufficiency, respiratory depression, sleep apnea (risk of further respiratory depression), obsessional states (inadequate evidence of safety and efficacy), severe hepatic insufficiency (may precipitate encephalopathy), neuromuscular respiratory weakness including myasthenia gravis, breast-feeding Temazepam should not be used alone in depression or anxiety with depression (may precipitate suicide)

6.7.14 Triazolam

Pharmacodynamic properties	Sedative-hypnotic. Agonist of the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex (IC_{50} 4 nM; see Table 6.2); amplification of the inhibitory function of GABAergic neurons
Pharmacokinetic properties	t_{max} 2 h; $t_{1/2}$ 1.5–5.5 h; protein binding 89 %; bioavailability, no data reported Triazolam undergoes hydroxylation in the liver and is excreted in the urine mainly in the form of its conjugated metabolites with only small amounts appearing unchanged
Indications	**Approved in the USA (FDA) and in Europe** Short-term treatment of insomnia (generally 7–10 days) Triazolam is not recommended for use in children and adolescents below the age of 18 years due to insufficient data on safety and efficacy
Dosage	Treatment should be as short as possible. The usual adult dose is 0.25 mg before going to bed. Dosage should be adjusted on the basis of the individual patient response to achieve effect without overdosage. A maximum dose of 0.25 mg should not be exceeded because of risk of unacceptable CNS adverse effects In patients previously untreated with hypnotics, initial dosage should be 0.125 mg
ADRs	Common (≥1/100 to <1/10) ADRs observed from placebo-controlled trials and post-marketing experience frequency are somnolence, dizziness, ataxia, and headache As with all benzodiazepines, amnesia, paradoxical reactions (e.g., excitement, agitation), and other adverse behavioral effects may occur unpredictably
Drug interactions	**Pharmacodynamic interactions** It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines) **Pharmacokinetic interactions** They can occur when triazolam is administered along with drugs that interfere with its metabolism. Compounds that inhibit CYP3A4 may increase the concentration of triazolam and enhance its activity. Based on the degree of interaction and the type of data available, the following **recommendations** are made: The coadministration of triazolam with ketoconazole, itraconazole, and nefazodone is contraindicated The coadministration of triazolam with other azole-type antifungals is not recommended Caution is recommended when triazolam is coadministered with isoniazid, fluvoxamine, sertraline, paroxetine, diltiazem, and verapamil Oral contraceptives and imatinib may lead to enhanced clinical effects of triazolam due to the inhibition of CYP3A4. Caution is therefore recommended in case of concomitant use with triazolam Rifampicin and carbamazepine cause CYP3A4 induction. Therefore, the effect of triazolam may be diminished significantly during therapy with rifampicin or carbamazepine. Patients should be switched to alternative hypnotics, which are mainly eliminated as glucuronides Increased bioavailability of triazolam has been shown when taken concomitantly with grapefruit juice
Contraindications	Patients with a known hypersensitivity to benzodiazepines, to triazolam, or to any component of the product's formulation; in patients with myasthenia gravis, severe respiratory insufficiency, sleep apnea syndrome, and severe hepatic insufficiency The coadministration with ketoconazole, itraconazole, nefazodone, and efavirenz

6.7.15 Zaleplon

Pharmacodynamic properties	Sedative-hypnotic. Agonist of the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex; amplification of the inhibitory function of GABAergic neurons Selective for type I benzodiazepine receptors containing the α_1 subunit. Type I $GABA_A$ receptors include the α_1 subunit containing $GABA_A$-receptors which are responsible for hypnotic properties of the drug
Pharmacokinetic properties	t_{max} 1 h, $t_{1/2}$ 1 h, protein binding 60 ± 15 %, bioavailability 30 %. Metabolized by aldehyde oxidase and, to a lesser extent, by CYP3A4
Indications	**Approved in the USA (FDA) and in Europe (EMA)** Short-term treatment of insomnia The safety and effectiveness in pediatric patients under the age of 18 years have not been established
Dosage	The dose should be individualized. The recommended dose for most nonelderly adults is 10 mg immediately be taken before bedtime. For certain low-weight individuals, 5 mg may be a sufficient dose. Doses above 20 mg have not been adequately evaluated and are not recommended It can be taken less than or equal to 2 h before awaking without "hangover" effects
ADRs	Apart from ADRs seen with other benzodiazepines with short $t_{1/2}$, daytime sedation with increased fatigue and impaired responsiveness can occur, as can memory disorders, especially at higher dosages. Further, increased mouth dryness and bitter taste have been described As with all benzodiazepines, amnesia, paradoxical reactions (e.g., excitement, agitation), and other adverse behavioral effects may occur unpredictably Rare cases of **angioedema** involving the tongue, glottis, or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zaleplon. Some patients have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zaleplon should not be rechallenged with the drug
Drug interactions	**Pharmacodynamic interactions** It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines) **Pharmacokinetic interactions** Because zaleplon is primarily metabolized by aldehyde oxidase, and to a lesser extent by CYP3A4, inhibitors of these enzymes might be expected to decrease zaleplon's clearance and inducers of these enzymes might be expected to increase its clearance. Indeed, it was shown that **paroxetine** did not alter the pharmacokinetics of zaleplon. However, multiple-dose administration of the potent CYP3A4 inducer **rifampicin** reduced zaleplon c_{max} and AUC by approximately 80 % Concomitant administration of zaleplon (10 mg) and **cimetidine** (800 mg) that inhibits both aldehyde oxidase and CYP3A4 produced an 85 % increase in the mean c_{max} and AUC of zaleplon. An initial dose of 5 mg should be given to patients who are concomitantly being treated with cimetidine
Contraindications	Hypersensitivity to the active substance or to any of the excipients, severe hepatic impairment, severe renal impairments, sleep apnea syndrome, myasthenia gravis, severe respiratory insufficiency, children (under 18 years of age)

6.7.16 Zolpidem

Pharmacodynamic properties	Sedative-hypnotic. Agonist of the benzodiazepine binding site of the $GABA_A$ receptor-Cl^- channel complex; amplification of the inhibitory function of GABAergic neurons Selective for type I benzodiazepine receptors containing the α_1 subunit. Type I $GABA_A$ receptors include the α_1 subunit containing $GABA_A$-receptors which are responsible for hypnotic properties of the drug
Pharmacokinetic properties	t_{max} 0.5–3 h, mean $t_{1/2}$ 2.4 h, protein binding 92.5 ± 0.1 %, bioavailability 70 % Metabolism primarily via CYP3A4 (minor metabolism by CYP1A2, 2C9, 2C19, and 2D6)
Indications	**Approved in the USA (FDA) and in Europe** Short-term treatment of insomnia The safety and effectiveness in pediatric patients under the age of 18 years have not been established
Dosage	The recommended daily dose for adults is 10 mg. Zolpidem acts rapidly and therefore should be taken immediately before retiring, or in bed In **January 2013**, the **FDA recommended** that the **initial dose** of immediate-release zolpidem is **5 mg** for women and either 5 or 10 mg for men, because new data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving
ADRs	There is evidence of a dose relationship for ADRs associated with zolpidem use, particularly for certain CNS and gastrointestinal events. The common (≥1 and <10 %) ADRs include diarrhea, nausea, vomiting, abdominal pain, hallucination, agitation, nightmare, somnolence, headache, dizziness, exacerbated insomnia, and anterograde amnesia (amnestic effects may be associated with inappropriate behavior) As with all benzodiazepines, amnesia, paradoxical reactions (e.g., excitement, agitation), and other adverse behavioral effects may occur unpredictably
Drug interactions	**Pharmacodynamic interactions** It may potentiate the sedative effects of alcohol and other CNS depressants (antipsychotics, tranquillizers, antidepressants, hypnotics, analgesics, anesthetics, barbiturates, and sedative antihistamines) **Pharmacokinetic interactions** Compounds which inhibit in particular CYP3A4 may enhance the activity of benzodiazepines and benzodiazepine-like agents. Coadministration of zolpidem with **ketoconazole** (200 mg twice daily) prolonged the $t_{1/2}$ of zolpidem, increased total AUC, and decreased apparent oral clearance when compared to zolpidem plus placebo. The total AUC for zolpidem, when coadministered with ketoconazole, increased by a factor of 1.83 when compared to zolpidem alone. A routine dosage adjustment of zolpidem is not considered necessary, but patients should be advised that use with ketoconazole may enhance the sedative effects
Contraindications	Patients with a hypersensitivity to zolpidem or any of the inactive ingredients, obstructive sleep apnea, myasthenia gravis, severe hepatic insufficiency, and acute and/or severe respiratory depression In the absence of data, zolpidem should not be prescribed for children or patients with psychotic illness

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Mood Stabilizers

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Manfred Gerlach and Andreas Warnke

Contents

M. Gerlach, PhD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Laboratory for Clinical Neurobiology and Therapeutic Drug Monitoring, University of Würzburg, Füchsleinstr.15, 97080 Würzburg, Germany
e-mail: manfred.gerlach@uni-wuerzburg.de

A. Warnke, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Würzburg, Füchsleinstr.15, 97080 Würzburg, Germany
e-mail: warnke@kjp.uni-wuerzburg.de

7.1 Definition

The term "mood stabilizer" refers to a class of pharmacological agents primarily employed in the treatment of **bipolar disorder**, a subcategory of affective disorders. According to formal contemporary classification, bipolar disorder (previously called manic–depressive psychosis) consists of at least one manic (bipolar disorder I), hypomanic (bipolar disorder II), or a mixed episode and a depressive episode (Fountoulakis et al. 2012). Bipolar disorder is a major, worldwide health problem with devastating consequences for affected individuals, their families, and society. Recently, the World Health Organization (WHO) has ranked bipolar disorder among the ten most disabling medical conditions worldwide. Underscoring severity, it is estimated that patients with bipolar disorder

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I have a 5- to 17-fold higher suicide rate than the general population (Bostwick and Pankratz 2000).

The current understanding of bipolar disorder suggests that the subcategory I is an episodic illness with a return to the premorbid level of functioning between the episodes and a favorable outcome in comparison with schizophrenia. "Mood stabilizers" **abolish** or **alleviate** the intense **mood swings** associated with episodes of the disorder as well as the **emotional instability** during and between episodes. The classic (conventional, traditional) representatives of this class of psychopharmacological agents are lithium salts and the antiepileptic agent valproic acid (or the corresponding salt, valproate).

7.2 Classification

After noting the calming effects of **lithium** carbonate in guinea pigs, Joseph Cade (1949), an Australian urologist, first described the successful treatment of mania with lithium salts in adults (see Cole and Parker 2012). Two decades after Cade's case reports, the Danish researchers Schou and Baastrup reported evaluative studies with a lithium salt in patients with manic–depressive illness, which became the basis for the approval of lithium salts (carbonate, citrate) by the US Food and Drug Administration (FDA) for the treatment of acute mania in 1970 and for the prophylaxis of bipolar disorder 4 years later (Cole and Parker 2012). Over 40 years ago, lithium salts were also used to treat "manic–depressive illness" in children (Annell 1969) and have been approved by the FDA for the "treatment of manic episodes and maintenance treatment of bipolar disorder" in patients aged 12 years and older. Lithium salts are the only licensed agents for this indication in Europe.

Valproic acid was first labeled for treatment of mania in the USA in 1995. Valproic acid dissociates to the valproate ion in the gastrointestinal tract. Valproate products that contain valproate sodium, divalproex sodium (an enteric-coated formulation of valproate), and valproic acid are now approved for treatment of mania in most developed countries. The psychotropic effects of valproic acid, particularly its positive influence on mood, were first noted by various authors in the 1930s during the treatment of epileptic seizures. This observation and several early hypotheses of kindling and sensitization as models of bipolar disorder progression (Weiss and Post 1998) have promoted controlled investigations of antiepileptic drugs such as carbamazepine, gabapentin, lamotrigine, oxcarbazepine, and topiramate as potential **mood-stabilizing anticonvulsants**.

Further exemplars of this group of pharmacological agents are **atypical second- and third-generation antipsychotics** that are first-line treatment for mania in children and adolescents (Hazell and Jairam 2012). The indication and age-specific aspects of approval status, clinical efficacy in the treatment of bipolar I disorder, recommended dosages, adverse drugs reactions (ADRs), interactions with other medications, restrictions on use, and special cautions are discussed in Chap. 5.

7.3 Mechanisms of Action

Lithium salts and the mood-stabilizing antiepileptics have a variety of neurobiological effects in vivo and in vivo, and in recent years, a diverse set of molecular and cellular targets of these agents has been identified. However, their psychotropic mechanisms of action are not clear and significant questions remain in understanding the neurobiological mechanisms underlying bipolar disorder.

It is hypothesized that **lithium salts** have **immediate effects** on the storage, release, biotransformation, and reuptake of **neurotransmitters** that leads to downstream changes in signal transduction cascades and gene expression (see Sect. 1.2.6), resulting eventually in the transcription and expression of neurotrophic, angiogenic, and neuroprotective proteins. The mood-stabilizing effect of **antiepileptics** is presumed to be associated with their anticonvulsant activity but direct **effects on neural transmission** have also been demonstrated. For a more thorough discussion of the extensive literature on the mechanisms of action of mood-stabilizing drugs and the neurobiological mechanisms con-

tributing to bipolar disorder, the reader is directed to the comprehensive review by Schloesser et al. (2012). In the following the most important data from this review are described.

Bipolar disorder pathophysiology is thought to arise from the interactions between genetic risk factors and environmental influences, which include exposure to adverse childhood experiences, chronic stress, and trauma (Schloesser et al. 2012). As with other major neuropsychiatric disorders, a neurodevelopmental component probably contributes to disease pathophysiology. It is hypothesized that bipolar disorder is caused by alterations in neural and synaptic plasticity, which was supported by reports of structural and functional changes in both neuroimaging and postmortem studies of subjects with bipolar disorder. Neuroplastic changes that occur during critical developmental windows may contribute to structural and functional changes in key circuits, which can have long-lasting effects on adult brain function.

Based on the **interference** of **lithium (Li)** with the **Na^+-K^+-ATPase**, it was originally postulated that mood disorders arise from ionic shifts and changes in membrane permeability, which led to direct impairments in neural excitability and transmission. Lithium is an element of group 1 of the periodic table (alkali metals), which also includes sodium (Na) and potassium (K). As its chemicophysical properties are similar to those of Na^+, the lithium cation (Li^+) can enter the cells via Na^+ channels. Intracellular Li^+, however, is transported in the reverse direction by Na^+-K^+-ATPase with less than one-tenth of the velocity of Na^+. As at the same time fewer K^+ ions consequently enter the cell by this ion pump, intracellular K^+ concentrations are reduced. Such **shifts in electrolyte balance** are believed to be responsible for the experimentally observed acute changes in the storage, release, biotransformation, and reuptake of neurotransmitters, particularly serotonin, dopamine, acetylcholine, and GABA (Lenox and Hahn 2000). It is therefore assumed that therapy with lithium salts leads via these electrolyte shifts to improved neurotransmission, particularly serotonergic transmission but also to enhanced dopaminergic, cholinergic, and GABAergic transmission as well as influencing circadian rhythms in the concentrations of various neurotransmitter receptors. It was also recently shown that lithium salts have an impact on the amplitude and period of the molecular circadian clockwork (Li et al. 2012).

More recent evidence suggests that **mood disorders**, including bipolar disorder, are associated with **alterations in glutamatergic neurotransmission** that affect intracellular signaling cascades, resulting eventually in impairments of structural and functional neural plasticity (reviewed in Schloesser et al. 2012). Glutamate, the most abundant excitatory neurotransmitter, is integral for synaptic transmission in brain circuitry and is a key regulator of synaptic strength and plasticity, which play major roles in the neurobiology of learning, memory, and general cognition (see Sect. 1.3.3.1). Altered glutamate concentrations in blood and cerebrospinal fluid have been observed in studies of patients with mood disorders. In addition, nuclear magnet resonance spectroscopy studies have shown altered levels of glutamate and related metabolites in diverse brain regions of patients with bipolar disorder (reviewed in Schloesser et al. 2012).

Accumulating evidence indicates that **lithium therapy** has also direct **effects on glutamatergic neural transmission** (reviewed in Schloesser et al. 2012). In particular, several lines of evidence suggest that Li^+ alters neuronal excitability at hippocampal CA1 synapses, resulting in increased excitatory postsynaptic potentials. A recent study has also demonstrated that the effect of Li^+ on synaptic enhancement at CA1 synapses may arise from its ability to potentiate currents through the AMPA subtype of ionotropic glutamate receptors (see Sect. 1.3.3.1) by selectively enhancing the probability of channel opening. These effects on hippocampal synaptic transmission may be of particular relevance for mood disorder treatment because the hippocampus is a key component of the limbic system network and is implicated in emotional regulation, cognition, and memory.

Laboratory tests have demonstrated that **Li^+** concentrations, within its therapeutic plasma range, **modulate different second messenger systems**, including the inositol phosphate,

cAMP, cGMP, and glycogen synthase kinase 3β systems, and thereby influence gene expression and neuronal plasticity via the upregulation of the brain-derived neurotrophic factor (BDNF) as well as the neuroprotective protein, B-cell lymphoma/leukemia-2 (Bcl-2). Bcl-2 plays a key role in controlling intracellular calcium dynamics, which is of special interest because impaired calcium signaling, as a result of alterations in glutamatergic neurotransmission, has been repeatedly recognized as a cellular abnormality in bipolar disorder. With respect to inositol phosphate metabolism, Li^+ blocks inositol polyphosphate-1-phosphatase and inositol mono-phosphatase and thus reduces inositol biosynthesis in particular, with the consequence that insufficient inositol is available for the synthesis of membrane phospholipids and of the second signal molecule phosphatidylinositol-4,5-bisphosphate. Evidence from numerous studies has also implicated protein kinase C in bipolar disorder pathophysiology, and both Li^+ and valproic acid decrease the levels of protein kinase C and its activity, which result in decreased free myo-inositol and production of diacylglycerol.

Direct **effects on neural transmission** have also been documented for **mood-stabilizing antiepileptics**. Carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid decrease high-frequency action potential firing by increasing inactivation of voltage-gated Na^+ channels and indirectly enhance GABAergic function. Lamotrigine in addition blocks L-type Ca^{2+} channels, which can give rise to substantial effects on baseline neurotransmission. Both valproic acid and lamotrigine upregulate excitatory amino acid transporter activity, leading to enhanced glutamate clearance. Topiramate inhibits the AMPA subtype of ionotropic glutamate receptors. Gabapentin activates glutamate decarboxylase, the GABA-metabolizing enzyme. In summary, these mood stabilizers may indirectly influence excitatory neurotransmission by modulating the rate of glutamate uptake or inhibiting excitatory neurotransmission by increasing GABAergic neurotransmission.

In the following, the clinical psychopharmacology of lithium salts and mood-stabilizing antiepileptics will be discussed. The antipsychotics are described in Chap. 5.

7.4 Clinical Psychopharmacology

7.4.1 Lithium Salts (Carbonate, Citrate)

Indications

Areas of application in children and adolescents are:

- Treatment of manic episodes of bipolar disorder
- Maintenance treatment of bipolar disorder
- Acute bipolar depression
- Bipolar patients accompanied by substance disorders
- Aggression in patients with neuropsychiatric disorders with comorbid ADHD, conduct disorder, and oppositional defiant disorder

However, as mentioned above, lithium salts have been approved by the FDA only for the "treatment of manic episodes and maintenance treatment of bipolar disorder" in patients aged 12 years and older.

An overview of therapy with lithium salts is given in Table 7.1.

Clinical Effects and Efficacy

The attenuation of manic symptoms effected by lithium therapy becomes manifest only after 1–2 weeks, so that antipsychotics are initially administered in cases of marked mania (see Chap. 20). Protection from symptomatic recurrence in bipolar disorder can be expected only after 6–12 months.

As discussed below, it seems that **children** and **adolescents** tend to **benefit less** from lithium therapy **than adults**. The reason for this remains unclear; however, such results are consistent with the hypothesis that pediatric-onset bipolar disorder may represent a different subtype of bipolar disorder that possibly responds to different treatments than those observed in adult-onset cases. The limited efficacy of lithium therapy in this population of subjects with

Table 7.1 Overview of therapy with lithium (Li^+) salts: indications, dosage, medication interactions, and requisite therapeutic monitoring

Effect/indications	Acute mania, phase prophylaxis in bipolar I disorder, mitigation of depressive symptoms and of explosive agitation states
Toxic dose	A blood level of more than 3.0 mmol/L is frequently lethal; toxic symptoms occur at a serum lithium level ≥1.5 mmol/L (at lower levels in exceptional cases) **Symptoms**: tiredness, psychomotor slowing, dysarthria, ataxia, cognitive confusion, clouded consciousness, deliriant symptoms, cerebral seizures Suspicion of intoxication should be met by immediate discontinuation of lithium therapy and intensive medical care: monitoring of water and electrolyte balance, diuresis (but not with thiazide diuretics!), hemodialysis for ca. 2 weeks
Dosage	**Children**: commence with 4–8 mmol/L daily (e.g., 150–300 mg Li^+ carbonate) divided into 2–3 doses; dosage increase every 3–5 days by 4–8 mmol/L daily (= 150–300 mg Li^+ carbonate); in children under 25 kg body weight the effective level of 0.6–1.2 mmol/L requires little more than 56 mmol/L/day (= 2,100 mg Li^+ carbonate) divided into several doses. Monitoring of serum Li^+ level every 3–5 days after dose adjustment, 12 h after most recent administration **Adolescents**: commence with 8 mmol/day (= 300 mg Li^+ carbonate) divided into 2–3 doses; increase of daily dosage by maximally 8 mmol/day (= 300 mg Li^+ carbonate) until a serum level of 0.6–1.2 mmol/L in bipolar disorder I or 0.4–0.8 mmol/L for enhancement of antidepressive medication is reached
Withdrawal	Abrupt withdrawal of the medication increases the risk of re-appearance of manic–depressive symptoms. As prophylaxis, medication should be administered for at least 18 months and slowly withdrawn over a period of about 3 months
Interactions with other medications and foodstuffs	Antipsychotics: possible increase in Li^+ blood levels Carbamazepine: neurotoxic effects can occur even at normal blood Li^+ concentrations – if rarely – during concurrent treatment with carbamazepine Phenytoin: elevated Li^+ toxicity Thiazide diuretics, loop diuretics: danger of intoxication through an increase of Li^+ concentrations Low sodium diet: danger of intoxication through increased Li^+ levels Antibiotics: can lead to increased Li^+ levels, depending upon the specific agent SSRIs: serotonin syndrome (rare)

From Gerlach and Warnke (2010)
SSRIs selective serotonin reuptake inhibitors

bipolar disorder characterized by mixed presentations and frequent cycling is consistent with findings in the adult literature, indicating limited efficacy for lithium carbonate in the management of adults with mixed presentations or dysphoric mania (McElroy et al. 1992).

Treatment of Manic Episodes of Bipolar Disorder

The efficacy of lithium salts in the treatment of acute mania in adults has been demonstrated repeatedly in double-blind placebo-controlled studies (Fountoulakis et al. 2012): For example, two studies showed that the percentage of acute manic patients who responded to lithium, i.e., at least 50 % reduction in symptoms, is 49–53 % (serum levels 1.5 and 0.6–1.4 mmol/L, respectively) versus 25–27 % for the placebo group.

In **children and adolescents** the **efficacy** and safety of **lithium salts** have **not** been **documented** in double-blind placebo-controlled studies. Of the two double-blind studies in the treatment of pediatric mania, one assessed the impact of lithium carbonate on substance abuse in substance-dependent bipolar adolescents (Geller et al. 1998); the other one used a blinded discontinuation study design but failed to demonstrate separation from placebo (Kafantaris et al. 2004). In the latter study, after 4 weeks on open-label lithium treatment, 40 patients aged 12–18 years with bipolar disorder I and in a manic episode who responded to lithium monotherapy,

resulted in a 33 % decline in the total Young Mania Rating Scale (YMRS), were enrolled in the double-blinded arm of the study, in which they either continued with lithium for another 2 weeks or received placebo after a quick taper period. Important limitations of this study include a small sample size, discontinuation before recovery, and rapid discontinuation.

In a recent randomized controlled trial, lithium, divalproex sodium, or risperidone was investigated to find out which medication to administer first to antimanic medication-naïve children and adolescents aged 6–15 years (Geller et al. 2012). Medications were increased weekly only if there was inadequate response, and no dose-limiting ADRs, to maximum doses of lithium carbonate (1.1–1.3 mmol/L), divalproex sodium (111–125 μg/mL), and risperidone (4–6 mg). Higher response rates occurred after treatment for 8 weeks with risperidone versus lithium (68.5 % vs. 35.6 %) and versus divalproex sodium (68.5 % vs. 24.0 %). **Response to lithium versus divalproex sodium** did **not differ**. The discontinuation rate was higher for lithium than for risperidone. Increased weight gain, body mass index, and prolactin level occurred with risperidone versus lithium and versus divalproex sodium.

As presented by Liu et al. (2011) there have been four **open-label clinical trials** involving lithium carbonate in the treatment of mania in children and adolescents with bipolar disorder. The response rate for manic symptoms in these studies ranged from 23 to 55 %, with an average response of 40 %. Of these four trials, only one assessed the acute effects of lithium as monotherapy in children and adolescents (aged 8–18 years); it reported a response rate of 38 % with 0.88 ± 0.35 mmol/L lithium (Kowatch et al. 2000).

Treatment of Acute Bipolar Depression

Acute bipolar depression is not well studied in children, adolescents, and adults; only a limited number of studies exist in adults (Fountoulakis et al. 2012; Liu et al. 2011), and the common practice to carry the limited data and wisdom from the treatment of unipolar to bipolar depression has proven to be wrong (Fountoulakis et al. 2012).

Although earlier studies were positive in adult patients with bipolar depression, one more recent double-blind placebo-controlled study was negative for lithium (reviewed in Fountoulakis et al. 2012). The mean lithium serum levels were 0.61 mmol/L, with 34.9 % of patients having levels below 0.6 mmol/L, which are lower than the generally recommended.

The only available prospective trial of lithium in the treatment of bipolar depression in **adolescents** was an **open-label** 6-week acute **trial**, in which 22 patients aged 12–18 years were enrolled and lithium was titrated to 1.0–1.2 mmol/L (Patel et al. 2006). There was a 40 % reduction in the Children's Depression Rating Scale-Revised (CDRS-R) scores at the end of the sixth week, and response (50 % reduction in the CDRS-R score from baseline to endpoint) and remission (SDRS-R score $\leq$ 28 and a CGI-Bipolar Improvement Score of 1 or 2, respectively) rates were 48 and 30 %, respectively.

Maintenance Treatment of Bipolar Disorder

There have been several small and underpowered clinical studies with different designs (placebo-controlled, nonrandomized case-control studies with placebo, crossover and discontinuation studies) of lithium salts in adults that suggest that lithium therapy prevents manic but not depressive episodes in spontaneously remitted patients, irrespective of index episode (Fountoulakis et al. 2012).

One **double-blinded study in children and adolescent** (Findling et al. 2005) demonstrated that lithium and divalproex had a similar long-term stabilizing effect (for up to 76 weeks) in patients with bipolar disorder I and II (aged 5–17 years) who had been previously stabilized on combination treatment with lithium plus divalproex. This study had a high dropout rate, with only three of 30 patients completing maintenance treatment.

The long-term effectiveness of lithium salts for the treatment of pediatric bipolar disorder was also shown in an open-label study within the context of combination mood stabilizer therapy for refractory mania and pharmacological treatment of comorbid psychiatric conditions (Findling et al. 2013). Outpatients, aged seven to 17 years, meeting DSM-IV diagnostic criteria for bipolar disorder I (manic or mixed) who demonstrated at least a partial response to 8 weeks of open-label

treatment with lithium (Phase I) were eligible to receive open-label lithium for an additional 16 weeks (Phase II). Up to two adjunctive medications could be prescribed to patients experiencing residual symptoms of mania or comorbid psychiatric conditions, following a standardized algorithm. Forty-one patients received treatment with lithium carbonate for a mean of 14.9 weeks during Phase II. The mean weight-adjusted total daily dose at end of Phase II was 27.8 mg/kg per day, with an average lithium concentration of 1.0 mmol/L. Twenty-five of the 41 patients (60.9 %) were prescribed adjunctive psychotropic medications for residual symptoms. The most frequent indications for adjunctive medications were refractory mania ($N=13$; 31.7 %) and ADHD ($N=15$; 36.6 %). At the end of this phase, 28 (68.3 %) patients met a priori criteria for response (≥50 % reduction from Phase I baseline in YMRS summary score and a Clinical Global Impressions-Improvement [CGI-I] score of one or two), with 22 (53.7 %) considered to be in remission (YMRS summary score ≤12 and CGI-Severity score of 1 or 2). These data suggest that patients who initially responded to lithium maintained mood stabilization during continuation treatment, but partial responders did not experience further improvement during Phase II, despite the opportunity to receive adjunctive medications.

Aggression in Patients with Neuropsychiatric Disorders with Comorbid ADHD, Conduct, and Oppositional Defiant Disorder

Although studies regarding treatment of aggression with lithium salts in children and adolescents are sparse and results are inconsistent, it was suggested that lithium is effective and safe in the treatment of aggression in children and adolescents with comorbid ADHD, conduct, and oppositional defiant disorder (Amaladoss et al. 2010; Nevels et al. 2010). However, all these studies have limited sample size, and subjects were primarily hospitalized patients. Furthermore, the longest duration for a randomized controlled trial was 8 weeks.

Combination and Add-on Treatment

Few rigorous studies have been carried out to examine the combination treatment in children and adolescents; however, they comprise a mixture of acute mania trials and continuation/maintenance treatment (reviewed in Goldstein et al. 2012; Liu et al. 2011). There have been six open-label and one double-blinded study of combination treatments. In one study that was an extension of an open-label study that compared monotherapy using carbamazepine versus divalproex versus lithium carbonate (Kowatch et al. 2000), it was found that 58 % of **patients needed combination treatment** with one or two mood stabilizers and a psychostimulant, second-generation antipsychotic, or antidepressant (Kowatch et al. 2003). Of those patients, 80 % responded to combination treatment after not responding to monotherapy. However, this is in contrast to a recent open-label study with lithium carbonate showing that partial responders to acute lithium did not appear to experience substantial symptom improvement during the continuation phase, despite the possibility that adjunctive medications could be prescribed (Findling et al. 2013).

In an open-label trial with 90 children and adolescents (aged 5–17 years) meeting DSM-IV criteria for bipolar I or bipolar II disorder that lasted up to 20 weeks, a 46.7 % remission rate for patients taking **divalproex plus lithium carbonate** could be shown (Findling et al. 2003). Thirty-eight patients with a mean age of 10.5 years who achieved biphasic symptom remission for four consecutive weeks entered a subsequent double-blind randomized maintenance phase during which time they received lithium or divalproex monotherapy (target serum concentrations of 0.6–1.2 mmol/L and 50–100 μg/mL, respectively) for up to 76 weeks (Findling et al. 2006). Ninety percent of the patients responded to this combination treatment.

In another 1-year open-label study, 21 patients who did not respond to 8 weeks of lithium monotherapy were given **risperidone augmentation** (Pavuluri et al. 2006). The response rate on the combination therapy was 85.7 % and the remission rate was 57.1 %. Risperidone adjunctive to lithium or divalproex was also investigated in an open-label, 6-month study of 37 subjects aged 5–18 years during acute manic or mixed episodes (Pavuluri et al. 2004). Both treatment strategies were well tolerated and produced response rates of 82.4 and 80 % and remission rates of 64.7

and 60 %, respectively. All subjects in the two treatment groups gained some weight, with mean weight gains of 6 kg in the risperidone/lithium group and 6.8 kg in the risperidone/divalproex group. There was a high dropout rate in the risperidone/lithium group (seven of 20, 35 %), but no subjects dropped out of the risperidone/divalproex group. In summary, lithium plus antipsychotic medications were found to have a response rate of 64.3 % (change in YMRS score ≥ 33 %) in patients with mania with psychosis (Liu et al. 2011).

Recommended Dosages

Dosage must be rigorously **guided by blood Li^+ concentrations**, given the very narrow therapeutic range of lithium therapy. Administration of the daily dosage as two doses (morning and evening) is generally appropriate (Table 7.1). Fundamentally, however, not only are Li^+ levels **crucial** for dosage calibration but also the **subjective** and **objective well-being** of the patient.

For children under 25 kg body weight, an initial dosage of 4–8 mmol/L per day (150–300 mg lithium carbonate; see Table 7.1) is recommended, which can be increased after 3–7 days by 4–8 mmol/L per day. In general, no more than 56 mmol/L Li^+ daily (daily dosage of 2,100 mg lithium carbonate), divided into two doses, is required to achieve an effective blood level. Serum levels should be assessed 3–5 days after each increase or change in dosage.

In the **acute therapy of a manic syndrome**, serum Li^+ levels of 1.0–1.2 mmol/L are desirable, whereby monitoring of levels during the acute phase (twice a week, always 12 h after the most recent dose) is to be recommended. In adolescents, the initial daily dosage is 8 mmol/L (e.g., 300 mg lithium carbonate), increased every 3–4 days by a further 8 mmol/L per day.

The dosage for **phase prophylaxis** is also determined by the serum Li^+ level, which should lie between 0.6 and 1.2 mmol/L, although these levels are based on studies of adults with bipolar disorder. Monitoring of the serum concentrations of Li^+ and creatinine once a month together with assessment of TSH/T3/T4, serum electrolytes, renal function, urine composition, and ECG is advisable; body weight and neck girth should also be assessed every 3–6 months.

In the treatment of **aggressive impulsive outbursts**, serum Li^+ concentrations between 0.6 and 1.2 mmol/L are similarly appropriate. The daily dosages are not necessarily lower than those for adults, whereby large intraindividual variations in serum concentrations can be observed (Geller et al. 1998).

> Should lithium therapy be resumed after a previous discontinuation, the dosage that had achieved an effective level prior to discontinuation can be immediately reinstated. Renewed titration is only necessary if in the meantime, for example, an age-related physical change or renal disease has intervened.

ARDs

Lithium-associated ADRs that were most commonly reported in studies were nausea, vomiting, increased appetite, weight gain, headaches, and stomachaches (Hazell and Jairam 2012). **Monitoring of ADRs** occurring during lithium therapy (Table 7.2) is of **decisive importance** because of their potential severity and the very narrow therapeutic range of the medication.

> Lithium intoxication can lead to cerebral seizures, disturbed consciousness (including coma), as well as cardiocirculatory collapse.

Fine tremor is the **most frequent ADR**. Should the tremor cause significant impairment (such as illegible handwriting) and if dosage reduction is not possible, medication with propranolol (β-adrenoceptor antagonist = β-blocker; 10–140 mg/day) is recommended (Schatzberg et al. 2003). Further neurological symptoms, such as coarse tremor, vertigo, rigidity, hyperreflexia, ataxia, dysarthria, and confusion ranging to deliriant behavior, indicate toxic Li^+ levels.

Table 7.2 Adverse drug reactions (ADRs) and monitoring during therapy with lithium salts

Type of ADR	Symptoms	Monitoring
Neuromuscular and CNS	Fine tremor (if needed, therapy with 10–40 mg/day propranolol) Ataxia Muscular asthenia Muscular spasms Cognitive slowing	At every blood level assessment
Gastrointestinal	Dyspepsia Weight gain (second most common ADR) Nausea Vomiting Diarrhea	At every blood level assessment
Dermatologic	Hair loss Acne (relatively frequent) Psoriasis	At every blood level assessment
Cardiac	T wave changes Sinus node dysfunction (rare) AV bundle branch block (rare)	Annual ECG check
Renal	Nephropathy (quite rare) Polydipsia	Annual assessment of serum creatinine
Hematologic	Leukocytosis	At every blood level assessment
Fluid balance	Edema	
Endocrinologic	Hypothyroidism (20 %) TSH increase (30 %) Struma	Measure neck girth annually

From Schatzberg et al. (2003)

The second most common ADR is weight gain and, together with the mentioned cognitive impairments (slowing, memory disturbances), represents the most important risk regarding compliance. Of the dermatologic symptoms, acne is the most frequent problem. Exacerbation of preexistent dermatoses such as psoriasis can also occur. Gastrointestinal disturbances are mostly transitory. Cardiac ADRs are reversible and very uncommon.

Rare renal lesions (interstitial nephritis) as an ADR dictate that renal function be checked at least annually (determination of serum creatinine as indicator; furthermore, even at constant lithium dosages, a change in serum lithium levels is a potential indicator of altered glomerular function). All the discussed ADRs (except rare renal injury) can be reversed either by dosage reduction and – if possible and necessary – by discontinuation of lithium therapy.

Drug Interactions

The most important interactions between lithium salts and other medications occur at the level of excretion, whereby serum Li^+ levels are increased and thus the **danger of intoxication** increased. A selection of medications potentially employed in combination with lithium salts and their possible interactions are summarized in Table 7.1. Interactions of lithium with tricyclic antidepressants are generally unlikely.

Caution is advisable with regard to angiotensin conversion enzyme (ACE) inhibitors and the administration of calcium antagonists because of elevated neurotoxicity even at normal serum concentrations of these agents. Furthermore, risks of intoxication can also occur during concurrent use of nonsteroidal antirheumatic agents, such as diclofenac, as the result of reduced renal clearance.

Contraindications

Absolute contraindications are:

- Severe renal dysfunction
- Severe cardiac disease
- Disturbances of sodium balance
- Addison's disease (chronic adrenal insufficiency)
- The first trimester of pregnancy

Relative contraindications are:

- Renal dysfunction
- Cardiac dysfunction
- Psoriasis
- Hypothyroidism
- Surgery with narcosis
- Low sodium diet
- Second and third trimesters of pregnancy. Female patients of child-bearing age treated with lithium salts should therefore also receive contraceptives to avoid pregnancy.

7.4.2 Carbamazepine

Indications

The FDA-approved areas of application are:

- Treatment of epilepsy in children, adolescents, and adults
- Treatment of pain associated with true trigeminal neuralgia in adults
- Treatment of bipolar disorder in adults (extended-release formulation)

In addition, it is approved in Canada, Japan, Australia, and several European countries for these indications in adults.

Clinical Effects and Efficacy

A recent systematic review (Fountoulakis et al. 2012) suggests that carbamazepine is **efficacious** in the treatment of **acute mania** in **adults**: For example, two clinical trials showed that carbamazepine (800 mg/day; mean plasma level 8.9 µg/mL) produces a significant improvement at week 2. Responders were also more likely to be under carbamazepine than under placebo (41.5 % vs. 22.4 %).

In contrast, there is only a small old withdrawal study during the maintenance phase and in general poor and inadequate data on the efficacy of antiepileptics against bipolar depression. The only study during the maintenance phase, in which 32 patients were enrolled, suggests that 60 % of patients in the carbamazepine group had a good response in comparison to 22.2 % of the patients treated with placebo (Fountoulakis et al. 2012).

In **children and adolescents**, carbamazepine has been studied in only two **open-label trials** (see Liu et al. 2011 for review). One study assessed the effect size (≥ 50 % change from baseline to exit in the YMRS scores) of carbamazepine compared to lithium and divalproex sodium for the acute-phase treatment of bipolar I or II disorder, mixed or manic episode, in children and adolescents aged 8–18 years (Kowatch et al. 2000). The study showed a modest response rate of carbamazepine and lithium (38 %) compared to sodium divalproex (53 %).

The second 8-week prospective open-label study of extended-release carbamazepine monotherapy (788 ± 252 mg/day) in 27 manic/mixed/hypomanic children (aged 6–12 years) showed a response rate of 44 % (Joshi et al. 2010): 52 % experienced at least 30 % reduction in manic symptoms and 34 % achieved remission (YMRS < 12). Interestingly, a 43 % response rate for symptoms of depression in this study was reported. The most common ADRs reported in this study included nausea and sedation.

Recommended Dosage

Prior to initiating treatment, patients with ancestry in genetically at-risk populations for the **presence of the HLA-B*1502 allele have to be tested**. The use of patients testing positive for the allele should be avoided, unless the benefit clearly outweighs the risk. In addition, prior to initiating therapy in all patients, a **complete blood count** including platelets and differential have to be obtained, and the complete blood count should be monitored periodically.

In one clinical study with carbamazepine to treat children and adolescents with bipolar disorders (Kowatch et al. 2000), the initial dose of carbamazepine was 15 mg/kg per day in three divided doses. The serum level was measured after 1 week of treatment, and the dosage was

then titrated until a serum level of 7–10 µg/mL was reached. The maximum daily dose of carbamazepine should not exceed 1,000 mg in children aged 6–12 years and 1,200 mg aged 13 years and older.

According to the prescribing information (PI) for the treatment of bipolar disorder with extended-release formulations in adults, the recommended initial dose is 200 mg twice daily. The dose should be adjusted in 200 mg increments to achieve optimal clinical response. Doses higher than 1,600 mg/day have not been studied in mania associated with bipolar disorder. When discontinuing treatment, the dose should be reduced gradually and abrupt discontinuation should be avoided in order to decrease the risk of seizure.

Adverse Drug Reactions

Carbamazepine carries a **black box warning** from the US FDA that serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have occurred. Patients of Asian ancestry have a ten-fold greater risk of epidermal necrolysis and Stevens-Johnson syndrome, compared to other populations. Discontinue the therapy if these reactions occur. In addition, aplastic anemia and agranulocytosis occurred.

Table 7.3 summarizes data on ADRs from randomized controlled trials and open-label studies of mood-stabilizing anticonvulsants in the treatment of mania in children and adolescents. Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have occurred according to the PI.

Teratogenicity has been described in connection with carbamazepine use, with minor and major malformations. The incidence of spina bifida has been reported as being 0.5 % in the PI. This rate increases when carbamazepine is used in combination with valproic acid.

Table 7.3 Adverse drug reactions (ADRs) described from open-label and randomized-controlled trials of mood-stabilizing antiepileptics for mania in children and adolescents

Medication	ADRs
Carbamazepine	Nausea and sedation
Lamotrigine	Gastrointestinal symptoms, headaches, and skin rashes
Oxcarbazapine	Dizziness, nausea, somnolence, diplopia, fatigue, and rash
Topiramate	Decreased appetite, nausea, and weight loss
Valproic acid (sodium valproate, divalproex sodium)	Sedation, gastrointestinal upset, headaches, dizziness, stomach pain, tremor, weight gain, decrease in mean platelet count, and increase in mean ammonia level

From Hazell and Jairam (2012)

Drug Interactions

Drug interaction results either to pharmacokinetic or pharmacodynamic interactions. Pharmacodynamic interactions occur when two drugs interact at the same neuroreceptor, resulting in additive, synergistic, or antagonistic effects. Pharmacokinetic interactions occur when absorption, distribution, metabolism, or excretion of a drug is influenced.

Potential Pharmacodynamic Interactions

According to the PI, concurrent administration of **antipsychotics** can increase the risk of neuroleptic malignant syndrome; parallel treatment with antipsychotics or metoclopramide can increase the risk of extrapyramidal motor ADRs.

Concurrent treatment with **lithium salts** amplifies the neurotoxicity of both substances. **Carbamazepine** can increase the release of thyroid hormones.

Administration together with selective serotonin reuptake inhibitors (**SSRIs**) such as fluoxetine can lead to a toxic serotonin syndrome. Concurrent treatment with **tricyclic antidepressants** or antibiotics increases the danger of cardiac conduction disturbances. **Alcohol** should be avoided during treatment because carbamazepine reduces alcohol tolerance.

Table 7.4 Pharmacokinetic interactions between carbamazepine and other medications, their consequences, and recommendations for dose adjustments

Coadministered agent	Consequence(s)	Recommendation(s)
Antiepileptics: Phenobarbital, phenytoin, primidone, valproic acid, and felbamate	Increased rate of metabolism of carbamazepine Increased levels of the active metabolite carbamazepine-10, 11-epoxide	
Theophylline, rifampicin, doxorubicin, cisplatin, St John's wort	Reduced serum level of carbamazepine	
CYP inhibitors Antidepressants (fluoxetine, fluvoxamine, desipramine) Antibiotics (erythromycin, clarithromycin) Calcium antagonists (verapamil, diltiazem) Antimycotics (itraconazole, ketoconazole, fluconazole)	Reduced metabolism of carbamazepine increasing the potential for overdosage (symptoms: vertigo, tiredness, unsteady gait, diplopia)	Dose reduction is necessary
Drugs that were metabolized by CYP enzymes which were induced by carbamazepine		
Antiepileptics (ethosuximide, felbamate, primidone, lamotrigine, tiagabine, topiramate, valproic acid)	Reduced metabolism	
Antipsychotics (haloperidol, clozapine, olanzapine, risperidone, quetiapine)	Reduced metabolism	
Benzodiazepines (clonazepam, alprazolam, clobazam)	Reduced metabolism	
Tricyclic antidepressants (amitriptyline, imipramine, clomipramine)	Reduced metabolism	
Tetracyclines, corticosteroids, antimycotics, methylphenidate, fentanyl, bupropion, zotepine, clotting inhibitors, and hormonal contraceptives	The result of the interaction with contraceptives can be the loss of effective contraception	Contraceptives should contain more than 50 mg estrogen, or an alternative contraceptive method should be considered

According to the prescribing information on carbamazepine

Potential Pharmacokinetic Interactions

Carbamazepine is primarily metabolized by CYP3A4 and itself exerts an inductive effect upon this enzyme. The metabolism of carbamazepine is thus accelerated by other CYP inducers and slowed by inhibitors of the enzyme system. On the other hand, carbamazepine, through its inductive properties, accelerates the metabolism of substances metabolized by this system, including its own metabolism. These **interactions are to some extent quite complex**, and it is, as a matter of principle, **advisable** in these cases to monitor blood drug levels by **TDM** during therapy. The pharmacokinetic interactions typically associated with carbamazepine and their potential consequences are summarized in Table 7.4. In addition, grapefruit juice can increase serum levels of carbamazepine.

Contraindications

Employment of this agent is contraindicated:

- Bone marrow depression.
- Known hypersensitivity to carbamazepine and to tricyclic antidepressants.
- Concomitant use with nonselective monoamine oxidase (MAO) inhibitors or use within 14 days of discontinuing a MAO inhibitor.
- Concomitant use with delavirdine or other non-nucleoside reverse transcriptase inhibitors because carbamazepine decreases efficacy of these drugs.
- Concomitant use of nefazodone.

Caution is required:

- In patients of **Asian ancestry** because the risk of epidermal necrolysis and Stevens-Johnson syndrome is ten times higher.

- With the use of oral **contraceptives** for birth control, as the interaction with estrogen and progestin in women who use oral contraceptives can lead to intermenstrual bleeding and reduced contraceptive protection.
- In combination therapy with other psychopharmacological agents, which can lead to changes in effective blood levels and increased frequency of additional ADRs (see Table 7.4).
- **Antiepileptic drugs**, including carbamazepine, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any antiepileptic drug for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for epilepsy and psychiatric indications.

7.4.3 Gabapentin

Indications

The FDA-approved areas of application are:

- Management of postherpetic neuralgia in adults.
- Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy.
- Adjunctive therapy in the treatment of partial seizures in pediatric patients aged 3–12 years.
- Treatment of moderate-to-severe primary restless legs syndrome (RLS) in adults (extended-release tablet).

In Europe, it is approved only for the treatment of epileptic syndromes and several types of neuropathic pain. Safety and effectiveness in patients below the age of 18 years with mood disorders have not been established.

Clinical Effects and Efficacy

There are no clinical trials that were carried out to assess the safety and efficacy of gabapentin in children and adolescents with bipolar disorder. However, a placebo-controlled study of monotherapy in adults showed no effects in a mixed unipolar–bipolar population of refractory depressives (Frye et al. 2000). In addition, a placebo-controlled trial of adjunctive therapy was also negative (Pande et al. 2000).

Recommended Dosage

For treatment of **epilepsy** in patients over 12 years of age (according to the PI), the effective dose is 900–1,800 mg/day and given in divided doses (three times a day) using 300 or 400 mg capsules, or 600 or 800 mg tablets. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300 or 400 mg capsules, or 600 or 800 mg tablets three times a day up to 1,800 mg/day. Dosages up to 2,400 mg/day have been well tolerated in long-term clinical studies. Doses of 3,600 mg/day have also been administered to a small number of patients for a relatively short duration and have been well tolerated. The maximum time between doses in the t.i.d. schedule should not exceed 12 hours.

Pediatric patients aged 3–12 years: The starting dose should range from 10 to 15 mg/kg per day in three divided doses and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose in patients 5 years of age and older is 25–35 mg/kg per day and given in divided doses (three times a day). The effective dose in pediatric patients aged 3 and 4 years is 40 mg/kg per day and given in divided doses (three times a day). Dosages up to 50 mg/kg per day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

Adverse Drug Reactions

Gabapentin use in pediatric patients with epilepsy 3–12 years of age is associated with the occurrence of CNS-related ADRs. The most significant of these can be classified into the following categories: (1) emotional lability (primarily behavioral problems), (2) hostility, including aggressive behaviors, (3) thought disorder, including concentration problems and change in school performance, and (4) hyperkinesia (primarily restlessness and hyperactivity). Among patients

treated with gabapentin, most of the events were mild to moderate in intensity according to PI.

Drug Interactions

Gabapentin exerts no known influence upon either xenobiotic-metabolizing enzymes or the plasma protein binding of other medications. For this reason significant **pharmacokinetic interactions** with other medications in combination therapy **are unlikely**. It can therefore be administered to patients using oral contraceptives. A 50 % increase in elimination half-life has, however, been reported for felbamate used in combination with gabapentin (Hussein et al. 1996).

Contraindications

Employment of this agent is contraindicated in patients with:

- Hypersensitivity to any of the formulation components
- Acute pancreatitis
- Galactosemia (galactose intolerance)

Patients treated with any antiepileptic drugs for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

7.4.4 Lamotrigine

Indications

The US FDA-approved areas of application are:

- Adjunctive epilepsy therapy in patients ≥2 years of age for the following seizure types:
  - partial seizures,
  - primary generalized tonic-clonic seizures,
  - generalized seizures of Lennox–Gastaut syndrome.
- Conversion to monotherapy in adults (≥16 years) with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single antiepileptic drug.
- Bipolar disorder
- Maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in adults (≥18 years of age) treated for acute mood episodes with standard therapy.

Lamotrigine is also approved in Europe for the treatment of epilepsy and bipolar disorder. Safety and effectiveness in patients below the age of 18 years with mood disorders have not been established.

Clinical Effects and Efficacy

A systematic review on the efficacy of pharmacotherapy in **adult bipolar disorder** showed that lamotrigine is efficacious in a mixed unipolar–bipolar population of refractory depressives, with response rates of 52 % for lamotrigine compared to 23 % for placebo (Fountoulakis et al. 2012). However, it remains to be clarified whether it is also efficacious for mania and depression. There are two unpublished negative double-blind randomized placebo-controlled trials of 3- and 6-week duration treatment concerning lamotrigine against acute manic episodes (SCAA2008 and SCAA2009) and five trials on the acute depression treatment (SCA100223, SCA30924, SCA40910, SCAA2010, and SCAB2001) with negative outcomes (reviewed in Fountoulakis et al. 2012).

In **children and adolescents** with bipolar spectrum disorders, there has been only one prospective **open-label study** of lamotrigine monotherapy (39 patients, aged 6–17 years) that found an antimanic response rate of 54 % (≥50 % reduction in symptoms; Biederman et al. 2010). Only 56 % completed the 12-week trial. Common ADRs reported in this study included gastrointestinal symptoms and headaches with marginal increase in body weight (47.0 ± 18.0 kg vs. 47.2 ± 17.9 kg). Fifteen subjects developed some form of skin rash, and of those, only six discontinued the study as a result deemed related to lamotrigine, all of which resolved

after treatment discontinuation. None developed Stevens-Johnson syndrome.

Recommended Dosage

Dosing is based on concomitant medications, indication, and patient age. To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations should not be exceeded (see Sect. 7.7.3).

If other psychotropic medications are withdrawn following stabilization, the dose of lamotrigine should be adjusted. For patients discontinuing valproate, the dose should be doubled over a 2-week period in equal weekly increments. For patients discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation, the dose should remain constant for the first week and then should be decreased by half over a 2-week period in equal weekly decrements.

In the only clinical study on the treatment of children and adolescents with bipolar disorders (Biederman et al. 2010), lamotrigine was slowly titrated to an average endpoint dose of 160.7 ± 128.3 in subjects <12 years of age and 219.1 ± 172.2 mg/day in children 12–17 years of age.

Adverse Drug Reactions

Table 7.3 summarizes data on ADRs from randomized controlled trials and open-label studies of mood-stabilizing anticonvulsants in the treatment of mania in children and adolescents. Based on the PI, the most commonly observed (≥5 % and more common on drug than placebo) ADRs seen in association with the use of lamotrigine as adjunctive treatment in pediatric patients 2–16 years of age, and not seen at an equivalent rate in the control group, were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia.

Drug Interactions

No significant effects of lamotrigine upon xenobiotic-metabolizing enzymes have been described, nor does it appear to compete with other medications for plasma protein binding, so that **noteworthy pharmacokinetic interactions** with other medications in combination therapy **are unlikely**. No changes in serum concentrations of carbamazepine, clobazam, phenytoin, phenobarbital, primidone, or valproic acid in combination therapy with lamotrigine have been found in clinical studies.

Combination therapy of lamotrigine with **antiepileptic drugs** that exert an influence upon xenobiotic-metabolizing enzymes can nevertheless **alter the pharmacokinetic properties** of lamotrigine. For example, antiepileptic drugs that induce CYP enzymes, such as carbamazepine, phenytoin, and phenobarbital, reduce the elimination half-life of lamotrigine in adults, in comparison with monotherapy, by approximately 14 h (shortened from 29 to about 15 h). In addition, valproate increases lamotrigine concentrations more than twice. On the other hand, carbamazepine, phenytoin, phenobarbital, and primidone decrease lamotrigine concentrations by approximately 40 %. Oral estrogen-containing contraceptives and rifampin also decrease lamotrigine concentrations by approximately 50 %.

Contraindications

Employment of this agent is contraindicated in patients with:hypersensitivity to the drug or its ingredients.

Multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and systemic symptoms, may be **fatal** or life threatening. Early signs may include rash, fever, and lymphadenopathy. These reactions could also be associated with other organ involvement, such as hepatitis, hepatic failure, blood dyscrasias, or acute multiorgan failure. Lamotrigine should be discontinued if alternate etiology for this reaction is not found.

Similar with other antiepileptics, caution is required in the therapy of children because the risk of developing exanthemata is about three times higher (1 %) as in adults. In addition, suicidal ideation/behaviors may be associated with treatment of bipolar disorder.

Lamotrigine carries a **black box warning** from the US FDA that children younger than the age of 16 are at increased risk of Stevens–Johnson syndrome, based on early epilepsy data. However, more recent data suggest that the incidence of serious rash in children taking lamotrigine may be one in 10,000 (Messenheimer 2002).

7.4.5 Oxcarbazepine

Indications

The US FDA-approved areas of application are:

- Monotherapy or adjunctive therapy in the treatment of partial seizures in adults.
- Monotherapy in the treatment of partial seizures in children 4–16 years.
- Adjunctive therapy in the treatment of partial seizures in children 2–16.

Oxcarbazepine is approved in Europe for the treatment of partial seizures with or without secondarily generalized tonic-clonic seizures in children of 6 years of age and above. Safety and effectiveness in patients below the age of 18 years with mood disorders have not been established.

Clinical Effects and Efficacy

All randomized placebo-controlled studies with the S-enantiomer (eslicarbazepine) and the racemic mixture of the primary metabolite of oxcarbazepine (licarbazepine) in **adults** showed **no efficacy** in acute manic episodes (Fountoulakis et al. 2012). However, an 8-week trial that enrolled 52 incomplete responders to lithium demonstrated an improvement (by lowering the YMRS score) with the addition of oxcarbazepine (600–1,200 mg daily) during maintenance treatment (reviewed in Fountoulakis et al. 2012).

In **children and adolescents**, there has been one double-blinded placebo-controlled study of flexibly dosed oxcarbazepine (maximum dose 900–2,400 mg/day) in the treatment of mania (Wagner et al. 2006). Although well powered with 116 participants, this **study failed** to separate oxcarbazepine from placebo (42 % vs. 26 %, respectively), and it had a very high rate of dropouts (66 % completed oxcarbazepine and 60 % completed placebo). Moreover, decreases in YMRS score were modest and did not differ between oxcarbazepine and placebo (−10.9 vs. −9.8, respectively). When separating children (7–12 years) from adolescents (13–18 years), however, 41 % of the children in the oxcarbazepine group and 17 % of those in the placebo group achieved at least a 50 % reduction in YMRS scores. Among the adolescents, the results on this measure were similar for both treatments (43 vs. 40 %). There were more ADRs in the oxcarbazepine group, which included dizziness, nausea, somnolence, diplopia, fatigue, and rash.

Recommended Dosage

The dosage strategy for immediate-release tablets and oral suspensions in the treatment of partial seizures is summarized in Table 7.5. In the only clinical study with oxcarbazepine to treat children and adolescents with bipolar disorders (Wagner et al. 2006) during the 2-week titration period, the oxcarbazepine dose was titrated upward by 300 mg every 2 days to a maximum dose level of 900–2,400 mg/day based on body weight or to the maximum dose tolerated.

ADRs

Table 7.3 summarizes data on ADRs from randomized controlled trials and open-label studies of mood-stabilizing anticonvulsants in the treatment of mania in children and adolescents. Gastrointestinal complaints with nausea and emesis as ADRs occur chiefly at the commencement of therapy. ADRs are significantly less severe than for carbamazepine, primarily because its metabolism, unlike that of carbamazepine, does not produce an epoxide metabolite. In contrast to carbamazepine, oxcarbazepine has not been associated with teratogenic effects.

Drug Interactions

In comparison with carbamazepine, oxcarbazepine is associated with fewer interactions with other medications. The concurrent administration of oxcarbazepine, in contrast to carbamazepine, with the antibiotic erythromycin is, for example, unproblematic. Furthermore, oxcarbazepine can be combined with anticoagulants.

Table 7.5 Recommended dosage scheme for mono- and combination therapy in partial seizures with immediate release and oral suspension of oxcarbazepine

	Children (4–16 years)	Adults
Initial dosage	8–10 mg/kg body weight, in 2 individual doses	600 mg, in 2 individual doses
Dosage increase		
Monotherapy	5 mg/kg body weight/day every third day	300 mg/day every third day
Adjunctive therapy	Target maintenance dose should be achieved over 2 weeks	Max. 600 mg/day at weekly intervals
Maintenance dosage		
Mono- and adjunctive therapy	Recommended daily dose is dependent upon patient weight and should not exceed 60 mg/kg body weight/day	1,200 mg/day, in 2–3 individual doses

According to prescribing information

The addition of oxcarbazepine or carbamazepine to therapy with valproic acid or phenytoin can increase their plasma levels by around 20–30 % compared with monotherapy (Hachad et al. 2002). On the other hand, oxcarbazepine, like carbamazepine, hastens the metabolism of oral **contraceptives**, so that reliable birth control requires adjustment of contraceptive dosage, or the adoption of nonhormonal methods. Coadministration with phenobarbital and phenytoin decreased blood levels of the active metabolite 10-monohydroxy-oxcarbazepine (PI). Therefore, greater dose of oxcarbazepine may be required.

Contraindications

Employment of this agent is contraindicated in patients with known hypersensitivity to oxcarbazepine or to any of its component.

Caution is required:

- In patients with a past history of hypersensitivity reaction to carbamazepine.
- With the use of oral contraceptives for birth control, as the interaction with estrogen and progestin in women who use oral contraceptives can lead to intermenstrual bleeding and reduced contraceptive protection.

7.4.6 Topiramate

Indications

The US FDA-approved areas of application are:

- Epilepsy monotherapy in patients older than 2 years of age with partial onset or primary generalized tonic-clonic seizures.
- Adjunctive epilepsy therapy for adults and pediatric patients (2–16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures and in patients older than 2 years of age with seizures associated with Lennox–Gastaut syndrome.
- Treatment for prophylaxis of migraine headache in adults.

Topiramate is also approved in Europe for these indications. Safety and effectiveness in patients below the age of 18 years with mood disorders have not been established.

Clinical Effects and Efficacy

Randomized placebo-controlled studies in **adults** with bipolar disorder demonstrated **no efficacy** of topiramate in acute manic episodes; in addition it was not efficacious as an adjunctive therapy (Fountoulakis et al. 2012). In **children and adolescents** there have been two open-label studies of topiramate and one double-blinded study in the management of mania (reviewed in Goldstein et al. 2012; Liu et al. 2011). Both open-label trials investigated topiramate in the **management of weight gain** associated with treatment of second-generation antipsychotics. The two studies reported significant decreases in weight gain. One study reported that topiramate treatment was also associated with lower YMRS scores, whereas the other did not.

The only available double-blinded study of topiramate had only modest statistical power ($N=56$) to detect between-group differences but **failed to separate topiramate from placebo** (35 vs. 22 %). According to its authors (Delbello et al. 2005), this study was prematurely terminated when similarly negative results were obtained in the double-blinded study of topiramate in adult bipolar disorder. Common ADRs

reported in these studies included decreased appetite, nausea, and weight loss.

Topiramate is unique because of its ability to cause weight loss at doses of 50–200 mg daily in adults. In an open-label trial, Tramontina et al. (2007) found topiramate to be effective during the maintenance phase in ten adolescents with bipolar disorder; a positive feature of the 11-week study was the **loss of body weight** gained during previous treatment with other medications. Thus, topiramate could be useful to treat weight gain, which is a common problem in bipolar patients.

Recommended Dosage

The dosage strategy for treatment of epilepsy and migraine with topiramate is summarized in Table 7.6. In the placebo-controlled study with topiramate to treat children and adolescents with bipolar disorders (Delbello et al. 2005), topiramate was titrated from a starting dose of 50 mg/day to the target dose of 400 mg/day over 5 days, based on tolerability. For those subjects who weighed <40 kg, target doses were 200 mg/day when the subject weighed 20–29.9 kg and 300 mg/day when the subject weighed 30–39.9 kg.

Adverse Drug Reactions

Table 7.3 summarizes data on ADRs from randomized controlled trials and open-label studies of mood-stabilizing anticonvulsants in the treatment of mania in children and adolescents. Based on the PI, the incidence of depression, mood lability, and suicide attempts increased during therapy with topiramate. In addition, development of **kidney stones** during chronic therapy in epilepsy has been reported in 1.5 % of **male patients**, so that attention should be paid to ensuring adequate fluid intake. The increased risk of kidney stones is attributable to inhibition of carbonic anhydrases, and the combination of topiramate with other carbonic anhydrase inhibitors, such as acetazolamide, increases this risk.

Drug Interactions

Concomitant administration of **phenytoin** or **carbamazepine** with topiramate decreased plasma concentrations of topiramate by 48 and 40 %, respectively, when compared to topiramate given alone (PI). Concomitant administration of **valproic acid** and topiramate has been **associated** with **hyperammonemia** with and without encephalopathy. Concomitant administration of topiramate with valproic acid has also been associated with hypothermia (with and without hyperammonemia) in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported.

Exposure to ethinyl estradiol was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18, 21, and 30 %, respectively) when topiramate was given as adjunctive therapy in patients taking valproic acid. However, norethindrone exposure was not significantly affected.

Contraindications

There are no contraindications reported.

Caution is required:

- In women of childbearing potential because data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts).
- In combination therapy with carbamazepine, phenobarbital, or phenytoin, which can cause changes in its effective blood levels and to increased frequency of additional ADRs.
- In pediatric patients, because oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported. Patients should be counseled to contact their healthcare professionals immediately if they develop a high or persistent fever, or decreased sweating.
- In males, as the development of kidney stones during chronic therapy has been reported. For this reason, attention should be given to sufficient fluid intake.

7.4.7 Valproic Acid (Sodium Valproate, Divalproex Sodium)

Indications

Valproate products that contain valproate sodium, divalproex sodium, and valproic acid are US FDA-approved drugs to treat:

Table 7.6 Recommended dosage scheme for mono- and combination therapy in epilepsy with topiramate

	Initial dose	Titration	Recommended dose
Epilepsy monotherapy: children 2 ≤10 years	Administered nightly for the first week	The dosage should be titrated over 5–7 weeks	Daily doses b.i.d., based on weight
Epilepsy monotherapy: adults and pediatric patients ≥10 years	50 mg/day b.i.d.	The dosage should be increased weekly by increments of 50 mg for the first 4 weeks then 100 mg for weeks 5–6	400 mg/day b.i.d.
Epilepsy adjunctive therapy: adults with partial onset seizures or Lennox–Gastaut syndrome	25–50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25–50 mg	200–400 mg/day b.i.d.
Epilepsy adjunctive therapy: adults with primary generalized tonic-clonic seizures	25–50 mg/day	The dosage should be increased weekly to an effective dose by increments of 25–50 mg	400 mg/day b.i.d.
Epilepsy adjunctive therapy: pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures or Lennox–Gastaut syndrome	25 mg/day (or less, based on a range of 1–3 mg/kg/day) nightly for the first week	The dosage should be increased at 1- or 2-week intervals by increments of 1–3 mg/kg/day (administered b.i.d.). Dose titration should be guided by clinical outcome	5–9 mg/kg/day b.i.d.
Migraine	25 mg/day administered nightly for the first week	The dosage should be increased weekly by increments of 25 mg. Dose and titration should be guided by clinical outcome	100 mg/day b.i.d.

According to Prescribing Information
b.i.d., 2 × day

- Seizures in adult patients and pediatric patients down to the age of 10 years.
- Manic or mixed episodes associated with bipolar disorder in adults.
- To prevent migraine headaches in adults.

The European Medicines Agency (EMA) has approved valproate-containing medicinal products for the treatment of manic episode in bipolar disorder in adults when lithium is contraindicated or not tolerated (EMA/809287/2010 Rev). The continuation of treatment after manic episode could be considered in patients who responded to valproate for acute mania.

Clinical Effects and Efficacy

Randomized placebo-controlled studies in **adults** with bipolar disorder demonstrated that valproate is **efficacious** in the treatment of acute mania already at day 5 but also at 12 weeks following treatment (Fountoulakis et al. 2012). In **children and adolescents**, divalproex sodium has been studied in eight **open-label trials** and three double-blinded studies (reviewed in Goldstein et al. 2012; Liu et al. 2011). Of these open-label studies, only three studies evaluated divalproex as an acute monotherapy; these studies reported an **average response rate of 43 %** (Liu et al. 2011). The other studies allowed additional antimanic medications, making it difficult to evaluate whether the reported benefits were the result of treatment with valproic acid or to the combination of valproic acid with other antimanic treatments.

Of the three **double-blinded studies** of divalproex sodium that showed a similar overall response rate as the open-label acute monotherapy, one compared divalproex immediate release against quetiapine and showed that quetiapine is markedly superior to divalproex (reviewed in Goldstein et al. 2012; Liu et al. 2011). The second one was a maintenance study of divalproex and lithium on previously stabilized subjects. The two groups did not differ in drug discontinuation, time to discontinuation, or time to relapse of their mood disorder. The third double-blinded study failed to separate divalproex extended-release from placebo (Wagner et al. 2009).

As described above, in a recent randomized controlled 8-week trial, lithium, divalproex sodium, or risperidone were investigated to find out which medication to administer first to antimanic medication-naïve children and adolescents aged 6–15 years (Geller et al. 2012). Higher response rates occurred after treatment with risperidone versus lithium (68.5 vs. 35.6 %) and versus divalproex sodium (68.5 vs. 24.0 %). Response to lithium versus divalproex sodium did not differ.

Recommended Dosage

Initial dose is 25 mg/kg/day, increasing as rapidly as possible to achieve therapeutic response or desired plasma level. The maximum recommended dosage is 60 mg/kg per day. In the double-blinded study of bipolar disorder in children and adolescents (aged 10–17 years) to evaluate the efficacy and safety of divalproex extended-release compared to placebo, initial daily doses of 15 mg/kg (max. 750 mg/day) and flexible dosing was used to achieve a clinical response and/or a target serum valproate level of 80–125 μg/mL with a maximum allowable dose set at 35 mg/kg (Wagner et al. 2009).

Adverse Drug Reactions

Table 7.3 summarizes data on ADRs from randomized controlled trials and open-label studies of mood-stabilizing anticonvulsants in the treatment of mania in children and adolescents. The ADRs were usually mild or moderate in intensity but sometimes were serious enough to interrupt treatment (Liu et al. 2011). In clinical trials, the rates of premature termination due to intolerance were not statistically different between placebo, valproate, and lithium carbonate. A total of 4, 8, and 11 % of patients discontinued therapy due to intolerance in the placebo, valproate, and lithium carbonate groups, respectively (PI).

Valproic acid possesses **teratogenic properties** (PI). There exists a 1–2 % risk of neural tube defects (spina bifida), but the risk can be significantly reduced by continuous folate supplementation, beginning prior to a planned pregnancy. Prenatal diagnostic tests (ultrasound, α-fetoprotein determination) can also be performed. While plasma valproic acid level remains fairly constant throughout the first two trimesters of pregnancy, during the final trimester it can both rise sharply (due to altered plasma binding) or decline (elevated renal and hepatic clearance).

Cases of life-threatening **pancreatitis** have been reported in both children and adults receiving valproate (PI). Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Drug Interactions

The **pharmacodynamic interaction** of valproic acid with clonazepam can elicit absence seizures in predisposed patients. Particular caution is required when valproic acid is combined with medications that influence platelet function or blood clotting. The dose of **lamotrigine** should be reduced when coadministered with valproate. Serious skin reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration (PI).

Concomitant administration of valproic acid and **topiramate** has been associated with hyperammonemia with and without encephalopathy. Concomitant administration of topiramate with valproic acid has also been associated with hypothermia in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported.

Pharmacokinetic interactions occur mainly in the combination therapy of valproic acid with **antiepileptic medications** that inhibit xenobiotic-metabolizing enzymes (such as phenobarbital and primidone that is metabolized in vivo to phenobarbital, ethosuximide, felbamate, and lamotrigine). This can lead to higher effective levels of these drugs. **TDM** should thus **be**

undertaken during such combination therapies and dosage adjusted as required.

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer elimination half-lives and higher concentrations than patients receiving polytherapy with antiepileptic drugs.

All patients receiving concomitant **barbiturate therapy** should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Contraindications

Employment of this agent is contraindicated in patients:

- With hepatic disease or significant hepatic dysfunction
- With known hypersensitivity to the drug
- With known urea cycle disorders

Valproate carries a **black box warning** from the US FDA that hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Children under the age of 2 years are at considerably higher risk of fatal hepatotoxicity. Therefore, patients should be closely monitored, and liver function tests prior to therapy and at frequent intervals thereafter have to be performed.

Caution is required:

- Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, abnormal coagulation parameters (e.g., low fibrinogen), platelet counts, and coagulation tests are recommended before initiating therapy and at periodic intervals.
- In combination therapy with other antiepileptic drugs that can lead to changes in effective blood levels and increased frequency of ADRs.
- In **pregnant patients**, given the potential teratogenic properties of valproic acid. The risk for neural tube defects can be considerably reduced by continuous employment of a folic acid supplement, but this must commence prior to a planned pregnancy. Prenatal diagnostic investigations should thus be undertaken.

7.5 Duration of Treatment

The **treatment guidelines** for children and adolescents with bipolar disorder of the Child and Adolescent Bipolar Foundation (CABF) recommended a minimum of 4–6 weeks at therapeutic blood levels and/or adequate dose for each medication trial (Kowatch et al. 2005). In some cases (e.g., treatment with lithium), 8 weeks of treatment may be required to assess the effectiveness of the particular mood stabilizer.

There is **paucity** of information regarding **how long treatment** should continue in children and adolescents with bipolar disorder. According to the CABF guidelines (Kowatch et al. 2005) and the American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters for treating bipolar disorders in children aged 6 and older (McClellan et al. 2007), medication tapering or discontinuation may be considered if the patient has achieved remission for a minimum of 12–24 consecutive months. For less severe cases or in patients without a clear diagnosis, a briefer treatment period may be indicated. The risk associated with a potential relapse should be compared with the risk associated with continued pharmacotherapy. Greatest caution should be taken with patients with a history of suicidal behavior, severe aggression, and/or psychosis. In these patients pharmacotherapy may require long-term or even lifelong treatment.

Medications should be tapered and **not abruptly discontinued**. Careful monitoring and education of patients and families about the early signs of relapse are essential. If lithium salts have been administered for a lengthy period and must be discontinued (because of ADRs, for instance), it must be explained to patients that depressive thoughts (weariness of life) may occur in more pronounced form for about 6 months following lithium withdrawal.

7.6 Therapeutic Monitoring

Unfortunately, there are very few long-term safety data available on many of the mood stabilizers used in the treatment of bipolar disorder. For this reason, diligent monitoring for ADRs must be considered, particularly for children and adolescents in whom ADRs are occurring. For the individual patient, the risks of ongoing treatment must be balanced against the manifested therapeutic benefits that are associated with any given agent. Because combinations of medications are increasingly being prescribed for children and adolescents with bipolar disorder and because long-term ADRs are likely to occur more frequently with polypharmacy, it is particularly important that ADRs associated with chronic treatment are tracked over time.

7.6.1 Lithium Salts

Lithium salts should not be prescribed without assurance of continuous monitoring of psychopathological development and laboratory data (Table 7.7). Some patients develop signs of intoxication (somnolence, nausea, vomiting, ataxia) even at lower normal range blood levels, and their optimal effective dosages are associated with relatively low blood levels, while other patients experience neither a sufficient therapeutic effect nor ADRs at serum lithium levels >1.5 mmol/L. For this reason **continuous monitoring** is required to establish adequate dosing. After a stable blood level has been achieved, blood level monitoring may be reduced from twice to once weekly. If a satisfactory therapeutic response is not achieved within 4 weeks, despite adequate blood levels, a supplementary medication should be considered.

During **long-term medication** with lithium salts, a mean **blood concentration of 0.8 mmol/L** is regarded as **optimal**. Following achievement of the individual optimal effective level, serum lithium level monitoring can be reduced from weekly to monthly and, after a stable course over 6–12 months, can be further reduced to a semiannual determination of serum levels. Frequency of monitoring, however, should always be based upon the reliable clinical status of the patient.

Compliance should be checked where symptoms of the disorder recur, and where indications of intoxication become apparent, an immediate assessment of lithium levels should be undertaken, regardless of the medication plan. Blood should be collected for determination of lithium concentrations 12 h after the most recent administration

Table 7.7 Recommended monitoring of therapy with lithium salts (Li^+) in children and adolescents

Prior to therapy	During therapy
Patient history: exploration, and examination regarding absolute and relative contraindications **Female adolescents**: pregnancy test (because of teratogenicity of Li^+ salts, ensure effective contraception!) **Laboratory**: urine status, creatinine clearance, thyroid function parameters (T3, T4, TSH), blood count, electrolytes, blood glucose **Clinical monitoring**: blood pressure, pulse, ECG, EEG, neck girth (struma?), body weight (weight gain?)	**Li^+ level monitoring**: during dosage increases, every 3–5 days following alteration of dosage; otherwise weekly during first month of therapy; thereafter one to two times a week until achievement of optimal effective level; then monthly for 6 months, and finally every 3 months **Determination of creatinine**: level in serum parallel to determination of Li^+ concentrations **Every consultation**: examination of psychopathological status and monitoring for potential adverse drug reactions (including weight gain, struma, indications of intoxication?) **At least annually**: laboratory investigations as prior to therapy

From Gerlach and Warnke (2010)

of lithium. In cases where a risk of renal dysfunction, vomiting, or diarrhea is present, closer monitoring of therapeutic course is necessary.

7.6.2 Mood-Stabilizing Antiepileptics

Antiepileptic drugs, including the mood-stabilizing anticonvulsants, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any antiepileptic drugs for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Careful **clinical and laboratory diagnostic** monitoring of the patient through assessment of blood count (especially hemoglobin and erythrocyte, leukocyte and platelet numbers), urine, hepatic function (γ-GT, GPT, alkaline phosphatase, serum calcium, sodium, and creatinine levels), and blood levels of the antiepileptic drugs is advised. The parameters that should be assessed by follow-up tests and the frequency of such assessment are determined in individual cases by the antiepileptic drug employed and its ADRs profile.

A number of reports have described high rates of **polycystic ovary syndrome** (PCOS) in women with epilepsy treated with **divalproex** (reviewed in Correll and Carlson 2008). These studies have prompted concern regarding the long-term use of divalproex in women with bipolar disorder, particularly when started at a young age. PCOS is defined as chronic anovulation and hyperandrogenism, with or without actual polycystic ovaries. Clinical features include oligomenorrhea, hirsutism, and acne. PCOS is linked with insulin resistance and dyslipidemia, and many (but not all) patients with PCOS are obese. Growth in stature is normal, as is the timing of puberty. Risk factors for PCOS include family history of PCOS, Caribbean Hispanic and African American ancestry, history of premature pubarche, and/or obesity. It was suggested to advise patients receiving divalproex about its potential effects on weight gain and the need for good diet and exercise; monitoring body weight and body mass index during treatment, including lipid profile monitoring at baseline and yearly; and evaluating a woman's menstrual functioning by obtaining an initial menstrual history (Kowatch et al. 2005). Age at menarche, cycle length, duration of menses, and pattern over the preceding 3 months are suggested important components of the menstrual history. Subsequent charting of menstrual pattern with treatment was then encouraged. Of note, pelvic ultrasonography was not recommended as part of the routine monitoring of these patients. In addition, it should be noted that ovarian cysts may occur in healthy adolescent females without PCOS as a normal variant. For this reason, routine pelvic ultrasounds are not recommended for teenagers on divalproex unless there is a clinical indication to do so.

7.7 Clinical Pharmacology of Lithium Salts and Mood-Stabilizing Antiepileptics: Overview

The following summaries are based upon information included in the summary of product characteristics (SPCs) and the PI, respectively, depending whether the drug is approved in the EU and USA. Issues concerning the preparation of SPCs and PI and their limitations were discussed in detail in Sect. 4.7. The most important pharmacological features of lithium salts and mood-stabilizing antiepileptics are presented as an orientation aid in their clinical employment.

Abbreviations used in the following tables: ADRs, adverse drug reactions; AUC, area under the curve; b.i.d., 2× day; c_{max}, maximal plasma concentration after oral dosing; CNS, central nervous system; CYP, cytochrome P_{450}; EMA, European Medicines Agency; FDA, Food and Drug administration; GABA, γ-amino-butyric acid; MAO monoamine oxidase; q.i.d., 4× day; t.i.d., 3× day; t_{max}, time required to reach peak plasma concentration (c_{max}); $t_{1/2}$, elimination half-life.

7.7.1 Carbamazepine

Pharmacodynamic properties	Primarily inhibition of voltage-gated Na^+ channels; reduces capacity of neurons to launch high-frequency bursts of action potentials Effects on receptor-mediated neurotransmission (GABAergic, glutamatergic, and monoaminergic) and intracellular signaling pathways in vivo and in vitro studies
Pharmacokinetic properties	For oral application of 200 mg extended-release dose of carbamazepine (CBZ): t_{max} 19 ± 7 h, t_{max} 5.9 ± 1.8 h (following repeat dose administration: 800 mg every 12 h); $t_{1/2}$ 35–40 h, $t_{1/2}$ 12–17 h (following repeat dose administration: 800 mg every 12 h); plasma protein binding 76 %, bioavailability, not reported Metabolism primarily in the liver via CYP3A4 (which is inhibited by CBZ) to the active metabolite carbamazepine-10,11-epoxide (CBZ-E): t_{max} 36 ± 6 h (following single administration of 200 mg), t_{max} 14 ± 8 h (following repeat dose administration: 800 mg every 12 h), $t_{1/2}$ 34 ± 9 h; plasma protein binding 50 %. Following repeat dose administration the AUC of CBZ-E was less than 30 % that of CBZ CBZ is more rapidly metabolized in young children than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age
Indications	**Approved in the USA (FDA) and in Europe** Use as an **anticonvulsant drug** in patients with the following seizure types: Partial seizures with complex symptomatology (psychomotor, temporal lobe) Generalized tonic-clonic seizures (grand mal) Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by carbamazepine Treatment of pain associated with true **trigeminal neuralgia** Treatment of **bipolar disorder** in adults Substantial evidence of CBZ effectiveness for use in the management of children with epilepsy is derived from clinical investigations performed in adults and from studies in several in vitro systems which support the conclusion that (1) the pathogenic mechanisms underlying seizure propagation are essentially identical in adults and children and (2) the mechanism of action in treating seizures is essentially identical in adults and children The evidence assembled was primarily obtained from short-term use. The safety in children has been systematically studied up to 6 months. No longer-term data from clinical trials is available
Dosage	**Prior** to initiating **treatment**, **test** patients with ancestry in genetically at-risk populations for the presence of the **HLA-B*1502 allele**. The high-resolution genotype test is positive if one or two HLA-B*1502 alleles are present. Avoid use in patients testing positive for the allele, unless the benefit clearly outweighs the risk Prior to initiating therapy in all patients, obtain a pretreatment **complete blood count** including platelets and differential. Monitor complete blood count periodically **Epilepsy** Adults: it is advised that with all formulations of CBZ, a gradually increasing dosage scheme is used, and this should be adjusted to suit the needs of the individual patient. It may be helpful to monitor the plasma concentration to establish the optimum dose. It should be taken in a number of divided doses although initially 100–200 mg once or twice daily is recommended. This may be followed by a slow increase until the best response is obtained, often 800–1,200 mg daily. In some instances, 1,600 mg or even 2,000 mg daily may be necessary Children: it is advised that with all formulations, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient. It may be helpful to monitor the plasma concentration to establish the optimum dose. Usual dosage 10–20 mg/kg bodyweight daily taken in several divided doses **Treatment of bipolar disorder with extended-release formulations in adults** Recommended initial dose 200 mg b.i.d. Adjust dose in 200-mg increments to achieve optimal clinical response. Doses higher than 1,600 mg/day have not been studied in mania associated with bipolar disorder. When discontinuing treatment, reduce dose gradually and avoid abrupt discontinuation in order to decrease the risk of seizure

ADRs	Most common (>5 % and two times placebo) ADRs were dizziness, somnolence, nausea, vomiting, ataxia, constipation, pruritus, dry mouth, asthenia, rash, blurred vision, and speech disorder **Serious and sometimes fatal dermatologic reactions** including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have occurred. For patients of Asian descent, the risk of TEN/SJS is ten times higher, compared to other populations. Discontinue the therapy if these reactions occur **Aplastic anemia and agranulocytosis** occurred. Consider discontinuing the therapy if significant bone marrow depression develops
Drug interactions	**CYP3A4 inhibitors**: acetazolamide, azole antifungals, cimetidine, clarithromycin, dalfopristin, danazol, delavirdine, diltiazem, erythromycin, fluoxetine, fluvoxamine, grapefruit juice, isoniazid, itraconazole, ketoconazole, loratadine, nefazodone, niacinamide, nicotinamide, protease inhibitors, propoxyphene, quinine, quinupristin, troleandomycin, valproate, verapamil, zileuton **Epoxide hydrolase inhibitors**: clarithromycin, erythromycin, and valproate also inhibit epoxide hydrolase, resulting in increased levels of the active metabolite CBZ-E **CYP3A4 inducers**: cisplatin, doxorubicin, felbamate, rifampin, phenobarbital, phenytoin, primidone, methsuximide, and theophylline **Drugs metabolized by CYP1A2 or CYP3A4**: oral contraceptives, delavirdine, nefazodone, phenytoin, CNS depressants, lithium, chloroquine, mefloquine
Contraindications	Bone marrow depression, known hypersensitivity to CBZ and to tricyclic antidepressants, concomitant use with MAO inhibitors or use within 14 days of discontinuing a MAO inhibitor, concomitant use with delavirdine or other non-nucleoside reverse transcriptase inhibitors because CBZ decreases efficacy of these drugs, concomitant use of nefazodone

7.7.2 Gabapentin

Pharmacodynamic properties	Gabapentin is structurally related to the neurotransmitter GABA, but it does not modify $GABA_A$ or $GABA_B$-radioligand binding, not converted metabolically into GABA or a GABA agonist, not an inhibitor of GABA uptake or degradation The mechanism of action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants
Pharmacokinetic properties	Gabapentin is absorbed from the proximal small bowel by a saturable L-amino transport system. Gabapentin bioavailability is not dose proportional; as the dose is increased, bioavailability decreases t_{max} 2–4 h (600 mg as immediate release), t_{max} 8 h (1,800 mg as extended-release); $t_{1/2}$ 5–7 h; plasma protein binding < 3 %, bioavailability (dose-dependent) 27–60 % No metabolism, no enzyme induction, excreted unchanged via the kidneys
Indications	**US FDA approval** Management of postherpetic neuralgia in adults Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy Adjunctive therapy in the treatment of partial seizures in pediatric patients aged 3–12 years Treatment of moderate-to-severe primary restless legs syndrome (RLS) in adults In **Europe** it is approved only for the treatment of epileptic syndromes and several types of neuropathic pain

Dosage	Treatment of epilepsy in **patients >12 years of age**: the effective dose is 900–1,800 mg/day and given in divided doses (t.i.d.) using 300 or 400 mg capsules, or 600 or 800 mg tablets. The starting dose is 300 mg t.i.d. If necessary, the dose may be increased using 300 or 400 mg capsules, or 600 or 800 mg tablets t.i.d. up to 1,800 mg/day. Dosages up to 2,400 mg/day have been well tolerated in long-term clinical studies. Doses of 3,600 mg/day have also been administered to a small number of patients for a relatively short duration and have been well tolerated. The maximum time between doses in the t.i.d. schedule should not exceed 12 h Pediatric patients **age 3–12 years**: the starting dose should range from 10–15 mg/kg daily t.i.d. and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose in patients 5 years of age and older is 25–35 mg/kg daily and given in divided doses (t.i.d.). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg daily and given in divided doses (t.i.d.). Dosages up to 50 mg/kg daily have been well-tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 h
ADRs	Antiepileptic drugs, including gabapentin, increase the **risk of suicidal thoughts** or behavior in patients taking these drugs for any indication. Patients treated with any antiepileptic drug for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications **In postherpetic neuralgia** Most common ADRs (10 % and greater than placebo) were dizziness, somnolence, and headache **In pediatric patients with epilepsy (3–12 years)** The most significant CNS-related ADRs can be classified into the following categories: (1) emotional lability (primarily behavioral problems), (2) hostility, including aggressive behaviors, (3) thought disorder, including concentration problems and change in school performance, and (4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity **In RLS** Most common ADRs (10 % and at least two times the rate of placebo) were somnolence/sedation and dizziness
Drug interactions	Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs
Contraindications	Hypersensitivity to any of the formulation components, acute pancreatitis, galactosemia (galactose intolerance)

7.7.3 Lamotrigine

Pharmacodynamic properties	The precise mechanism(s) of action is/are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock and pentylenetetrazol tests and prevented seizures in the visually and electrically evoked after-discharge tests for antiepileptic activity In vitro pharmacological studies showed that lamotrigine inhibits voltage-sensitive Na^+ channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate)
Pharmacokinetic properties	t_{max} 1.4–4.8 h, $t_{1/2}$ 15–30 h (in monotherapy), 48.3–70.3 h (in combination with valproate); plasma protein binding 55 %, bioavailability 98 % Metabolized by glucuronic acid conjugation (UGT1A4) without induction, no active metabolites, no interaction with CYP-metabolized agents

Indications

US FDA approval

Epilepsy

Adjunctive therapy in patients ≥2 years of age for the following seizure types: partial seizures, primary generalized tonic-clonic seizures, generalized seizures of Lennox–Gastaut syndrome

Monotherapy for conversion to monotherapy in adults (≥16 years) with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single antiepileptic drug

Bipolar disorder

Maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in adults (≥18 years of age) treated for acute mood episodes with standard therapy

The effectiveness of lamotrigine in the acute treatment of mood episodes has not been established

Safety and effectiveness in patients below the age of 18 years with mood disorders have not been established

Lamotrigine is also approved in **Europe** for the treatment of epilepsy and bipolar disorder

Dosage

To **avoid** an increased risk of **rash**, the **recommended** initial **dose** and subsequent dose escalations should **not be exceeded**

Epilepsy

Adjunctive therapy: See PI

Conversion to monotherapy: See PI

Bipolar disorder

The target dose in adults is 200 mg/day (100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine, and 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that increase the apparent clearance of lamotrigine). Treatment is introduced, based on concurrent medications, according to the regimen outlined in the following table

If other psychotropic medications are withdrawn following stabilization, the dose of lamotrigine should be adjusted. For patients discontinuing valproate, the dose should be doubled over a 2-week period in equal weekly increments. For patients discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation, the dose should remain constant for the first week and then should be decreased by half over a 2-week period in equal weekly decrements

Escalation regimen for lamotrigine for patients with bipolar disorder

	For taking valproate	No other antiepileptic drug	Other antiepileptic drug but no valproate
Weeks 1 and 2	25 mg every other day	25 mg daily	50 mg daily
Weeks 3 and 4	25 my daily	50 mg daily	100 mg daily, in divided doses
Week 5	50 my daily	100 mg daily	200 mg daily, in divided doses
Week 6	100 mg daily	200 mg daily	300 mg daily, in divided doses
Week 7	100 my daily	200 mg daily	Up to 400 mg daily, in divided doses

ADRs

Most common ADRs (incidence ≥ 10 %) in adult **epilepsy** clinical studies were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, and rash. Additional ADRs (incidence ≥10 %) reported in children in epilepsy clinical studies included vomiting, infection, fever, accidental injury, pharyngitis, abdominal pain, and tremor

Most common ADRs (incidence >5 %) in adult **bipolar disorder** clinical studies were nausea, insomnia, somnolence, back pain, fatigue, rash, rhinitis, abdominal pain, and xerostomia

Clinical worsening, emergence of new symptoms, and suicidal ideation/behaviors may be associated with treatment of bipolar disorder. Patients should be closely monitored, particularly early in treatment or during dosage changes

Drug interactions	Valproate increases lamotrigine concentrations more than two-fold Carbamazepine, phenytoin, phenobarbital, and primidone decrease lamotrigine concentrations by approximately 40 % Oral estrogen-containing contraceptives and rifampin also decrease lamotrigine concentrations by approximately 50 %
Contraindications	Hypersensitivity to the drug or its ingredients. Fatal or life-threatening hypersensitivity reaction: multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and systemic symptoms, may be fatal or life threatening. Early signs may include rash, fever, and lymphadenopathy. These reactions may be associated with other organ involvement, such as hepatitis, hepatic failure, blood dyscrasias, or acute multiorgan failure. Lamotrigine should be discontinued if alternate etiology for this reaction is not found. Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia) may occur, either with or without an associated hypersensitivity syndrome

7.7.4 Lithium Salts (Carbonate, Citrate)

Pharmacodynamic properties	Interference with the Na^+-K^+-ATPase; shifts in electrolyte balance that results in acute changes in the storage, release, biotransformation, and reuptake of neurotransmitters, particularly serotonin, dopamine, acetylcholine, and GABA. Accumulating evidence indicates that lithium therapy has also direct effects on glutamatergic neural transmission. These effects leads to downstream changes in signal transduction cascades and gene expression resulting eventually in the transcription and expression of neurotrophic, angiogenic, and neuroprotective proteins
Pharmacokinetic properties	t_{max} 1–3 h: $t_{1/2}$ about 24 h Elimination is renal. Following glomerular filtration, around 80 % is reabsorbed in the proximal tubulus, competing with Na^+ for the same transport system. For this reason Li^+ reabsorption is increased when tubular Na^+ concentrations are reduced (hyponatremia as the result of, for instance, vomiting, pronounced sweating, sodium-poor diet) and its excretion reduced. There is accordingly an increased risk of intoxication during periods of higher Na^+ loss
Indications	Lithium salts have been **approved by the US FDA** only for the treatment of manic episodes and maintenance treatment of bipolar disorder in patients aged 12 years and older Since information regarding the safety and effectiveness of lithium in children under 12 years of age is not available, its use in such patients is not recommended. There has been a report of a transient syndrome of acute dystonia and hyperreflexia occurring in a 15-kg-child who ingested 300 mg of lithium carbonate **Approved in European countries for** Management of acute manic or hypomanic episodes Management of episodes of recurrent depressive disorders where treatment with other antidepressants has been unsuccessful Prophylaxis against bipolar affective disorders Control of aggressive behavior or intentional self harm The treatment in children is not recommended
Dosage	**Acute mania** Optimal patient response to Li^+ carbonate usually can be established and maintained with 600 mg t.i.d. Optimal patient response to lithium oral solution usually can be established and maintained with 10 ml (16 mmol/L of lithium) t.i.d. Such doses will normally produce an effective serum Li^+ level ranging between 1.0 and 1.5 mmol/L Dosage must be individualized according to serum levels and clinical response. Regular monitoring of the patient's clinical state and of serum Li^+ levels is necessary. Serum levels should be determined twice per week during the acute phase and until the serum level and clinical condition of the patient have been stabilized

	Long-term medicaton The desirable serum Li^+ levels are 0.6–1.2 mmol/L. Dosage will vary from one individual to another, but usually 300 mg of Li^+ carbonate t.i.d. or q.i.d., or 5 ml (8 mmol/L of Li^+) of lithium oral solution t.i.d. or q.i.d. will maintain this level Serum Li^+ levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every 2 months. Patients abnormally sensitive to lithium may exhibit toxic signs at serum levels of 1.0–1.5 mmol/L **N.B.** Blood samples for serum Li^+ determination should be drawn immediately prior to the next dose when Li^+ concentrations are relatively stable (i.e., 8–12 h after the previous dose). Total reliance must not be placed on serum levels alone. Accurate patient evaluation requires both clinical and laboratory analysis
ADRs	The **likelihood of toxicity** increases with increasing serum Li^+ levels. Serum Li^+ levels greater than 1.5 mmol/L carry a greater risk than lower levels. However, patients sensitive to lithium may exhibit toxic signs at serum levels below 1.5 mmol/L. Diarrhea, vomiting, drowsiness, muscular weakness, and lack of coordination may be early signs of lithium toxicity and can occur at Li^+ levels below 2.0 mmol/L. At higher levels, giddiness, ataxia, blurred vision, tinnitus, and a large output of dilute urine may be seen. Serum Li^+ levels above 3.0 mml/L may produce a complex clinical picture involving multiple organs and organ systems. Serum Li^+ levels should not be permitted to exceed 2.0 mmol/L during the acute treatment phase Fine hand tremor, polyuria, and mild thirst may occur during initial therapy for the acute manic phase and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration. These side effects are an inconvenience rather than a disabling condition and usually subside with continued treatment or a temporary reduction or cessation of dosage. If persistent, a cessation of dosage is indicated The following **ADRs** have been reported and do **not** appear to be **directly related to serum Li^+ levels** **Neuromuscular**: tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), ataxia, choreoathetotic movements, hyperactive deep tendon reflexes **CNS**: blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, acute dystonia, downbeat nystagmus **Cardiovascular**: cardiac arrhythmia, hypotension, peripheral circulatory collapse, sinus node dysfunction with severe bradycardia (which may result in syncope), unmasking of Brugada syndrome **Neurological**: cases of pseudotumor cerebri (increased intracranial pressure and papilledema) have been reported. If undetected, this condition may result in enlargement of the blind spot, constriction of visual fields, and eventual blindness due to optic atrophy. Lithium should be discontinued, if clinically possible, if this syndrome occurs **Gastrointestinal**: anorexia, nausea, vomiting, diarrhea **Genitourinary:** albuminuria, oliguria, polyuria, glycosuria **Dermatologic**: drying and thinning of hair, anesthesia of skin, chronic folliculitis, xerosis cutis, alopecia, and exacerbation of psoriasis **Autonomic nervous system**: blurred vision, dry mouth **Thyroid abnormalities**: euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T3 and T4. Iodine uptake may be elevated. Paradoxically, rare cases of hyperthyroidism have been reported **EEG changes**: diffuse slowing, widening of frequency spectrum, potentiation, and disorganization of background rhythm **EKG changes**: reversible flattening, isoelectricity, or inversion of T-waves **Miscellaneous**: fatigue, lethargy, transient scotomata, dehydration, weight loss, tendency to sleep

Drug interactions	Combined use of **haloperidol** and lithium salts. An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, blood urea nitrogen and fasting blood sugar) followed by irreversible brain damage has occurred in a few patients. A causal relationship between these events and the concomitant administration of lithium and haloperidol has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. The possibility of similar adverse interactions with other antipsychotic medication exists Lithium salts may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium **Nonsteroidal anti-inflammatory drugs** (NSAIDS). Li^+ levels should be closely monitored when patients initiate or discontinue NSAID use. In some cases, lithium toxicity has resulted from interactions between an NSAID and lithium salts. Indomethacin and piroxicam have been reported to increase significantly steady-state plasma Li^+ concentrations. There is also evidence that other nonsteroidal anti-inflammatory agents, including the selective cyclooxygenase2 (COX-2) inhibitors, have the same effect. In a study conducted in healthy subjects, mean steady-state Li^+ plasma levels increased approximately 17 % in subjects receiving lithium 450 mg b.i.d. with celecoxib 200 mg b.i.d. as compared to subjects receiving lithium alone Caution should be used when lithium salts and **diuretics** or **angiotensin converting enzyme** (ACE) **inhibitors** are used concomitantly because sodium loss may reduce the renal clearance of lithium and increase serum Li^+ levels with risk of lithium toxicity. When such combinations are used, the lithium dosage may need to be decreased, and more frequent monitoring Li^+ plasma levels is recommended
Contraindications	Patients with significant renal or cardiovascular disease, severe debilitation or dehydration, or sodium depletion, and to patients receiving diuretics, since the risk of lithium toxicity is very high in such patients If the psychiatric indication is life threatening and if such a patient fails to respond to other measures, lithium treatment may be undertaken with extreme caution, including daily serum Li^+ determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity

7.7.5 Oxcarbazepine

Pharmacodynamic properties	The pharmacological activity is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine. The precise mechanism of action is unknown; however, in vitro electrophysiological studies indicate that it produces blockade of voltage-sensitive Na^+ channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. In addition, increased K^+ conductance and modulation of high-voltage activated Ca^{2+} channels may contribute to the anticonvulsant effects of the drug Oxcarbazepine and MHD exhibit anticonvulsant properties in animal seizure models. They protected rodents against electrically induced tonic extension seizures and, to a lesser degree, chemically induced clonic seizures, and abolished or reduced the frequency of chronically recurring focal seizures in Rhesus monkeys with aluminum implants
Pharmacokinetic properties	t_{max} 4.5 h (tablets), t_{max} 6 h (oral suspension); t_{max} 7 h (MHD); $t_{1/2}$ 2 h, $t_{1/2}$ 9–11 h (MDH); plasma protein binding 40 % (MHD), bioavailability not reported Metabolized by CYP enzymes, induction of CYP3A4 and CYP3A5
Indications	**US FDA approval** Monotherapy or adjunctive therapy in the treatment of partial seizures in adults Monotherapy in the treatment of partial seizures in children 4–16 years of age Adjunctive therapy in the treatment of partial seizures in children 2–16 years of age **Approval in Europe** Treatment of partial seizures with or without secondarily generalized tonic-clonic seizures Use as monotherapy or adjunctive therapy in adults and in children of 6 years of age and above

Dosage	For immediate-release tablets and oral suspensions **Adults**: initiate with a dose of 600 mg/day, given b.i.d. Adjunctive therapy: maximum increment of 600 mg/day at approximately weekly intervals. The recommended daily dose is 1,200 mg/day Conversion to monotherapy: concomitant antiepileptic drugs should be completely withdrawn over 3–6 weeks, while maximum dose of oxcarbazepine should be reached in about 2–4 weeks. Maximum increment of 600 mg/day at approximately weekly intervals to a recommended daily dose of 2,400 mg/day Initiation of monotherapy: increments of 300 mg/day every third day to a dose of 1,200 mg/day **Children**: initiation with 8–10 mg/kg daily, given b.i.d. For patients aged <4 years and under 20 kg, a starting dose of 16–20 mg/kg daily may be considered. Recommended daily dose is dependent upon patient weight Adjunctive patients (aged 2–16 years): for patients aged 4–16 years, target maintenance dose should be achieved over 2 weeks. For patients aged 2 ≤ 4 years, maximum maintenance dose should be achieved over 2–4 weeks and should not to exceed 60 mg/kg daily Conversion to monotherapy for patients (aged 4–16 years): Maximum increment of 10 mg/kg daily at weekly intervals, concomitant antiepileptic drugs can be completely withdrawn over 3–6 weeks Initiation of monotherapy for patients (aged 4–16 years): increments of 5 mg/kg daily every third day
ADRs	The most commonly observed (≥ 5 %) ADRs were dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait, and in pediatric patients <4 years old also infections and infestations
Drug interactions	Coadministration of carbamazepine, phenobarbital, and phenytoin decreased blood levels of the active metabolite MHD. Greater dose of oxcarbazepine may be required Oral contraceptives: advise patients that oxcarbazepine may decrease the effectiveness of hormonal contraceptives. Additional nonhormonal forms of contraception are recommended
Contraindications	Known hypersensitivity to oxcarbazepine or to any of its components

7.7.6 Topiramate

Pharmacodynamic properties	The precise mechanisms of action are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and migraine prophylaxis. Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant concentrations, blocks voltage-dependent Na^+ channels, augments the activity of the neurotransmitter GABA at some subtypes of the $GABA_A$-receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isoenzymes II and IV Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure tests. It is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat, and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia
Pharmacokinetic properties	t_{max} 2 h (following 400 mg tablet), $t_{1/2}$ 21 h (in combination with CYP-inducing medications 8–15 h); plasma protein binding 15–41 %, bioavailability, not reported; It is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70 % of an administered dose) In vitro studies indicate that topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5 isoenzymes. In vitro studies indicate that topiramate is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4

Indications	**Approval in the USA (FDA) and in Europe** *Epilepsy* Monotherapy in patients ≥2 years of age with partial onset or primary generalized tonic-clonic seizures Adjunctive therapy for adults and pediatric patients (2–16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures and in patients ≥2 years of age with seizures associated with Lennox–Gastaut syndrome *Migraine* Treatment for adults for prophylaxis of migraine headache
Dosage	The dosage strategy for treatment with topiramate in epilepsy is summarized in Table 7.6
ADRs	The most common (≥ 5 % more frequent than placebo or low-dose topiramate in monotherapy) ADRs in controlled **epilepsy** clinical **trials** were paresthesia, anorexia, weight decrease, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, difficulty with memory, difficulty with concentration/attention, cognitive problems, confusion, mood problems, fever, infection, and flushing The most common (≥ 5 % more frequent than placebo) ADRs in controlled **migraine** clinical **trials** were paresthesia and taste perversion
Drug interactions	Concomitant administration of **phenytoin** or **carbamazepine** with topiramate decreased plasma concentrations of topiramate by 48 and 40 %, respectively, when compared to topiramate given alone Concomitant administration of **valproic acid** and topiramate has been associated with **hyperammonemia** with and without encephalopathy. Concomitant administration of topiramate with valproic acid has also been associated with **hypothermia** (with and without hyperammonemia) in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported Exposure to **ethinyl estradiol** was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18, 21, and 30 %, respectively) when topiramate was given as adjunctive therapy in patients taking valproic acid. However, norethindrone exposure was not significantly affected Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any **other carbonic anhydrase inhibitor** (e.g., zonisamide, acetazolamide, or dichlorphenamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if topiramate is given concomitantly with another carbonic anhydrase inhibitor, the patient should be monitored for the appearance or worsening of metabolic acidosis
Contraindications	Hypersensitivity to the active substance or to any of the excipients. Migraine prophylaxis in pregnancy and in women of childbearing potential if not using effective methods of contraception

7.7.7 Valproic Acid (Sodium Valproate, Divalproex Sodium)

Pharmacodynamic properties	Valproic acid dissociates to the valproate ion in the gastrointestinal tract. Divalproex sodium is an enteric-coated formulation of valproate The mechanisms by which valproate exerts its antiepileptic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of GABA
Pharmacokinetic properties	t_{max} 3.3–4 h (immediate-release tablets and oral solution), t_{max} 3.5 (delayed-release tablet); $t_{1/2}$ 9–16 h; plasma protein binding 10–18.5 %, bioavailability, not reported Metabolism almost entirely by the liver. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40 % of the dose. Usually, less than 15–20 % of the dose is eliminated by other oxidative mechanisms Pediatric patients (i.e., between 3 months and 10 years) have 50 % higher clearances expressed on weight (i.e., ml/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults

Indications	Valproate products that contain valproate sodium, divalproex sodium, and valproic acid are **US FDA-approved** drugs to treat: Seizures in adult patients and pediatric patients Manic or mixed episodes associated with bipolar disorder in adults Migraine headaches in adults Efficacy was not established in children and adolescent (aged 10–17 years) for the treatment of mania in two double-blinded placebo-controlled using divalproex sodium extended-release tablets The **EMA** has **approved** valproate-containing medicinal products for the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who responded to valproate for acute mania
Dosage	For divalproex sodium extended-release tablet for the treatment of mania in adults The recommended initial dose is 25 mg/kg daily given once daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations. In a placebo-controlled clinical trial of acute mania or mixed type, patients were dosed to a clinical response with a trough plasma concentration between 85 and 125 μg/mL. The maximum recommended dosage is 60 mg/kg per day
ADRs	The most common drug-related ADRs (reported >5 % and twice the rate of placebo) reported in the controlled pediatric mania study were nausea, upper abdominal pain, somnolence, increased ammonia, gastritis, and rash Antiepileptic drugs, including valproic acid, increase the risk of **suicidal thoughts** or behavior in patients taking these drugs for any indication. Patients treated with any antiepileptic drug for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior **Hepatic failure** resulting in fatalities has occurred in patients receiving valproate. These incidents usually have occurred during the first 6 months of treatment. Serious or fatal hepatotoxicity may be preceded by nonspecific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months. However, healthcare providers should not rely totally on serum biochemistry since these tests may not be abnormal in all instances but should also consider the results of careful interim medical history and physical examination
Drug interactions	**Hepatic enzyme-inducing drugs** (e.g., phenytoin, carbamazepine, phenobarbital, rifampin) can increase valproate clearance, while enzyme inhibitors (e.g., felbamate) can decrease its clearance. Monitor valproate and concomitant drug concentrations whenever enzyme-inducing or inhibiting drugs are introduced or withdrawn **Aspirin**, carbapenem **antibiotics**: monitoring of valproate concentrations is recommended Coadministration of valproate can affect the pharmacokinetics of other drugs (e.g., diazepam, ethosuximide, lamotrigine, phenytoin) by inhibiting their metabolism or protein binding displacement. Dosage adjustment of amitriptyline/nortriptyline, warfarin, and zidovudine may be necessary if used concomitantly with valproic acid Concomitant administration of valproate and **topiramate** has been associated with **hyperammonemia** with and without encephalopathy. Concomitant administration of topiramate with valproate has also been associated with **hypothermia** in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported
Contraindications	In patients with known hypersensitivity to the drug, with hepatic disease or significant hepatic dysfunction, in patients with known urea cycle disorders Because of the risk to the fetus of decreased IQ and major congenital malformations (including neural tube defects), which may occur very early in pregnancy, valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition

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8 Psychostimulants and Other Drugs Used in the Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD)

Susanne Walitza, Marcel Romanos, Andreas Warnke, Laurence Greenhill, and Manfred Gerlach

Contents

S. Walitza, MD (✉)
Department of Child and Adolescent Psychiatry, University of Zurich, Neumuensterallee 9, P.O. Box 1482, 8032 Zurich, Switzerland
e-mail: susanne.walitza@kjpdzh.ch

M. Romanos, MD • A. Warnke, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: romanos@kjp.uni-wuerzburg.de; warnke@kjp.uni-wuerzburg.de

L. Greenhill, MD
NYS Psychiatric Institute, New York Presbyterian Hospital, Riverside Drive 1051, New York, NY 10032, USA
e-mail: llg2@columbia.edu

M. Gerlach, PhD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Laboratory for Clinical Neurobiology and Therapeutic Drug Monitoring, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: manfred.gerlach@uni-wuerzburg.de

8.1 Definition

The term "psychostimulants" (synonym stimulants) refers to a group of psychopharmacological agents whose predominant effect is the **enhancement of cognitive and behavioral functions** by stimulation of the central nervous system (CNS). In healthy humans, they relieve feelings of tiredness and languor, elevate mood as well as improve concentration and performance. In animals, psychostimulants increase locomotor activity and are readily self-administered due to their powerful reinforcing properties (Rothman and Baumann 2003). It should again be emphasized that classification of psychopharmacological agents is based upon the psychopathologic symptoms influenced

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Table 8.1 Representative examples of typical psychostimulants

Therapeutic drugs	US FDA-approved indications
Amphetamine	ADHD in pediatric patients (ages 3–16 years)
	Narcolepsy
Benzphetamine	Exogenous obesity (not recommended in children aged below 12 years)
Diethylproprion	Exogenous obesity (not recommended in children aged below 16 years)
Methylphenidate	ADHD in pediatric patients (aged above 6 years)
	Narcolepsy
Modafinil	Reducing sleepiness in obstructive sleep apnea, narcolepsy, and shift-work disorder in adults
Natural products	
Cathinone: ingredient in the khat shrub whose leaves have been chewed by the people of East Africa and the Arab Peninsula for their psychostimulant properties for many hundreds of years	
Caffeine: a xanthine alkaloid that is found in the seed of the coffee plant and leaves of the tea bush	
Ephedrine: a salt that was originally isolated from the plant *Ephedra vulgaris*. It is still used in kampo, the traditional Chinese herbal medicine practiced in Japan, and is still popular in China as ma huang	
Phenylethylamine: found in many foodstuffs, particularly cheeses and some wines	
Abused drugs	
Cocaine	
Methamphetamine	
Methylenedioxymethamphetamine (MDMA) commonly known as "ecstasy"	

ADHD attention-deficit/hyperactivity disorder, *FDA* Food and Drug Administration

by these agents and is independent of the different neuropsychiatric disorders in which these symptoms can be presented.

Psychostimulants such as amphetamine and methylphenidate are chiefly employed in the symptomatic treatment of attention-deficit/hyperactivity disorder (**ADHD**) and narcolepsy (Table 8.1). ADHD is characterized by marked motor restlessness (hyperactivity), concentration disturbances that impair cognitive performance (inattention, elevated distractibility), as well as severe difficulties with regard to the planning and control of the patient's own behavior (impulse control disorder).

Narcolepsy is characterized by daytime somnolence, falling asleep at inappropriate times, and abrupt loss of voluntary muscle tone. Modafinil was the first wakefulness-promoting agent that was approved by the US Food and Drug Administration (FDA) for the treatment of excessive daytime sleepiness associated with narcolepsy.

Beyond their use for the treatment of ADHD and narcolepsy, psychostimulants have been used for the relief of symptoms such as asthenia and depression in cancer patients (Portela et al. 2011), for the treatment of fatigue in Parkinson's disease (Seppi et al. 2011), and as illicit substances as "cognitive enhancers" in healthy people based on their effects on mood and hedonic drive.

8.2 Classification

Table 8.1 lists a number of agents that are classified as psychostimulants. In addition to medically used agents, psychostimulants include natural products and synthetic derivatives, which were illicitly abused. Psychostimulants also include, in a broader sense, psychomotor-activating antidepressants as well as certain nootropic drugs employed in the treatment of dementia. This chapter deals solely with psychostimulants in the stricter sense and in particular with those employed in the therapy of ADHD in children and adolescents.

Psychostimulants are often described as **amphetamine-like agents** (amphetamines) because amphetamine is the prototypical psychostimulant (Fig. 8.1). The chemical structure of amphetamine resembles that of the naturally occurring neurotransmitter dopamine and noradrenaline. There are structural similarities between the man-made psychostimulants amphetamine, methamphetamine, methylenedioxymethamphetamine (MDMA), and methylphenidate. Cocaine, first used as a local anesthetic agent, is structurally different from these agents.

The **drugs** used **for** the treatment of **ADHD** are diverse but can be roughly separated into two groups:

- **Psychostimulants** such as amphetamine, methylphenidate, and modafinil
- **Non-psychostimulants** such as atomoxetine, clonidine, guanfacine, and pemoline

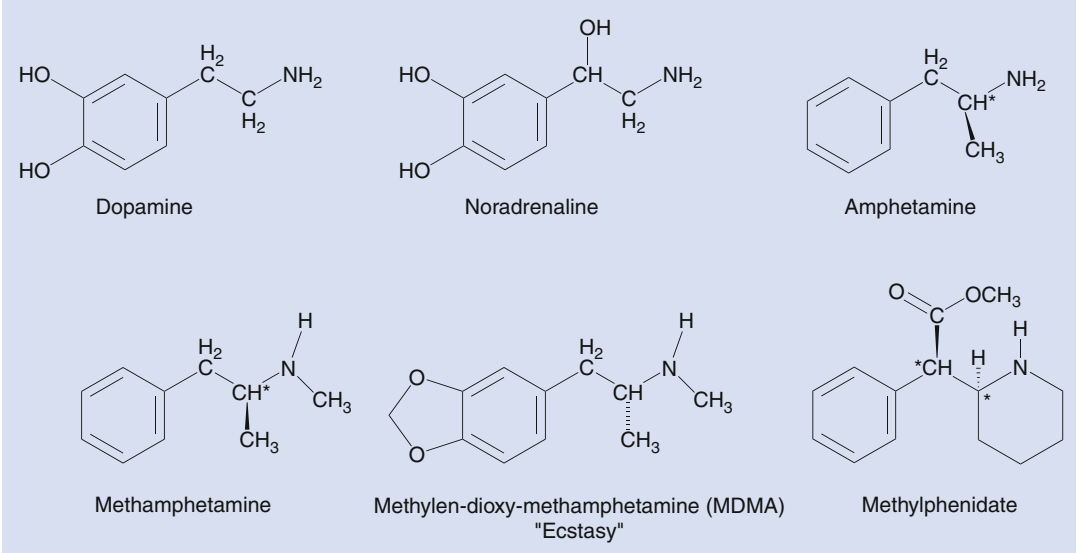

Fig. 8.1 Structural formulas of dopamine, noradrenaline, and typical psychostimulants

However, this **classification** used by the US FDA is **not justified** by preclinical and clinical data showing similar preclinical and clinical effects of atomoxetine and typical psychostimulants such as amphetamine and methylphenidate on cognitive and behavioral functioning. For example, following intraperitoneal injections of atomoxetine, an improvement in attention set-shifting and improved attention on the five choice serial reaction time task could be shown in Long Evans rats (see Turner et al. 2013). In boys with ADHD, it was demonstrated that treatment with methylphenidate vs. atomoxetine could be associated with comparable improvements in both response inhibition on the go/no-go test and mean improvements in ratings of ADHD symptoms (Schulz et al. 2012).

Amphetamine and **methylphenidate** are currently classified as **schedule II drugs** by the US Controlled Substance Act, indicating that while they have an approved medical use, they also have significant abuse liabilities, which raises concerns about nonmedical use in patients with ADHD, including misuse, abuse, or diversion to individuals without ADHD (Substance Abuse and Mental Health Services Administration 2006; The National Center on Addiction and Substance Abuse at Columbia University 2007). In contrast, atomoxetine, clonidine, and guanfacine have not been scheduled as controlled substances. The positive and negative features of typical psychostimulants are more dependent upon their mode of employment or indication than is the case for almost all other classes of medication. In the pharmacological treatment of ADHD, methylphenidate and amphetamine in per oral form are safe and not associated with the development of dependence (see Sect. 8.4.1). Amphetamines in parenteral form without appropriate indication, however, are frequently misused as recreational drugs or as doping agents. In these circumstances, the potential for dependence is dangerously high.

Atomoxetine, the first FDA-approved non-psychostimulant medication for the treatment of ADHD, was originally developed (as tomoxetine) for clinical use as an antidepressant (Chouinard et al. 1984). **Modafinil** has been shown to be effective for ADHD in randomized controlled trials (Biederman and Pliszka 2008; Wigal et al. 2006); however, FDA approval for the treatment of ADHD was not sought by its manufacturer after report of a suspected case of Stevens-Johnson syndrome (Vaughan and Kratochvil 2012). **Pemoline** has been removed from the market in Canada and Europe and is no longer used in the USA because of its severe liver toxicity. Therefore, modafinil and pemoline are

not being discussed in this chapter. We do also not discuss methamphetamine, which is currently labelled by the FDA for the treatment of ADHD and exogenous obesity, as it is, in contrast to amphetamine, an established dopaminergic neurotoxin (Gerlach and Riederer 1996), and obsolete in clinical practice.

8.3 Mechanisms of Action

Psychostimulants exert their effects through a number of different pharmacological mechanisms, the most prominent of which include facilitation of dopamine and/or noradrenaline activity via monoamine transporter reuptake inhibition or reversal (Table 8.2). In peripheral tissues, amphetamine stimulates the release of noradrenaline from the nerve endings of the sympathetic nervous system which controls a variety of peripheral functions. Because of its ability to mimic the action of the sympathetic nervous system, amphetamine is also known as a sympathomimetic amine (Trendelenburg 1963). Peripheral actions include elevations of systolic and diastolic blood pressure, weak bronchodilator and respiratory stimulant action. In addition to its effect on peripheral tissues, amphetamine releases noradrenaline in the CNS producing performance enhancement, suppressing hunger, and increasing vigilance through suppression of sleep and fatigue, for which reason amphetamine derivatives are referred to colloquially as "uppers."

Clonidine and **guanfacine**, which are **α_2-adrenoceptor agonists**, were originally developed and clinically utilized as centrally active antihypertensive agents, which exert their antihypertensive activity by decreasing the sympathetic tone in the CNS and reducing vascular resistance (see Sallee et al. 2013). Although the mechanism through which clonidine and guanfacine bring about improvement in individuals with ADHD is unknown, there is preclinical evidence suggesting that clonidine and guanfacine both act directly in the prefrontal cortex via postsynaptic α_2-adrenoceptors and indirectly by modulating locus ceruleus input to the prefrontal cortex through modulation of autoreceptors. Action of α_2-adrenoceptor agonists modulate tonic and phasic locus ceruleus firing and thus modulate noradrenergic input to the prefrontal cortex (see Sallee et al. 2013). Ascending noradrenergic afferent projections from the locus ceruleus to the prefrontal cortex are thought to modulate

Table 8.2 Pharmacodynamics of drugs used in the treatment of attention-deficit/hyperactivity disorders (ADHD)

Drugs	Pharmacodynamic effect
Psychostimulants	
Amphetamine	Non-exocytotic, transporter-mediated release of dopamine and noradrenaline by reverse transport through monoamine transporter in the striatum
	Inhibition of dopamine and noradrenaline transporters in the striatum
	In higher doses inhibition of monoamine oxidase
	Indirect agonists of peripheral and central dopamine and noradrenaline receptors
Methylphenidate	Inhibition of dopamine and noradrenaline transporters in the striatum
	Indirect agonists of peripheral and central dopamine and noradrenaline receptors
Non-psychostimulants	
Atomoxetine	Inhibition of noradrenaline transporters central in the prefrontal cortex
	Indirect agonist of peripheral and central noradrenaline receptors in the prefrontal cortex
Clonidine	α_2-Adrenoceptor agonist
	Facilitates both direct action in the prefrontal cortex via postsynaptic α_2-adrenoceptors and indirect action through modulation of α_2-adrenergic autoreceptors in the locus ceruleus
Guanfacine	α_2-Adrenoceptor agonist
	Facilitates both direct action in the prefrontal cortex via postsynaptic α_2-adrenoceptors and indirect action through modulation of autoreceptors in the locus ceruleus

Table 8.3 Pharmacological profile of selected drugs used in the treatment of attention-deficit/hyperactivity disorder in monoamine uptake inhibition assays

Drug	DAT K_i or IC_{50} (nmol/L)	NET K_i or IC_{50} (nmol/L)	SERT K_i or IC_{50} (nmol/L)
Amphetamine			
(R)-amphetamine[a]	34; 41	38.9; 23.2	3,830; 11,000
(S)-amphetamine[a]	138	30.1	57,000
Atomoxetine[a]	1,600	2.6	48
Methylphenidate[b]	34	339	>10,000

From Madras et al. (2005)
IC_{50} half maximal inhibitory concentration, K_i inhibitory constant. The smaller the value of each, the higher the affinity of the substance
DAT dopamine transporter, *NET* noradrenaline transporter, *SERT* serotonin transporter
[a]Transporter affinity: DAT [^{3}H]dopamine; NET [^{3}H]noradrenaline; SERT [^{3}H]serotonin
[b]Binding affinity: DAT [^{3}H]WIN35,425; NET [^{3}H]nisoxetine; SERT [^{3}H]paroxetine

attention and working memory by enhancing functional connectivity between the prefrontal cortex and other brain regions. In the brain, clonidine has been shown to decrease noradrenergic activity and regional cerebral blood flow in brain regions such as the prefrontal cortex (Broese et al. 2012). In nonhuman primates, guanfacine increased working memory in a dose-dependent manner and reduced distractibility (see Sallee et al. 2013).

Amphetamine and **methylphenidate** are substrates for both dopamine transporter (DAT) and noradrenaline transporter (NET) as well as competitive **inhibitors** of **dopamine** and **noradrenaline uptake** (Table 8.3) in in vitro studies (Heikkila et al. 1975; Markowitz et al. 2006). In addition, amphetamine promotes dopamine efflux by reverse transport through monoamine uptake transporters (Table 8.2). Microdialysis studies in rats showed that these mechanisms lead to an increase in extracellular dopamine and noradrenaline concentrations in the striatum (Kuczenski and Segal 1997): Amphetamine (2.5 mg/kg intravenously) induced an approximately three times greater effect than a behaviorally similar dose of methylphenidate (20 mg/kg intravenously) which is the result of the additional effect on dopamine release. The elevated synaptic dopamine concentrations are believed to cause the psychostimulant-induced increase in locomotor activity usually seen in animals. However, in DAT knockout mice, which are already hyperactive, amphetamine and methylphenidate decreased locomotor activity (Gainetdinov 2010).

In contrast to amphetamine and methylphenidate, **atomoxetine** is a **selective inhibitor** of the **NET** (Table 8.3). In microdialysis studies, atomoxetine increased the extracellular levels of noradrenaline in the prefrontal cortex to three times, but did not alter serotonin levels in rats (Bymaster et al. 2002). Atomoxetine also increased dopamine concentrations in the prefrontal cortex threefold, but did not alter dopamine in the striatum or nucleus accumbens. In contrast, methylphenidate increased noradrenaline and dopamine equally in the prefrontal cortex, and in addition dopamine in the striatum and nucleus accumbens to the same level. These data indicate a potential difference in the mechanism of action between methylphenidate and atomoxetine. As hypothesized by Bymaster et al. (2002), the absence of extracellular dopamine accumulation in the nucleus accumbens and striatum suggests that atomoxetine is unlikely to produce tics or have abuse potential.

In addition to the indirect effects on central dopamine and noradrenaline receptors, all of these drugs showed a number of other acute effects in preclinical studies, that can, directly or indirectly, further modify monoamine (and other) neurotransmission (see Steiner and van Waes 2013). For example, it was shown that acute methylphenidate administration alters the distribution and function of the vesicular monoamine transporter-2 in the striatum, produces enhanced

phosphorylation of glutamate receptors in the prefrontal cortex, and affects second messenger cascades that mediate dopamine signaling. It was also reported that daily methylphenidate and atomoxetine treatment impacts clock gene protein expression in mouse brains indicating that drugs used in the clinical management of ADHD can alter molecular factors that are believed to underpin circadian timekeeping (Baird et al. 2013).

The **mechanisms of action** underlying the clinical effects of drugs used in the therapy of ADHD and narcolepsy are **only partially known**, as the etiology and pathogenesis of these disorders are largely unknown. There is much debate about what core neuropsychological deficits might cause both ADHD symptoms and neuropsychological impairments. Candidates for core deficits include failure of inhibitory control; dysregulation of brain systems mediating reward and response cost; and deficits in arousal, activation, and effortful control (Biederman and Faraone 2005). Structural neuroimaging studies have shown small volume reductions in the basal ganglia of ADHD patients (see Sobel et al. 2010). Using anatomical magnetic resonance imaging (MRI), it could also be shown that the basal ganglia surface morphology reveals significant inward deformations. As suggested by Sobel et al. (2010) psychostimulants may normalize morphological features of the basal ganglia in children with this disorder. But other studies have implicated structures such as cerebellum and corpus callosum (Biederman and Faraone 2005), which are outside the basal ganglia-thalamocortical circuits. Functional neuroimaging studies that assessed the degree of brain activation associated with neuropsychological tasks of attention and disinhibition are consistent with the structural studies locating abnormalities of brain activation in patients with ADHD. For example, a functional MRI study revealed that striatal activation is reduced in ADHD children on the stimulus-controlled task without drug treatment, which was ameliorated by methylphenidate treatment (Vaidya et al. 1998).

Dopamine has long been known to be a crucial **modulator of striatal processing** of cortical and thalamic signals mediated through glutamatergic synapses on the principal (medium spiny) striatal neurons. Regulation of these neurons by dopamine is important for a wide array of psychomotor functions ascribed to the basal ganglia, including motor, cognitive, and motivational functions. Recent studies have strongly suggested that **disturbance of the dopaminergic system** is also involved in the pathophysiology of **ADHD** (Genro et al. 2010; Mehler-Wex et al. 2006). Genetic studies (Albayrak et al. 2008) have shown an association between ADHD and genes involved in dopaminergic neurotransmission (e.g., the dopamine receptor genes DRD-4 and DRD-5, and the DAT gene DAT-1). DAT knockout mice display a phenotype with increased locomotor activity, which is normalized by psychostimulant treatment (Gainetdinov 2010). Finally, neuroimaging studies demonstrated an increased density of DAT in the striatum of ADHD patients using positron emission tomography (PET; Fusar-Poli et al. 2012) and a structural abnormality of the substantia nigra (dopamine neurons from this region project to the striatum) in children with ADHD using transcranial sonography (Krauel et al. 2010; Romanos et al. 2010). The transcranial sonography studies revealed an increase in the echogenic size of the substantia nigra that was correlated with symptoms of inattention, hyperactivity, and impulsivity, but not oppositional or dissocial symptoms (Krauel et al. 2010).

Failed dopaminergic neurotransmission results in dysregulation of dopamine-modulated corticobasal ganglia-thalamocortical neurocircuits including frontal, striatal, and limbic regions. Based on what is known about the physiological brain function of dopamine, ADHD may in part result from disturbances in the dopaminergic system in cortical brain structures such as the prefrontal cortex and subcortical areas such as the nucleus accumbens and the striatum. However, there is an ongoing debate on whether in ADHD there is a hyper- or a hypodopaminergic dysfunction.

Amphetamine, methylphenidate, and atomoxetine are thought to exert their effect on ADHD via the inhibition of the DAT and/or NET although the brain regions involved in their cognition-enhancing and therapeutic effects are

poorly understood. Indirect and/or correlative evidence suggests that the cognition-enhancing and therapeutic effects of psychostimulants may involve actions directly within the prefrontal cortex or extended frontostriatal circuitry (Spencer et al. 2012). The DAT and NET are presynaptically located proteins that play a key role in the regulation of dopamine and noradrenaline concentrations by removing dopamine and noradrenaline from the synaptic cleft and returning them to the presynaptic neurons (Giros et al. 1996).

Using PET imaging, it was shown that **methylphenidate occupies** the **DAT** in the striatum (Volkow et al. 1999). More recently, PET studies in healthy individuals have demonstrated that methylphenidate also occupies the **NET** in the thalamus and other noradrenaline-rich regions with a higher affinity than for the DAT (Hannestad et al. 2010). When using [^{11}C]cocaine-PET to measure DAT occupancy, it was demonstrated that clinical doses of orally administered methylphenidate caused more than 50 % blockade of the DAT sites in the striatum of normal subjects, which is comparable to the effect of the powerful psychostimulant drug cocaine which also acts as an inhibitor of dopamine uptake in the brain (Swanson and Volkow 2003; Volkow et al 1999). However, unlike cocaine, orally administered methylphenidate does not cause marked euphoria and is unlikely to lead to substance dependence. As suggested by Swanson and Volkow (2003), this may be due to the slow onset of the effect of methylphenidate on the DAT, while that of cocaine is very fast.

The increase in extracellular striatal dopamine and noradrenaline concentrations following amphetamine and methylphenidate administrations in rats (Kuczenski and Segal 1997) was also indirectly demonstrated in healthy humans using PET imaging (Riccardi et al. 2006; Volkow et al. 2001). For example, when using PET with [^{11}C] raclopride, a dopamine D2 receptor radioligand which competes with endogenous dopamine for binding to the receptor, it was indirectly shown that therapeutic doses of oral methylphenidate (0.8 ± 0.11 mg/kg) **increased extracellular dopamine**, as assessed by a reduction in B_{max}/K_d, measures of dopamine D2 receptor availability (Volkow et al. 2001). Since dopamine also decreases background firing rates (tonic function) and increases signal-to-noise in target neurons, Volkow et al. (2001) claimed that the amplification by methylphenidate of weak dopamine signals in subjects with ADHD enhances task-specific signalling, thereby improving attention and decreasing distractibility.

In a subsequent PET study by Volkow et al. (2004), it was demonstrated in healthy subjects that clinical doses of methylphenidate (20 mg) when coupled with a mathematical task, significantly increased extracellular dopamine, but this was not observed when coupled with the neutral task. The significant association between methylphenidate-induced dopamine increases, and the interest and motivation for the task confirmed the prediction that methylphenidate enhances the saliency of an event by increasing dopamine. The authors concluded that the enhanced interest for the task could increase attention and improve performance and could be one of the mechanisms underlying methylphenidate's therapeutic effects.

This effect of methylphenidate on the tonic mode of dopamine release illustrates an important **difference between methylphenidate and amphetamine**. As an inhibitor of dopamine reuptake with little ability to displace the vesicle stores of dopamine, methylphenidate enhances dopamine concentrations most effectively only in those brain regions where dopamine is being released, e.g., during a difficult mental task. In this respect, methylphenidate may differ qualitatively from amphetamine, which causes dopamine release irrespective of the underlying activity state of the dopaminergic neurons.

8.4 Clinical Psychopharmacology of Drugs Used in the Treatment of ADHD

Drugs are discussed here only in connection with the therapy of ADHD. The three target symptoms (attention deficit, motor hyperactivity, impulsivity) are significantly improved by treatment with these agents. Rapid, impulsive movements are reduced as well as disruptive behavior in school and at

home. Individual functions such as visuo-motor coordination and memory retention are improved, although a general enhancement of cognitive performance cannot be expected. Table 8.4 summarizes drugs used in the treatment of ADHD, their FDA approval status, some of their pharmacokinetic properties, and their therapeutic dosages.

8.4.1 Amphetamine and Methylphenidate

The **amphetamine** molecule has one asymmetric C-atom (Fig. 8.1) and therefore occurs as **two stereoisomers** with differing physiological effects, i.e., (R)-amphetamine (synonym levo- or L-amphetamine) and (S)-amphetamine (synonym dextro- or D-amphetamine). A racemic mixture is denoted by the prefix (R,S)- or DL-, indicating an equal (1:1) mixture of both isomers. Racemic amphetamine was introduced to the market in 1935 with the trade name "Benzedrine®" as a treatment for narcolepsy, mild depression, post-encephalitic parkinsonism, and a variety of other disorders (see Heal et al. 2013). Bradley (1937) was the first to report the beneficial effects of racemic amphetamine in treating 30 children who would now be diagnosed as suffering from ADHD. Fourteen of 30 treated subjects with behavior problems showed a remarkable improvement in school performance, behavior, and demeanor during 1 week of treatment.

Currently available **amphetamine products** for the treatment of ADHD are either a combination of (R)-and (S)-amphetamine (consists of a 3:1 enantiomeric mixture (R)-amphetamine/(S)-amphetamine salts) or (R)-amphetamine alone (Table 8.4). Clinical trials comparing (R)-and (S)-amphetamine in treating ADHD children have shown that (R)-amphetamine is very effective although, but, as expected, not as effective as the pharmacologically more potent (S)-isomer (Arnold 2000). In preclinical studies, (S)-amphetamine has ten times the amphetamine potency of the corresponding R-isomers (Taylor and Snyder 1974).

The **methylphenidate** molecule has **two asymmetric C-atoms** (Fig. 8.1), and thus occurs as four different stereoisomers with differing physiological effects, but only D-*threo-(2R, 2'R)*-methylphenidate and L-*threo*-(2S, 2'S)-methylphenidate are included in the currently available methylphenidate formulations. The *erythro* forms of methylphenidate were removed in the 1950s because they caused elevated blood pressure (Swanson and Volkow 2001). Available data suggest that many of the behavioral effects of methylphenidate are conferred by D-*threo*-methylphenidate, although most methylphenidate formulations are composed of a racemic mixture of D-*threo*-methylphenidate and L-*threo*-methylphenidate (Markowitz et al. 2003; Quinn et al. 2004).

A number of **long-acting formulations** of amphetamine and methylphenidate have been developed with the goal of providing once-daily dosing, employing various means to extend duration of action (Table 8.4), including a transdermal delivery system, an osmotic-release oral system (OROS®), capsules with a mixture of immediate- and delayed-release beads, and prodrug technology (Ermer et al. 2011). The administration of a single-daily dose can improve compliance. The disadvantages of long-acting preparations in comparison with conventional preparations include the greater difficulties associated with a finer adjustment of the dosage, and thus the reduced opportunity for an individual adjustment according to daily requirements.

The methylphenidate transdermal system delivers the active agent into the systemic circulation directly through the skin, reducing first-pass metabolism by the liver. The **osmotic-release oral system** has a two-phase release dynamic and delivers methylphenidate at a controlled rate via the use of osmotic pressure: 30 % of the active agent is released immediately and 70 % is delayed. The uniquely designed capsules consist of an external, enteric-soluble film from which methylphenidate is rapidly released, and an inner core consisting of a hydrocolloid polymer matrix from which methylphenidate is released slowly

Table 8.4 Summary of psychostimulant and non-psychostimulant drugs for the treatment of attention-deficit/hyperactivity disorder in children and adolescents

Medication	t_{max} (h)	$t_{1/2}$/duration of action (h)	Therapeutic dose	US Food and Drug Administration (FDA) approval status		
				Age (years)	Therapy	Maximum dose
Amphetamine, short acting						
Mixed (R,S)-amphetamine salts	3	Mean 9.8/6	2.5–20 mg q.d. to b.i.d.	Children ≥ 3	Monotherapy	Less than 1 mg/kg or 40 mg
(R)-Amphetamine (dextra-amphetamine)	3	Mean 11.5/4	2.5–40 mg q.d. to b.i.d.	Children ≥ 3 and 6, respectively	Monotherapy	40 mg q.d.
Amphetamine, long acting						
Lisdexamfetamine	3–6	Mean 1/10	20–70 mg q.d.	Children ≥ 6	Monotherapy	Less than 1 or 70 mg
Mixed (R,S)-amphetamine salts	~7	Mean 11.5/10	10–30 mg q.d.	Children 6–12	Monotherapy	Less than 1 mg/kg or 30 mg
(R)-Amphetamine (dextra-amphetamine)	~8	~12/10	5 mg q.d. to 20 mg b.i.d.	Children ≥ 6	Monotherapy	Less than 1 mg/kg or 40 mg
Atomoxetine	1–2	~5/24	0.5–1.8 mg/kg daily in 2 divided doses (max. 100 mg/day)	Children and adolescents (≥ 6)	Monotherapy	Less than 1.4 mg/kg or 100 mg
Clonidine, immediate release	~2	Not reported/mean 12.6	0.05 mg at bedtime to 0.3 mg/day (in 4 divided doses)			
Clonidine, extended release	~6.5	Not reported/mean 12.6	0.1–0.4 mg/day b.i.d.	Children and adolescents (6–17)	Mono- and adjunctive therapy	0.2 mg b.i.d.
Guanfacine, extended release	~5	~18/8–12	0.5 mg at bedtime	Children and adolescents (6–17)	Mono- and adjunctive therapy	4 mg q.d.
Methylphenidate, short acting						
Methylphenidate	1–2	Mean 2/4	2.5–30 mg/day or 0.15–1.0 mg/kg daily q.d. to t.i.d.	Children ≥ 6	Monotherapy	Less than 2 mg/kg or 60 mg q.d.

(continued)

Table 8.4 (continued)

Medication	t_{max} (h)	$t_{1/2}$/duration of action (h)	Therapeutic dose	US Food and Drug Administration (FDA) approval status		
				Age (years)	Therapy	Maximum dose
D-Methylphenidate	1–2	1.5–3/4	2.5–20 mg b.i.d.	Children and adolescents (6–17)	Monotherapy	Less than 1 mg/kg or 20 mg q.d.
Methylphenidate, long acting						
Methylphenidate, sustained release	Mean 4.7	Not reported/up to 8	10–60 mg q.d.	Children ≥ 6	Monotherapy	60 mg q.d.
Methylphenidate, extended release	1–2 and 5–6[a]	Mean 3.5/7–8	10–60 mg q.d.	Children ≥ 6	Monotherapy	Less than 2 mg/kg or 60 mg q.d.
Methylphenidate, controlled release	1–2 and 4–6[a]	Mean 6.8/8–9	20–60 mg q.d.	Children ≥ 6	Monotherapy	Less than 2 mg/kg or 60 mg q.d.
Methylphenidate, long acting	1–2 and 5–6[a]	Mean 3.5/7–9	20–60 mg q.d.	Children ≥ 6	Monotherapy	60 mg q.d.
Methylphenidate, OROS	Mean 6–10	Mean 3.5/up to 12	18–72 mg q.d.	Children ≥ 6	Monotherapy	Less than 2 mg/kg or 72 mg q.d.
Methylphenidate, transdermal patch	2–4	4–5[b]/12	10–30 mg q.d.	Children ≥ 6	Monotherapy	Less than 1 mg/kg or 30 mg q.d.
D-Methylphenidate, extended release	1–2 and 5–7[a]	2–4.5/up to 12	5–30 mg q.d.	Children ≥ 6	Monotherapy	Less than 1 mg/kg or 30 mg q.d.

From Huang and Tsai (2011), Vaughan and Kratochvil (2012)
The following pharmacokinetic data are based upon the information included in the Prescribing Information
b.i.d. twice daily, *OROS* osmotic-release oral system, *q.d.* once a day, t.i.d. three times a day, t_{max} time required to reach peak plasma concentration (c_{max}), $t_{1/2}$ elimination half-life
[a]Biphasic drug release
[b]After removal the patch

and continuously, providing effective treatment for up to 12 h.

A number of long-acting formulations of amphetamine and methylphenidate use **bead technology** to modify the release of the active drug. This delivery system also has a two-phase release dynamics, but is achieved through the combination of two different pharmaceutical forms of methylphenidate. The rapid release component consists of spheres with an enteric-soluble coating, the delayed release form of spheres with an enteric coating.

A long-acting **amphetamine prodrug formulation** is lisdexamfetamine, which comprises the naturally occurring amino acid (S)-lysine, covalently bound to (R)-amphetamine via an amide linking group. The metabolic route of lisdexamfetamine is unusual because after absorption into the bloodstream, it is metabolized by red blood cells to yield the active agent, (S)-amphetamine, and (R)-lysine by rate-limited, enzymatic hydrolysis (Pennick 2010). The drug's unavailability of the amphetamine moiety, except if taken orally, prevents the user from obtaining the drug's effects if it is snorted or injected intravenously, which accounts for its decreased risk of abuse or overdose. Furthermore, its delayed onset of action and the long duration of effect are believed to make it safer to use in a college-aged or young adults.

Indications

The US FDA-approved areas of application are the following:

- Treatment of ADHD in pediatric patients (aged 3–17 years depending on the formulation, see Table 8.4)
- Narcolepsy in adults

Methylphenidate is also used as an agent of first choice in the treatment of aggression in youth comorbid with ADHD (see Chap. 9). In addition, methylphenidate is applied in the treatment of aggressive behavior in children with autism (see Chap. 9) as well as in children with ASDs and comorbid hyperactivity (see Chap. 13). Finally, methylphenidate is used in the pharmacotherapy of giggle incontinence based on the overlap between giggle incontinence and cataplexy/narcolepsy (see Chap. 19).

Clinical Effects and Efficacy

Immediate-release formulations of amphetamine and methylphenidate are rapidly and almost completely resorbed following oral administration: The onset occurs within about 30 min after administration. Excretion of both agents is primarily renal. The rapid metabolic de-esterification of methylphenidate limits its elimination half-life ($t_{1/2}$) to only 2–3 h following oral administration of immediate-release products (see Table 8.4) and results in a low bioavailability. In addition, methylphenidate products show a great interindividual variability in plasma concentrations and response. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved in the formation of 4-hydroxy amphetamine and noradrenaline that are both active.

The **efficacy** of amphetamine and methylphenidate products in the treatment of ADHD has been **confirmed** by numerous double-blind, randomized, placebo-controlled clinical studies (e.g., AACAP Official Action 2002; Ahmann et al. 2001; MTA Cooperation Group 1999, 2004; Pliszka et al. 2000; Spencer et al. 1996b; Steer et al. 2012). Methylphenidate is the best-investigated medication employed in child and adolescent psychiatry. In 2000, already more than 40 review articles and meta-analyses had been published, and more than 5,000 ADHD patients had participated in methylphenidate efficacy studies. More than ten meta-analyses and systematic reviews comparing different formulations of long-acting methylphenidate preparations have been published between 2000 and 2012.

The largest controlled therapeutic study to date has been the National Institute of Mental Health (NIMH) Collaborative Multimodal Treatment Study of Children with ADHD (**MTA-study**), an American study of 579 children with ADHD (MTA Cooperation Group 1999, 2004). Methylphenidate therapy (mean dose: 32 mg/day) combined with comprehensive counseling showed the greatest efficacy for the treatment of the core symptoms (attention deficit, hyperactivity, and impulsivity). Where there were comorbid disorders, behavioral therapeutic measures also played an important role. A follow-up study reporting

key outcomes at 6 and 8 years, demonstrated that, despite overall maintenance of improvement in functioning relative to baseline (pretreatment), the MTA group did much worse than the non-ADHD classmate sample recruited at 24 months (Molina et al. 2009). As the authors suggested, these findings provide evidence that the differential effects of ADHD treatments, evident when the interventions were delivered, attenuated when the intensity of treatment was relaxed.

The **effect sizes** of **methylphenidate** on behavioral measures (change in hyperactivity and impulsivity) **ranged between 0.6 and 0.8** (Pliszka et al. 2000; Spencer et al. 1996b; Tucha et al. 2006; Van der Oord et al. 2008). A systematic review of published and unpublished data on the use of long-acting medications in ADHD and hyperkinetic disorder (Banaschewski et al. 2006) reported that mean effect sizes of long-acting stimulants are strikingly similar and comparable to the figures reported across raters for this class of medication in a meta-analysis; no significant difference in effect size was observed for immediate-release stimulants compared with long-acting psychostimulants (Faraone et al. 2006). Mean effect sizes of immediate-release methylphenidate on core symptoms of ADHD in children from randomized, double-blind, placebo-controlled trials are between 0.8 and 1 (Banaschewski et al. 2006); mean effect sizes vary among symptom domains, with the strongest effects of stimulant medication on measures of attention, distractibility, and impulsivity and observable social and classroom behavior.

It is generally accepted that the efficacy of amphetamine products is the same as that of methylphenidate (Heal et al. 2013). Although head-to-head trials are needed to make definitive statements about efficacy differences, a meta-analysis by Faraone and Buitelaar (2010) shows moderately greater efficacy for amphetamine medications. This is in line with preclinical findings discussed above showing an additional effect of amphetamine on dopamine release in the rat striatum.

As discussed in detail in Chap. 13, there is strong evidence supporting the use of methylphenidate in children with **ASDs** and comorbid hyperactivity, but less so for inattentiveness. One sufficiently powered double-blind placebo-controlled crossover trial, conducted by the RUPP Autism Network, studied methylphenidate in children with pervasive developmental disorder and moderate to severe hyperactivity (Research Units on Pediatric Psychopharmacology Autism Network 2005). During the crossover phase, participants received three different doses of methylphenidate and placebo for 1 week, each in random order. The maximum daily dose was up to 1.5 mg/kg divided into three separate doses. Methylphenidate, especially at a medium dose of smaller than 1 mg/kg daily, was consistently superior to placebo in reducing ADHD symptoms as measured by the teacher-rated ABC hyperactivity subscale with small to medium effect sizes. Forty-nine percent of the participants were classified as responders ("much improved" or "very much improved" on the CGI-improvement scale). A recent meta-analysis has reported an effect size of 0.66 on hyperactivity in children and adolescents with pervasive developmental disorder based on four randomized controlled trials with methylphenidate (Reichow et al. 2013). In addition, two double-blind, randomized studies demonstrated the efficacy of methylphenidate in the treatment of aggressive behavior in children with autism (review: Parikh et al. 2008). Psychostimulants are possibly also effective in the treatment of conduct disorders, but there have been only a few investigations, and they have yielded somewhat contradictory results (reviewed: Gerardin et al. 2002; Ipser and Stein 2007).

Recommended Dosages

Pharmacotherapy using amphetamine and methylphenidate products should be individualized for each patient, assessing the dose response and duration of action as well as tolerability when initiating and optimizing treatment (Vaughan and Kratochvil 2012). Dosages of amphetamine and methylphenidate products usually administered to children and adolescents with ADHD are summarized in Table 8.4. Amphetamine and methylphenidate should be gradually introduced. The appropriate dosages of amphetamine and methyl-

phenidate products vary according to their pharmaceutical form. Higher daily dosages than dosages shown in Table 8.4 can be employed in individual therapeutic trials, but this should be subject to strict monitoring (pulse, blood pressure, and other adverse drug reactions, ADRs).

Symptoms of overdosage and intoxication with methylphenidate are the consequences of sympathomimetic overstimulation and can be expressed as tachycardia, arrhythmias, hypertonia, mydriasis, vomiting, agitation, tremor, hyperreflexia, hyperpyrexia, and seizures. There is no specific antidote. Stimuli that might exacerbate this overstimulation must be avoided. Symptomatic therapy, including intensive care where appropriate, is based upon the severity of intoxication. Agitation and seizures, for example, are to be treated with benzodiazepines; hyperpyrexia must be reduced by external cooling.

Adverse Drug Reactions (ADRs)

When employed as recommended, amphetamine and methylphenidate have shown good safety profiles and only minor ADRs. Any ADRs that occur are generally dose-dependent. There is no evidence that the legal application of psychostimulants in recommended fashion has significant deleterious consequences (National Institutes of Health Consensus Development Conference Statement 2000).

Although head-to-head trials are needed to make definitive statements about differences in the ADR profile of amphetamine and methylphenidate products, it seems that they have a similar profile (Table 8.5). Common ADRs include reduced appetite, weight loss, headache, stomach upset, increases in heart rate and blood pressure, irritability, and delayed sleep onset if given late in the day.

A less common ADR is dysphoria, which can occur at the beginning of therapy and is more marked with amphetamine than with methylphenidate. Dysphoria can indicate overdosage, especially if the development of a primary depression can be excluded. Overdosage can also cause impaired cognitive performance as well as triggering reversible psychotic

Table 8.5 Adverse drug reactions (ADRs) and pharmacotherapy of attention-deficit/hyperactivity disorder

Drugs	Common ADRs
Amphetamine products	**US FDA black box warning**: History of substance abuse/dependence, cardiac history, psychosis
Short acting	Appetite suppression, weight loss, stomach aches, headaches, irritability, possible growth inhibition, exacerbation of psychosis and tics, and possible increase in blood pressure and pulse
Long acting	Insomnia, decreased appetite, irritability, dizziness, headaches, and weight loss
Atomoxetine	**US FDA black box warning**: suicidality
	Headache, nausea, abdominal pain, decreased appetite, moodiness, and somnolence
Clonidine	
Immediate release	Sedation, dry mouth, constipation, nausea, and dizziness
Extended release	Somnolence, sedation, fatigue, nightmares, constipation, irritability, and throat pain
Guanfacine, extended release	Somnolence, headache, sedation, upper abdominal pain, and fatigue
Methylphenidate products	**US FDA black box warning**: History of substance abuse/dependence, cardiac history, psychosis
	ADRs of different methylphenidate formulations are similar, including decreased appetite, stomach upset, insomnia or sleep disturbance, dizziness, irritability, nausea, vomiting, tachycardia, increased blood pressure, moodiness, and weight loss (higher dose)

According to Huang and Tsai (2011) and Wigal et al. (2006)

symptoms. Psychotic reactions (hallucinations, autistic behavior, mutism, social withdrawal) do normally not occur at therapeutic doses and are only seen at recommended dosages in individual cases, for example, in preschool children. A systematic reanalysis of randomized controlled trials using psychostimulant in ADHD by the US FDA revealed that psychotic or manic-like reactions occurred only rarely (in about one of 400 treated patients), and in the majority of cases (55 of 60), the symptoms resolved within two days (Gelperin and Phelan 2006; Ross 2006).

Despite many decades of clinical use, psychostimulant drugs have been controversial because of concerns that they might cause tics, kindle substance abuse, delay growth, and be neurotoxic to brain dopamine system (Gerlach et al. 2013; Huang and Tsai 2011; Volkow and Insel 2003). In addition, it has been discussed that they increase the cardiovascular risk (Shaw 2011) and the risk of genetic damage in patients with ADHD (Stopper et al. 2008).

In the absence of preexisting cardiovascular disease, **cardiovascular effects** of psychostimulant treatment in pediatric ADHD consist of minimal increases in blood pressure (≤5 mmHg) and pulse (≤10 beats/min) without changes in electrocardiographic parameters (Hammerness et al. 2011). Analyses conducted with data from the MTA trial that was followed by naturalistic treatment for a cumulative 10-year period of evaluation, demonstrated that treatment with psychostimulants did not increase the risk for prehypertension or hypertension (Vitiello et al. 2012). Although psychostimulants had a persistent adrenergic effect on heart rate during treatment (Vitiello et al. 2012), a prospective 33-year follow-up of 135 boys of white ethnicity with ADHD in childhood and without conduct disorder demonstrated that psychostimulant treatment did not predict cardiac illness (Olazagasti et al. 2013). In addition, a large cohort study with 241,417 incident users (primary cohort) showed that the rate of cardiovascular events in exposed children was very low and in general not higher than that in unexposed control subjects (Schelleman et al. 2011). Finally, a retrospective cohort with 1,200,438 children and young adults showed no evidence that the current use of ADHD drugs could be associated with an increased risk of serious cardiovascular events such as sudden cardiac death, acute myocardial infarction, and stroke (Cooper et al. 2011).

Concerns about the cardiovascular safety of psychostimulant medications have led to specific recommendations for pretreatment evaluation, treatment selection, and monitoring (Cortese et al. 2013; Hammerness et al. 2011).

The data from clinical studies regarding **decreases in growth velocity** during therapy with psychostimulants is currently contradictory: some studies indeed identified slower growth rates in children with ADHD, but there was no difference between treated and untreated patients, and the rates had, in any case, normalized during late adolescence (Greenhill et al. 1999; Spencer et al. 1996a). Significant effects on height and weight were seen with psychostimulant treatment in a meta-analyses of 22 studies with more weight than height deficits (Faraone et al. 2008). As suggested by Faraone et al. (2008), these growth effects may be dose-related but were not unique to either methylphenidate or amphetamine. It was hypothesized that, in general, children with ADHD may display different growth trajectories than their peers without the disorder (Vaughan and Kratochvil 2012). The study by Sund and Zeiner (2002) found that neither age- nor dose-dependent effects upon growth were evident, although weight loss occurred in some patients, more frequently during treatment with amphetamine than with methylphenidate. With respect to bone density, a sensitive parameter of bone development, the values for children who had been treated for 1–2 years were not different from those of a control group (Lahat et al. 2000). More recent studies have detected an effect upon physical development, but it was generally not clinically

significant (Spencer et al. 2006). A final judgment is not yet possible.

Because psychostimulants have been shown to affect growth, evidence and expert-based guidance concerning the management of ADRs with medications for ADHD specifically addresses monitoring height and weight, including serial plotting of growth parameters (AACAP Official Action 2007; Cortese et al. 2013).

Increased **susceptibility for convulsions** during therapy with psychostimulants has been repeatedly discussed, but the data from clinical studies actually suggests a positive influence of methylphenidate upon the EEG (Kerdar et al. 2007). Despite a warning in the Summary of Product Characteristics (SPCs, issues concerning the preparation of SPCs, and their limitations were discussed in detail in Sect. 4.7) advising against the use of methylphenidate in the face of seizures, the evidence to support this warning is very limited. In ADHD patients without epilepsy, the incidence of seizures does not differ among methylphenidate or placebo (Wernicke et al. 2007). In patients with well-controlled epilepsy and even with infrequent seizures, methylphenidate is effective and associated with a low seizure risk (Cortese et al. 2013; Gucuyener et al. 2003).

As discussed above, amphetamine and methylphenidate are indirect dopamine agonists. It has been suggested that increased dopamine activity in the basal ganglia underlies the pathogenesis of tics (Albin 2006). Therefore, drugs used in the treatment of ADHD might, from a theoretical standpoint, **exacerbate tic severity**. However, it has been shown in 34 prepubertal children with ADHD and chronic multiple tic disorder (who had participated in an 8-week, double-blind, placebo-controlled methylphenidate evaluation and were evaluated at 6-month intervals for 2 years as part of a prospective, nonblind, follow-up study) that long-term treatment with methylphenidate seems to be safe and effective for the management of ADHD behaviors in many (but not necessarily all) children with mild to moderate tic disorder (Gadow et al. 1999). This was most impressively demonstrated in a study, which was not supported by the pharmaceutical industry and used double-blind, placebo-controlled methods to examine the effect of methylphenidate on tics (The Tourette's Syndrome Study Group 2002). One hundred and thirty-six children with ADHD and a chronic tic disorder were randomly assigned to 16-week treatment with methylphenidate, clonidine, clonidine and methylphenidate, or placebo. Tic symptoms increased slightly (not statistically significant) in all four groups during the first 4 weeks of treatment and decreased again towards the end of the observation period; there were no differences between the groups, so that it could be concluded that the initial minor increase in tics was not attributable to the action of methylphenidate.

A meta-analysis including nine double-blind, randomized, placebo-controlled trials examining the efficacy of medications in the treatment of ADHD in children with comorbid tics (total: 477 subjects) concluded that there is **no evidence** that **methylphenidate worsens tic severity** in the short-term and supra-therapeutic doses of amphetamine worsen tics (Bloch et al. 2009). As concluded in a recent Cochrane group systematic review (Pringsheim and Steeves 2011), while psychostimulants have not been shown to worsen tics significantly in most people with tic disorders, they may exacerbate tics in individual cases. Initial evidence also shows that psychostimulants do not contribute to a new onset of tics (Roessner et al. 2006).

Therefore, although the SPCs of several ADHD medications used to include tics as a contraindication for ADHD drug use, **tics** are **no** longer a **contraindication** for the use of ADHD drugs in the EU, but caution is recommended (European Medicines Agency 2010). A confounding factor is that the incidence of tic disorders increases across the developmental phase during which psychostimulant therapy of concurrent ADHD is frequently initiated, the result of which is an apparent, but deceptive connection with the psychostimulant medication. Furthermore, tic disorders exhibit a fluctuating, phasic course. Trial

medication withdrawals and longer observation periods are helpful for drawing appropriate diagnostic conclusions.

Despite positive results from clinical studies, the employment of psychostimulants in patients also presenting epilepsy or a tic disorder should be accompanied by a particularly close observation of the symptom course and by counseling of the patients and their parents (Cortese et al. 2013).

As prescribing of psychostimulants has markedly increased in recent years, fears have been expressed that psychostimulants are improperly used and may even **trigger substance dependence** when employed as recommended. In the literature, the relationship between the use of ADHD drugs and the risk of future substance use disorders is sometimes treated alongside, and sometimes confused, with the risk of illicit abuse and misuse of ADHD drugs. We try to keep these concepts separate and provide the following **definitions** in order to guide the reader:

1. **Substance Use Disorders**: The International Classification of Diseases, 10th revision (ICD-10), refers to a wide variety of disorders that differ in severity (from uncomplicated intoxication and harmful use to obvious psychotic disorders and dementia), but are all attributable to the use of one or more psychoactive substances which may or may not have been medically prescribed (World Health Organization 1996). Disorders that arise directly from the misuse of these substances are classified by ICD-10 as follows: acute intoxication, withdrawal syndrome, substance-induced psychotic disorder, harmful use, and the dependence syndrome (see Chap. 15 for details). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), combines substance abuse and substance dependence into one disorder: substance use disorders (American Psychiatric Association 2013). Substance abuse refers to the maladaptive pattern of nonmedical use of substances leading to functional impairment and/or risks over the past 12 months, while substance dependence implies the presence of drug tolerance, preoccupation with drug seeking and drug taking, and continued use despite knowledge of risks and despite repeated attempts to stop.
2. **Misuse**: The use of ADHD drugs for purposes not consistent with legal or medical guidelines (e.g., the use of psychostimulants to achieve a narcotic effect or for other reasons, such as to stay awake or aid weight loss); the use of drug dosages different than those prescribed is also referred to as misuse.

We consider here only the evidence on the relationship between the use of amphetamine and methylphenidate in the treatment of ADHD and risk of future substance use disorders. The substance use disorders arising from illicit abuse and misuse of ADHD drugs as well as other psychostimulants (such as cocaine and methamphetamine) which were traditionally abused if taken by a non-oral route are discussed in Chap. 15.

According to ICD-10, the characteristic features of the **dependence syndrome** (F1X.2) are a strong desire or compulsion-like need to consume the drug ("craving"); reduced control of the initiation, termination, and level of drug consumption; a physical withdrawal syndrome; evidence of tolerance; progressive neglect of interests in favor of drug use; and persistent consumption despite the damaging physical, psychological, and social consequences, whereby these features can be manifested with differing degrees of intensity during the use of various dependence-inducing psychopharmacological agents, and, indeed, may not necessarily occur with particular agents. Tolerance enables a compensatory physiological response to the effects of the pharmacological agent, so that they are not as marked following repeated administration, and elevation of dosage is required to reproduce its original efficacy.

When amphetamine and methylphenidate products are used as recommended, there is **no empiric evidence for** the development of a **dependence syndrome**. These medications can be discontinued without presentation of withdrawal symptoms and there is no evidence that long-term treatment is associated with an increase in dosage to achieve a therapeutic effect. Some

animal investigations of the dependence potential of methylphenidate supported these clinical findings: methylphenidate induced an aversion against a cocaine-associated environment in prepubertal rats (Andersen et al. 2002).

There is data from long-term clinical studies that therapy with methylphenidate during childhood reduces the danger of later addiction and substance abuse, including alcohol, nicotine, and drug abuse (Biederman et al. 1999; Huss et al. 2008; Wilens et al. 2003). Regarding the age at initiation of psychostimulant treatment, there is some evidence to suggest that early age at initiation of methylphenidate treatment in children with ADHD may have beneficial long-term effects on later substance abuse (Mannuzza et al. 2008). A 10-year prospective follow-up study in 140 boys with ADHD revealed no evidence that psychostimulant treatment increases or decreases the risk for subsequent substance use disorders in patients with ADHD when they reach young adulthood (Biederman et al. 2008b). Interestingly, children with ADHD are significantly more likely to develop substance use disorders in adolescence and adulthood than children without ADHD (Charach et al. 2011). A meta-analysis suggests a 1.5-fold increase to develop any substance use disorder and a nearly three times higher risk for nicotine dependence in ADHD samples (Lee et al. 2011).

A chief concern of medication with amphetamine and methylphenidate in the treatment of children and adolescents with ADHD has been the potential **adverse effects to the developing brain**, specifically as they relate to dopamine brain function, possibly eliciting a parkinsonian syndrome. These suggestions have unsettled not only physicians but also, in particular, ADHD patients and their families. The currently available data from long-term studies of psychostimulant therapy as well as more than 50 years of long-term clinical experience has provided **no indication** of negative long-term effects upon the developing brain (AACCP Official Action 2007; Gillberg et al. 1997; Vitiello 2001). A recent review on the potential neurotoxic effects of amphetamine and methylphenidate to the developing brain in animals supports the hypothesis that the administration of these agents to animals, using procedures simulating clinical treatment conditions, does not lead to long-term adverse effects with regard to development, neurobiological, or behavior as related to the central dopaminergic system in nonhuman primates (Gerlach et al. 2013).

Based on a case-control study on environmental and chemical exposures using a telephone survey, it was hypothesized that previous prolonged amphetamine exposure was a risk factor for Parkinson's disease; rates of exposure were also elevated in cohorts of individuals with amyotrophic lateral sclerosis and peripheral neuropathy compared to spouse or caregiver controls (Garwood et al. 2006). In most individuals, exposure occurred long before diagnosis (e.g., on average 27 years in Parkinson's disease). "Amphetamine" was defined in this study as amphetamine, methamphetamine, or dextroamphetamine. Prolonged exposure was defined as a maximum administration rate of twice a week for at least 3 months or weekly use for less than 1 year. Out of the 16 Parkinson's disease patients exposed to "amphetamine," seven subjects used "amphetamine" for a prescribed purpose, while nine used it recreationally (Christine et al. 2010). However, it is not specified to which "amphetamine" the subjects were previously exposed and what dose they used. One can, therefore, not conclude that amphetamine exposure is a risk factor for Parkinson's disease. Methamphetamine is an established dopaminergic neurotoxin whose behavioral effect mimics Parkinson's disease (Gerlach and Riederer 1996). Interestingly, Christine et al. (2010) found that age at diagnosis was younger in groups exposed to "amphetamine" (49.8 ± 8.3 vs. 53.1 ± 7.4 years).

A case-control study (88 patients with Parkinson's disease and 88 control subjects) was carried out to gain information about ADHD-like symptoms that may precede Parkinson's disease motor symptoms and the exposure of psychostimulants in childhood (Walitza et al. 2007a). This study did not find that Parkinson's disease patients had suffered from childhood ADHD and found no evidence that Parkinson's disease patients had been exposed to psychostimulants such as amphetamine and methylphenidate.

It has also been discussed that psychostimulants increase the **risk of genetic damage** in

ADHD patients. The study by El-Zein et al. (2005) found a threefold elevation of cytogenetic damage in 12 children with ADHD after 3 months of therapy with methylphenidate. Elevated mutation rate and cancer risk was discussed as a potential consequence. Methylphenidate had not been previously regarded as genotoxic (review: Stopper et al. 2008); nevertheless, this study naturally aroused a great deal of concern. Methodological limitations of the study were critically discussed in a letter to the editor (Preston et al. 2005). A subsequent investigation, involving a larger patient collective, did not find an increase in genomic damages following treatment with methylphenidate (Walitza et al. 2007b). Additionally, a recent study in which the sample was further enlarged, and both a control group and a group undergoing longer methylphenidate treatment (at least 12 months) were added, similarly found **no increase in genetic damage** (in the form of increased micronucleus frequencies; Walitza et al. 2010). In summary, the available data does not support a genotoxic effect of methylphenidate.

Drug Interactions

Interactions during amphetamine use are potentially more marked than with methylphenidate, particularly interactions with medications that act as inhibitors of the CYP2D6 enzyme (Markowitz and Patrick 2001). This particularly applies to selective serotonin reuptake inhibitors (SSRIs) as well as to nonselective monoamine oxidase (MAO) inhibitors. There have been few preclinical investigations of the potential interactions between psychostimulants and **SSRIs**. Combination therapy with SSRIs and methylphenidate in patients with comorbidities have been reported to be well tolerated (Markowitz and Patrick 2001), whereas there has been only a single case report of epileptic seizures developing during therapy with methylphenidate and sertraline. One or two patients showed symptoms of methylphenidate overdosage when used together with citalopram or fluoxetine. In combination with moclobemide, methylphenidate can cause hypertensive crises with headache, palpitations, nuchal rigidity, nausea, and vomiting (Baxter 2007).

Concomitant use of **amphetamine** and gastrointestinal **alkalinizing agents** such as sodium bicarbonate should be **avoided** because they increase absorption of amphetamine and thus increase blood levels of amphetamine. On the other hand, gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamate, ascorbic acid) lower absorption of amphetamine and thereby lower blood levels of amphetamine. Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts) increase the concentration of the ionized species of the amphetamine molecule, thereby lowering increasing urinary excretion.

Methylphenidate is not metabolized by cytochrome P450 (CYP) to a clinically relevant extent. Therefore, inducers or inhibitors of CYP enzymes are not expected to have any relevant impact on methylphenidate pharmacokinetics. It is not known how methylphenidate may affect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, especially those with narrow therapeutic window.

Methylphenidate can inhibit the catabolism of **antiepileptics** (including phenytoin, phenobarbital, primidone), **antipsychotics**, and **tricyclic antidepressants** (Grob and Coyle 1986). The concurrent administration of tricyclic antidepressants and methylphenidate enhances sympathomimetic effects and can lead to hypertension and increased cardiovascular ADRs, possibly requiring reduction of respective dosages. The use of carbamazepine is associated with the induction of CYP3A4, thereby possibly reducing the effect of methylphenidate (Behar et al. 1998; Schaller and Behar 1999).

ADHD patients with underlying cardiovascular and metabolic disorders should be treated in collaboration with the appropriate medical specialists, especially because of interactions between the various medications employed in the treatment of the different disorders.

Contraindications

Absolute contraindications include:

- Psychotic disorders (US FDA black box warning)
- History of substance abuse/dependence (US FDA black box warning)
- Hyperthyroidism
- Cardiac history (US FDA black box warning)

The age of patients encountered in child and adolescent psychiatry reduces the relevance of contraindications such as pregnancy and nursing, but these must nevertheless be considered in individual cases.

Caution is required but the evidence from studies finds several of these to be a consistent problem, including presence of seizures under control or presence of tics (either in patients or in relatives):

- In children under 6 years of age (Ghuman et al. 2001).
- If tic disorders in the child or its family are present (see ADRs).
- If the child suffers cerebral seizures (see ADRs).
- When those caring for the child or persons at his/her school or place of employment abuse drugs or are addicted to drugs.
- If insufficient monitoring of compliance and the course of therapy cannot be guaranteed.
- During extreme anxiety states.
- With cardiovascular abnormalities including hypertension.
- Profound developmental disturbances and intellectual disability.
- The employment of nonselective MAO inhibitors.

8.4.2 Atomoxetine

Indications

The US FDA-approved area of application is the monotherapy of ADHD in children from the age of 6 years and adolescents. Atomoxetine has been approved also in various European countries. Atomoxetine is usually the recommended second-line therapy for ADHD (see Chap. 12). In the case of patients with comorbid anxiety, comorbid tics, or comorbid substance abuse disorders, atomoxetine is considered the first-line therapy. It is not classified as a psychostimulant and is not a controlled substance in the USA. Neurochemical, preclinical, and early clinical studies predicted and supported a lack of abuse potential of atomoxetine, which is consistent with the clinical trial and postmarketing spontaneous event data in the past 10 years (Upadhyaya et al. 2013).

Clinical Effects and Efficacy

Atomoxetine is rapidly resorbed in adults and children; the maximal plasma concentration (c_{max}) is reached after 1–2 h. Metabolism is hepatic via CYP2D6, the activity of which in 7-year old children corresponds to that of adults (Witcher et al. 2003). The $t_{1/2}$ in normal metabolizers (extensive metabolizers, see Sect. 2.2.1) is about 5 h. In poor metabolizers with lower CYP2D6 activity, however, this can be considerably longer, leading to a fivefold increase in c_{max}.

The **clinical efficacy** of atomoxetine in the treatment of the core symptoms of ADHD in children and adolescents has been **demonstrated** in several randomized, placebo-controlled short-term studies, with 64.1 and 58.7 % of pediatric patients responding to atomoxetine (Spencer et al. 2002). The effect size (as assessed with the ADHD Rating Scale IV) of treatment was 0.5–0.7, whereby the attention disturbance as well as hyperactivity and impulsivity were significantly improved in comparison with placebo treatment (Kelsey et al. 2004; Michelson et al. 2002; Spencer et al. 2002). In these studies, atomoxetine (single-daily dose, mean daily dosage: 1.2 mg/kg body weight) exerted a positive effect throughout the day upon the core symptoms of ADHD and upon other tasks of daily living, as well as having an acceptable ADRs profile (Buitelaar et al. 2004; Spencer et al. 2002). The psychosocial situation of the child was also significantly improved by atomoxetine (Spencer et al. 2001). Kratochvil et al. (2006) reported, on the other hand, a dropout rate over 2 years of around 26 %, as efficacy was not perceived as being satisfactory. Tolerance was generally good,

as medication was discontinued in only 4 % of the children because of ADRs. In contrast to methylphenidate and amphetamine, full clinical efficacy was not evident immediately after the first dose, but developed gradually after repeated administration (between 3 and 7 weeks).

The **efficacy** of atomoxetine **compared with other ADHD medications** in the treatment of children and adolescents (aged 6–16 years) with ADHD has been evaluated in six randomized, open-label or double-blind, multicenter, fully published trials lasting 3–10 weeks (review: Garnock-Jones and Keating 2009). Active comparators included immediate-release methylphenidate, osmotically released methylphenidate, extended-release mixed amphetamine salts, and a standard current therapy (any combination of medicines excluding atomoxetine and/or behavioral counseling, or no treatment). It should be noted that two of these trials (comparing atomoxetine with extended-release mixed amphetamine salts and osmotically released methylphenidate) ran for only 3 weeks; to achieve full benefits of atomoxetine often takes several weeks potentially up to 8 weeks (see Garnock-Jones and Keating 2009). Atomoxetine did not differ from or was non-inferior to immediate-release methylphenidate with regard to the primary endpoints (change from baseline in ADHD Rating Scale total score) and response rate in children and adolescents with ADHD (see Garnock-Jones and Keating 2009). In a randomized, double-blind, multicenter, parallel group, forced-dose escalation laboratory school study in school-aged children (6–12 years old), atomoxetine was significantly less effective than extended-release mixed amphetamine salts in the change from baseline in the SKAMP behavioral rating scale (−013 vs. −0.56; Wigal et al. 2005).

In a large placebo-controlled, double-blind study including 635 children and adolescents with ADHD, the **response rates** for both **atomoxetine** (45 %) and **methylphenidate** (56 %) were markedly superior to placebo (24 %), but the response to osmotically released methylphenidate was superior to that for atomoxetine (Newcorn et al. 2008). Data from a subsequent crossover from methylphenidate (after 6 weeks of treatment) to atomoxetine provided evidence for differential response to the two treatments in approximately one-third of the patients. About one-half of these subjects responded robustly to both treatments. However, approximately two-thirds of the others responded preferentially to one treatment, divided approximately equally between methylphenidate and atomoxetine. Furthermore, a smaller but significant number (22 %) were nonresponders to both treatments. This finding suggests that subgroups of patients may benefit more from either a methylphenidate or atomoxetine treatment and may be attributable to differential sensitivity to the pharmacologic mechanisms, individual metabolic and pharmacokinetic responses, or other reasons (Newcorn et al. 2008).

As discussed in detail in Chap. 13, one small (Arnold et al. 2006) and one adequately powered randomized, double-blind trial examined the efficacy and safety of atomoxetine in children and adolescents with **ASDs** and concomitant ADHD symptoms (Harfterkamp et al. 2012). After 8 weeks there was a significantly greater improvement of symptoms on the investigator administered ADHD Rating Scale. However, there was no statistically significant difference in the number of participants who improved much or very much according to the CGI-improvement subscale between atomoxetine (20.9 %) and placebo (8.7 %). Atomoxetine improved both hyperactive-impulsive symptoms and inattentiveness with larger improvements on measures of hyperactivity-impulsivity (Harfterkamp et al. 2012). An open-label extension of this study (Harfterkamp et al. 2013) for a period of 20 weeks found that ADHD symptoms further decreased with continued treatment.

Recommended Dosages

Atomoxetine dosage for children and adolescents is weight-dependent. Atomoxetine is usually administered as a single morning dose, but can, if necessary, also be given in the evening or divided into two doses (see Table 8.4). The recommended starting dosage is 0.5 mg/kg body weight per day divided into two equal doses during the first week; the maintenance dosage of 1.2 mg/kg body

weight per day can be administered from the second week. A slow increase in dosage from the first to the third week (e.g., 10, 18, 25 mg) probably increases the number of treatment-emergent adverse events based on analyses of multisite studies. In patients weighing more than 50 kg, treatment can commence with 18 mg during the first week; those weighing more than 70 kg can start with 40 mg. Where tolerability to atomoxetine is a problem, slower increase in dosage is recommended. Administration of the capsule with food can increase tolerability to atomoxetine; daytime sleepiness can be addressed by administering the drug in the evening.

Symptoms of overdosage include somnolence, agitation, hyperactivity, gastrointestinal symptoms, and indications of sympathetic activation (mydriasis, tachycardia). QT interval prolongation is very rarely observed. Cases of fatal overdose with atomoxetine have been reported, but this has only occurred where patients had been treated with at least one other medication (US Prescribing Information, PI). Treatment of overdosage includes respiratory support, administration of activated charcoal during the first few hours, and symptomatic measures with regard to cardiac and vital functions.

Adverse Drug Reactions

This section and the following sections discuss primarily data from the US PI (issues concerning the preparation PI and their limitations were discussed in detail in Sect. 4.7.) and a recent review on atomoxetine (Garnock-Jones and Keating 2009). Atomoxetine was generally **well tolerated** in the long-term treatment of children and adolescents with ADHD. It appears better tolerated among extensive metabolizers than poor metabolizers. In poor metabolizers, ADRs such as reduced appetite, problems with falling and staying asleep, urinary incontinence, depressive mood, and tremor are considerably more frequent than in normal metabolizers (Garnock-Jones and Keating 2009).

ADRs (Table 8.5) are mostly temporary. In children and adolescents, sedation, abdominal pain, reduced appetite, nausea, and vomiting are the most frequent ADRs (≥ 5 %) and can lead to discontinuation of medication. Loss of appetite and the associated weight reduction appear to be dose-dependent. Following initial weight loss, patients treated with atomoxetine tend, however, to increase in weight 6–9 weeks later. Increased cardiac rate of up to 6 beats/min often occurs, as does a mild increase in blood pressure, but orthostatic hypotonia may also be experienced (Kratochvil et al. 2006; Spencer et al. 2001).

Dryness of mouth, insomnia, constipation, and mood swings infrequently can also be experienced. Attention should therefore be given to the possible development of depression. Rare instances of **jaundice** mean that attention should be paid to clinical symptoms of hepatic disease; at the first sign of such symptoms, treatment should be discontinued and not resumed (Bangs et al. 2008a).

There is a potential for **cardiovascular effects** with atomoxetine administration. Both the US and the UK PI include precautions regarding cardiovascular effects. The US PI carries also a FDA black box warning regarding suicidal ideation in children and adolescents: the frequency of suicidal ideation was greater among atomoxetine (0.37 %) than placebo (0 %) recipients in a meta-analysis including 14 pediatric clinical trials (Bangs et al. 2008b). However, no suicides occurred in the trials included in the meta-analysis by Bangs et al. (2008b). In addition, no difference was found between atomoxetine- and methylphenidate-treated patients.

Although a meta-analysis (Bloch et al. 2009) including nine double-blind, randomized, placebo-controlled trials, examining the efficacy of medications in the treatment of ADHD in children with comorbid tics, showed that atomoxetine significantly improves comorbid tics, some case reports have described an exacerbation of tics during atomoxetine treatment (summarized in Graham et al. 2011).

Drug Interactions

Concurrent administration of CYP2D6 inhibitors, including paroxetine, fluoxetine, levomepromazine, melperone, thioridazine, metoprolol, or propanolol, can require downward adjustment of the atomoxetine dosage, as levels of atomoxetine and its major metabolites may be increased three- to fourfold.

The cardiac effects (increased blood pressure and cardiac rate) of β-adrenoceptor antagonists (β-blockers, such as salbutamol) and α_2-adrenoceptor agonists are intensified or potentiated by concurrent atomoxetine. The simultaneous employment of medications that modulate noradrenaline metabolism may involve additive effects (e.g., imipramine, venlafaxine or phenylephrine, employed as a mucous membrane decongestant).

Contraindications

Contraindications and relative contraindications are:

- Patients with congenital or acquired long QT syndrome
- Family history of prolonged QT interval
- Cerebral seizures or a history of seizures
- Hepatic dysfunction

Caution should be exercised when prescribing atomoxetine to children and adolescents with serious cardiac abnormalities or other serious heart problems. Caution is required where atomoxetine is combined with other medications (see above). It cannot, for instance, be combined with nonselective MAO inhibitors (discontinuation of the one agent must have been completed at least 2 weeks prior to initiating therapy with the other).

8.4.3 Clonidine and Guanfacine

Clonidine and guanfacine were originally developed and clinically utilized as centrally active antihypertensive agents, which exert their antihypertensive activity by decreasing sympathetic tone in the CNS and reducing vascular resistance. Clonidine is a central α_2-adrenenoceptor agonist with a high affinity for all three α_2-receptor subtypes α_{2A}, α_{2B}, and α_{2C}; guanfacine is the most selective agonist for the α_{2A}-receptor subtype (Broese et al. 2012).

Indications

The areas of application in psychiatry are:

- Mono- and adjunctive therapy of ADHD in children and adolescents
- Aggression in children and adolescents with ADHD and autistic syndromes
- Tic disorders in children and adolescents
- Opioid and alcohol withdrawal symptoms in adults
- Insomnia

Several formulations are available. However, only the extended-release formulations of clonidine and guanfacine are US FDA-approved as monotherapy or as adjunctive therapy for the treatment in pediatric patients aged 6–17 years.

Clinical Effects and Efficacy

Although immediate-release formulations of clonidine and guanfacine have long been studied in the field of ADHD, their usage is limited due to pharmacokinetic profile with each formulation achieving c_{max} relatively quickly (approximately 1–2 h; Sallee et al. 2013). Rapid absorption of these agents leads to high-peak plasma concentrations that are associated with ADRs such as sedation, dry mouth, and hypotension. The limitations of immediate-release formulations would subsequently be addressed by their respective extended-release formulation.

To date, a number of studies have shown that clonidine and guanfacine improve the clinical course of ADHD in children and adolescents (Broese et al. 2012; Childress and Sallee 2012; Sallee et al. 2013). Data suggest that they may be helpful in treating symptoms of impulsivity, conduct disorder, and disorganization, while amphetamine and methylphenidate appear to have a greater overall effect (see Arnsten et al. (2007) for a review). However, there are only few double-blind, placebo-controlled studies so far. In 1999, Connor et al. published a meta-analysis in which they reviewed data from 11 small double-blind and open-label studies (less than 50 subjects) evaluating the effects of treatment with

immediate-release **clonidine** or the clonidine patch on ADHD symptoms alone or comorbid with developmental, conduct, or tic disorders. All in all, clonidine was **useful in reducing ADHD symptoms**, with a moderate mean effect size of 0.58. The efficacy of extended-release clonidine as monotherapy in the treatment of ADHD was evaluated by Jain et al. (2011) in an 8-week, randomized, placebo-controlled, parallel-group, forced-dose titration study. All subjects in the active treatment groups started with 0.1 mg/day administered at bedtime, and the dose was increased by 0.1 mg/week until the target dose (0.2 or 0.4 mg/day) was reached. The primary efficacy variable was the change from baseline to week 5 in the ADHD Rating Scale IV total score. A limitation of this fixed dose was the high discontinuation rate in all treatment cells, particularly that for the 0.4 mg/day assignment. Despite this fact, there was ample power to demonstrate a robust treatment effect (change from baseline of 15–16 points on ADHD Rating Scale IV total score) with effect sizes of 0.71 and 0.77 (0.2 and 0.4 mg/day, respectively).

There are few studies of immediate-release **guanfacine** in children and adolescents with ADHD showing significant improvements in parent and teacher ratings of ADHD symptoms, and all have small sample sizes (summarized in Sallee et al. 2013). Extended-release guanfacine **has proved efficacious** and safe for children and adolescents with ADHD in short-term (8 and 9 weeks), double-blind, multicenter trials (summarized in Huang and Tsai 2011; Sallee et al. 2013). Significant efficacy could be seen in all weight-adjusted dose groups (effect sizes ranged between 0.43 and 0.86), but the adolescent age subgroup did not exhibit a significant improvement in ADHD Rating Scale IV total score from baseline to end-point. In two recent studies, it was also shown that guanfacine is generally a safe drug, with only transient ADRs reported during up to 24 months of treatment with extended-release guanfacine, and effectiveness was maintained over the treatment period (see Huang and Tsai 2011). Effect sizes and response rates for extended-release guanfacine seemed dose-related (effect size 0.43–0.86, with response rates 43 and 62 % for doses of 3 and 4 mg once daily, respectively). In a double-blind, placebo-controlled study in 34 children suffering from ADHD and a coexisting tic disorder, treatment with an immediate-release formulation of guanfacine resulted in a mean improvement of 37 % on the teacher-rated ADHD scales, and the severity of tics decreased by 31 % (Scahill et al. 2001).

The efficacy and safety of clonidine and guanfacine have also been evaluated in **combination with psychostimulants**. In a 16-week, randomized, double-blind, placebo-controlled trial in 122 children with ADHD, immediate-release **clonidine** (maximal dose 0.6 mg/kg) yielded a clinical benefit but was overall inferior to immediate-release methylphenidate (mean dose 25.4 mg) as measured by the change from baseline to week 16 on the Conners Teachers Abbreviated Symptom Questionnaire (Palumbo et al. 2008). The use of extended-release clonidine added to psychostimulants in 198 children and adolescents with ADHD who were partial responders to psychostimulants was evaluated in a flexible-dose, double-blind, placebo-controlled, parallel-group, 8-week trial (Kollins et al. 2011). Eligible subjects were treated with a stable dose of methylphenidate or amphetamine for 4 weeks prior to screening and had an ADHD Rating Scale IV total score $\geq$26. During the first 5 weeks, clonidine was titrated in 0.1 mg weekly increments to an optimal dose based on improvements in the ADHD Rating Scale IV total score and tolerability of the drug. Significant improvement was seen at the beginning of week 2 in the clonidine group compared with the placebo group, and improvement continued through dose tapering at week 7. The reported effect size for extended-release clonidine as an adjunctive therapy with psychostimulants was 0.34.

A randomized, double-blind, placebo-controlled, dose-optimization study of extended-release **guanfacine** in children and adolescents (age 6–17 years) with suboptimal response to psychostimulants found significantly greater improvement from baseline ADHD Rating Scale IV total scores compared with placebo (Wilens et al. 2012). Subjects continued their stable morning psychostimulant dosing and were

randomized to receive optimized doses of extended-release guanfacine (1–4 mg/day) in the morning, in the evening, or placebo. The reported effect sizes were 0.38 and 0.45 for the groups that received guanfacine in the morning and evening, respectively.

Additional studies have demonstrated the **efficacy** and tolerability of clonidine and guanfacine in treating ADHD with **comorbid tic disorders** (see Chap. 27) and **aggressive behaviors** (see Chap. 9). For example, clonidine improved aggression in a small number of cases in children, particularly in those with ADHD. According to the meta-analysis of 11 double-blind, placebo-controlled, randomized studies, clonidine was effective in the treatment of aggressive behavior in youths (Connor et al. 1999). The medium effect sizes were ranging from 0.5 to 0.9 (Pappadopulos et al. 2006). In a double-blind, placebo-controlled trial in children aged 6–12 years with ADHD, the oppositional symptoms were significantly reduced within 9 weeks of treatment with guanfacine (Connor et al. 2010).

Recommended Dosages

Dosages of clonidine and guanfacine products usually administered to children and adolescents with ADHD are summarized in Table 8.4. According to the PI, extended-release **clonidine** dosing should start at 0.1 mg/day given at bedtime. Dosing can increase by 0.1 mg/day weekly until optimal response is achieved. Doses higher than 0.1 mg/day should be given twice a day with an equal or higher dose given at bedtime.

Guanfacine as an extended-release formulation should be taken once per day, either in the morning or evening, at approximately the same time each day. Begin at a dose of 1 mg/day and adjust in increments of no more than 1 mg/week. Maintain the dose within the range of 1–4 mg once daily, depending on clinical response and tolerability, for both monotherapy and adjunctive therapy to a psychostimulant. Clinically relevant improvements were observed beginning at doses in the range of 0.05–0.08 mg/kg once daily in both mono- and adjunctive therapy. Efficacy increased with increasing weight-adjusted dose. If well tolerated, doses up to 0.12 mg/kg once daily may provide additional benefit.

The approved dose ranges for the clinical use of each of the extended-release formulations (1–4 mg/day for guanfacine and 0.1–0.4 mg/day for clonidine) may, however, be insufficient to achieve efficacy in adolescent patients with ADHD (Sallee et al. 2013).

As is the case with other antihypertensives, sudden discontinuation of clonidine or guanfacine treatment is not recommended. Discontinuation should be accomplished by tapering. Because the absorption and pharmacokinetic characteristics of both clonidine and guanfacine immediate-release formulations differ from those of the extended-release formulations and because switch studies are lacking in the literature, there remains no guidance for dose substitution on a milligram-for-milligram basis (Sallee et al. 2013).

Adverse Drug Reactions

The safety of all the guanfacine and clonidine formulations is generally consistent with what might be expected of α_2-adrenoceptor agonists, and as centrally active antihypertensive agents, these drugs produce small but consistent decreases in pulse and blood pressure, both systolic and diastolic, within the dose range used for clinical effects in ADHD (Sallee et al. 2013). Blood pressure and pulse reductions are dose-dependent and across all studies, greatest effects are noted at higher doses and at c_{max}. Cardiovascular-related ADRs were uncommon for long-term use of extended-release guanfacine, although small reductions in mean blood pressure and pulse rate were evident at monthly visits (Biederman et al. 2008a; Sallee et al. 2009).

Both clonidine and guanfacine are associated with sedation, fatigue, and somnolence (Table 8.5). However, it could be shown that equivalent doses of guanfacine and clonidine led to less sedation in both aged monkeys and humans when receiving guanfacine (Broese et al. 2012). ADRs at higher doses include a dry mouth, sedation, constipation, orthostatic hypotension, and sexual dysfunction. However, the incidence

of these effects is low and most ADRs were reported as mild or moderate.

Drug Interactions

The past experience of clonidine used as an **adjunct to psychostimulants** has **raised questions regarding** the **cardiovascular safety** of this augmentation strategy (Sallee et al. 2013). Potentially harmful interactions of clonidine and psychostimulants were hypothesized as a result of reports of untoward cardiac events such as syncope and catastrophic events, including three case reports of sudden death in children. However, an FDA report documenting these cases concluded that there was no reason to postulate a drug interaction; any cardiovascular effects exerted by clonidine and methylphenidate were deemed independent of each other, and the causes of death in those cases were either determined to be unknown or not attributable to the medication (Popper 1995). In addition, recent studies have uniformly not supported the presence of harmful interactions (summarized in Sallee et al. 2013). Similarly, studies of guanfacine formulations have not found harmful interactions between guanfacine and psychostimulants (Spencer et al. 2009).

No drug interaction studies have been conducted with the extended-release formulation in children. The following interaction has been reported with other oral immediate-release formulations of clonidine: clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates, or other sedating drugs. Tricyclic antidepressants may reduce the hypotensive effect of clonidine. Caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers, and β-blockers) due to a potential for additive effects such as bradycardia and AV block. Caution is also warranted in patients receiving clonidine concomitantly with antihypertensive drugs.

Guanfacine does not significantly affect exposures of methylphenidate and lisdexamfetamine when coadministered. Guanfacine is primarily metabolized by CYP3A4, and its plasma concentrations can be affected significantly by CYP3A4 inhibitors or inducers. Coadministration of strong CYP3A4 inhibitors (e.g., ketoconazole) increases guanfacine exposure. The guanfacine dose should be limited to no more than 2 mg/day. When discontinuing CYP3A4 inhibitors, the guanfacine may have to be increased depending on patient tolerability. The maximum dose should not exceed 4 mg/day.

In contrast, coadministration of strong CYP3A4 inducers (e.g., rifampin) decreases guanfacine exposure. Guanfacine dose may be titrated up to 8 mg/day. When discontinuing CYP3A4 inducers, the guanfacine dose should be decreased by half in 1–2 weeks based on patient tolerability. The maximum dose should not exceed 4 mg/day.

Contraindications

The use of clonidine and guanfacine is contraindicated in patients with a history of hypersensitivity to clonidine and guanfacine, respectively.

Since clonidine is excreted in human milk, **caution** should be exercised when it is administered to a **nursing woman**. It is not known whether guanfacine is excreted in human milk; however, guanfacine is excreted in rat milk. Because many drugs are excreted in human milk, caution should be exercised when guanfacine is administered to a nursing woman.

Caution should be used when prescribing clonidine and guanfacine to patients with a history of syncope or its predisposing factors (e.g., hypotension, orthostatic hypotension, bradycardia, or dehydration), and patients should be advised to avoid dehydration and becoming overheated (Sallee et al. 2013).

8.5 Duration of Treatment

Therapy with psychostimulants should be long-term; it will generally continue for a period of years. ADHD can persist into adulthood, necessitating continuance of pharmacological treatment.

According to the practice parameter for the assessment and treatment of children and adolescents with ADHD (AACAP Official Action

2007), a **medication withdrawal trial** should be considered at least **once a year**. The observation period should be based on a typical demand condition (school time). If a patient with ADHD has been symptom free for at least 1 year, then inquiries should be made about whether the patient and his/her family still think the medication is beneficial. Signs that ADHD has remitted include lack of any need to adjust the dose despite robust growth, lack of deterioration when a dose of psychostimulant medication is missed, or newfound abilities to concentrate during drug holidays. Low-stress times such as vacations are a good time to attempt a withdrawal from medication, but parents should assign some cognitively demanding tasks (reading a book, practicing mathematics problems) to be sure that remission has occurred. The start of a new school year is not a particularly good time to attempt a drug holiday, but once a patient's school routine is established, the medication can be withdrawn and teacher input solicited. Medication should be reinstituted if the patient, his or her parents, or teachers report deterioration in functioning.

8.6 Therapeutic Monitoring

Prior to commencement of a pharmacotherapy, physical, neurological, and psychiatric examinations (including height and body weight, cardiac frequency, blood pressure) should be undertaken. Resting EEG should also be assessed if clinically appropriate.

According to the practice parameter for the assessment and treatment of children and adolescents with ADHD (AACAP Official Action 2007), patients with ADHD should have **regular follow-ups for medication adjustments** to ensure that the medication is still effective, the dose is optimal, and ADRs are clinically insignificant. For pharmacological interventions, follow-ups should be carried out at least several times per year. The number and frequency of psychosocial interventions should be individualized as well. The procedures performed at each office visit will vary according to clinical need, but during the course of annual treatment, the clinician should review the child's behavioral and academic functioning; periodically assess height, weight, blood pressure, and pulse; and check whether comorbid disorders and medical conditions are present. Psychoeducation should be provided on an ongoing basis. The need to initiate formal behavior therapy should be assessed, and the effectiveness of any current behavior therapy should be reviewed.

Monitoring of therapy by the treating physician should include regular assessment of eating behavior, physical development, cardiac and circulatory functions, and general behavioral development (occurrence of tics?). The amount of medication consumed should also be compared with that prescribed in order to prevent inappropriate usage (e.g., sale for recreational drug purposes).

Concerns with the **cardiovascular safety** of psychostimulant medications have led to specific recommendations for pretreatment evaluation, treatment selection, and monitoring (Cortese et al. 2013; Hammerness et al. 2011). The practice parameter for the assessment and treatment of children and adolescents with ADHD (AACAP Official Action 2007) recommends that blood pressure and pulse should be measured in children before the treatment with psychostimulants. The examination should explicitly assess physical capacity and episodes of fatigue, exhaustion, and chest pain during exercise. The physician should also enquire about cardiac disease in the patient and his or her family as well as about sudden, unexplained deaths in the family, and, where any such history is established, refer the patient to a pediatric cardiologist. This is clearly also necessary where abnormal ECG findings or pulse and blood pressure values have been determined.

Because psychostimulants have been shown to affect **growth**, evidence- and expert-based guidance concerning the management of ADRs with medications for ADHD specifically addresses monitoring of height and weight, including serial plotting of growth parameters (AACAP Official Action 2007; Cortese et al. 2013).

Rare instances of jaundice during **atomoxetine** therapy mean that **attention** should be paid

to **clinical symptoms** of **hepatic disease**; at the first indications of such, treatment should be discontinued and not resumed (Bangs et al. 2008a). The European Guidelines Group does not recommend routine investigations of transaminases and ECG, in the absence of clinical symptoms or risk factors, as necessary during therapy with atomoxetine, given the rarity of hepatotoxicity and QT interval prolongation (Cortese et al. 2013). Other monitoring recommendations are the same as those for methylphenidate and amphetamine. Because the US PI carries a **FDA black box warning** regarding **suicidal ideation** in children and adolescents, patients starting atomoxetine therapy should be closely monitored for suicidal thinking and behavior, clinical worsening, or unusual changes in behavior (Garnock-Jones and Keating 2009).

As discussed above, the primary indication of clonidine has historically been the treatment of hypertension. It is therefore likely to be associated with some reduction in blood pressure. Hence, when administering **clonidine** and **guanfacine** for the treatment of ADHD, **heart rate** and **blood pressure** should be **measured** prior to the initiation of therapy, periodically during therapy, and after dose increases (Sallee et al. 2013).

8.7 Clinical Pharmacology of Drugs Used in the Treatment of ADHD: Overview

The following summaries are based upon the information included in the SPCs and the PI, respectively, depending on whether the drug is approved in the EU and USA. In addition, information is included from recent comprehensive reviews on atomoxetine and clonidine (Garnock-Jones and Keating 2009; Sallee et al. 2013). Issues concerning the preparation of SPCs and PI, and their limitations were discussed in detail in Sect. 4.7. The most important pharmacological features of the selected drugs used in the treatment of ADHD are presented as an orientation aid in clinical employment.

Abbreviations used in the following tables are the following: ADRs, adverse drug reactions; AUC, area under the curve; $c_{max,}$ maximal plasma concentration after oral dosing; CNS, central nervous system; CSA, Controlled Substance Act CYP, cytochrome P_{450}; EMA, European Medicines Agency; FDA, Food and Drug Administration; t_{max}, time required to reach peak plasma concentration (c_{max}); $t_{1/2}$, elimination half-life.

8.7.1 Amphetamine

Pharmacodynamic characteristics	A psychostimulant classified as a schedule II drug by the US CSA Sympathomimetic amine. Non-exocytotic, transporter-mediated release of dopamine and noradrenaline (to a lesser degree: serotonin); inhibition of transport systems for the reuptake of dopamine and noradrenaline (to a lesser degree: serotonin); indirect agonist of peripheral and central dopamine and noradrenaline neuroreceptors (S)-amphetamine is three to four times more potent than (R)-amphetamine with respect to CNS effects and conveniently has fewer sympathomimetic effects
Pharmacokinetic characteristics	t_{max} = 3 h (immediate release), 7 h (extended release); mean $t_{1/2}$ = 9.8 and 11.5 h for immediate-release (S)- and (R)-amphetamine, respectively; protein binding and bioavailability, unknown Metabolism to hydroxy-amphetamine and noradrenaline that are both active Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved in the formation of 4-hydroxy-amphetamine
Indications	Currently available amphetamine products for the treatment of ADHD deliver either a combination of (S)- and (R)-amphetamine (consists of a 3:1 enantiomeric mixture (R)-amphetamine/(S)-amphetamine salts) or (R)-amphetamine alone as immediate-release and long-acting formulations. A further long-acting amphetamine prodrug formulation is lisdexamfetamine **The US FDA-approved** indication is: Treatment of ADHD in children aged above 6 years and adolescents Narcolepsy In addition, some amphetamine products are also licensed in various **European countries** for the treatment of children and adolescents with ADHD
Dosage	Regardless of indication, amphetamines should be administered at the lowest effective dosage, and the dosage should be individually adjusted according to the therapeutic needs and response of the patient. Late evening doses should be avoided because of the resulting insomnia In children from 3–5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will be necessary to exceed a total of 40 mg/day. Give first dose after awakening; additional doses (1 or 2) at intervals of 4–6 h
ADRs	Appetite reduction, moodiness, and dysphoria; problems with falling asleep following afternoon administration; (transient) tachycardia, increased blood pressure, nausea, and irritability Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some structural heart problems alone may carry an increased risk of sudden death, psychostimulant drugs generally should not be used in children or adolescents with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a psychostimulant drug

Drug interactions	In vitro experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine, and minor inhibition of CYP1A2, -2D6, and -3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to in vivo concentrations, no predictions regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes in vivo can be made **Agents that increase blood levels of amphetamine** MAO inhibitors and gastrointestinal alkalinizing agents (e.g., sodium bicarbonate) that increase absorption of amphetamines. Coadministration of amphetamine and gastrointestinal alkalinizing agents, such as antacids, should be avoided **Agents that lower blood levels of amphetamine** Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamate, ascorbic acid, grapefruit juice) lower absorption of amphetamines. Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion
Contraindications	Symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, agitated states, patients with a history of drug abuse during or within 14 days following the administration of MAO inhibitors The US PI carries a FDA black box warning regarding a history of substance abuse/dependence, cardiac history, and psychotic suicidal ideation in children and adolescents

8.7.2 Atomoxetine

Pharmacodynamic characteristics	A non-psychostimulant that is not classified as schedule II drugs by the US CSA Central acting sympathomimetic. Selective inhibition of presynaptic reuptake of noradrenaline; indirect agonist of peripheral and central noradrenaline neuroreceptors
Pharmacokinetic characteristics	t_{max} = 1–2 h; mean $t_{1/2}$ = 3.6 h (extensive metabolizers), 21 h in poor metabolizers; protein binding 98 %; bioavailability 63–94 % Metabolism primarily via CYP2D6. The major oxidative metabolite formed is 4-hydroxyatomoxetine that is equipotent to atomoxetine but circulates in plasma at much lower concentrations **Poor metabolizers** represent about 7 % of the Caucasian population and have **higher plasma concentrations** of atomoxetine compared with people with normal activity (extensive metabolizers). For poor metabolizers, AUC of atomoxetine is approximately 10 times greater, and c_{max} is about 5 times greater than extensive metabolizers
Indications	Approval in the **USA** (FDA) and **Europe** for: The treatment of ADHD in children of 6 years and older, in adolescents, and in adults as part of a comprehensive treatment program

Dosage	For children/adolescents weighing **up to 70 kg body**, atomoxetine should be initiated at a total daily dose of approximately 0.5 mg/kg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is approximately 1.2 mg/kg daily (depending on the patient's weight and available dosage strengths of atomoxetine) For children/adolescents **over 70 kg body of weight**, atomoxetine should be initiated at a total daily dose of 40 mg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is 80 mg
ADRs	Reduced appetite, nausea, moodiness, and dysphoria; disturbance of sleep initiation and maintenance; increased pulse and blood pressure; aggression; irritability; suicidal tendency Rare instances of jaundice mean that attention should be paid to clinical symptoms of hepatic disease; at the first indications of such, treatment should be discontinued and not resumed
Drug interactions	Atomoxetine did not cause clinically significant inhibition or induction of CYP enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9 CYP2D6 inhibitors (SSRIs such as **fluoxetine**, **paroxetine**): In patients receiving these drugs, atomoxetine exposure may be 6- to 8-fold increased, and c_{max} three to four times higher. Slower titration and final lower dosage of atomoxetine may be necessary in patients who are already taking CYP2D6 inhibitor drugs Caution is advised when combining atomoxetine with potent inhibitors of CYP enzymes other than CYP2D6 in patients who are poor CYP2D6 metabolizers as the risk of clinically relevant increases in atomoxetine exposure in vivo is unknown Atomoxetine should be administered with caution to patients treated with high-dose nebulized or systemically administered salbutamol (or other β-agonists) because cardiovascular effects can be potentiated There is a potential for an increased risk of QT interval prolongation when atomoxetine is administered with other QT prolonging drugs (such as **antipsychotics**, class IA and III antiarrhythmics, moxifloxacin, erythromycin, methadone, mefloquine, **tricyclic antidepressants**, **lithium**, or cisapride); drugs that cause electrolyte imbalance (such as thiazide diuretics), and drugs that inhibit CYP2D6 Caution is advised with concomitant use of **medicinal drugs** which are known to **lower the seizure threshold** (such as tricyclic antidepressants or SSRIs, antipsychotics, phenothiazines or butyrophenone, mefloquine, chloroquine, bupropion, or tramadol). In addition, caution is advised when stopping concomitant treatment with benzodiazepines due to potential withdrawal seizures **Drugs that affect noradrenaline** should be used cautiously when coadministered with atomoxetine because of the potential for additive or synergistic pharmacological effects. Examples include antidepressants such as imipramine, venlafaxine, and mirtazapine, or the decongestants pseudoephedrine or phenylephrine
Contraindications	Severe cardiovascular disorders; hypersensitivity to atomoxetine or other constituents of the product, within 2 weeks after discontinuing MAO inhibitors or other drugs that affect brain monoamine concentrations; pheochromocytoma or history of pheochromocytoma, hepatic dysfunction The US PI carries a FDA black box warning regarding suicidal ideation in children and adolescents. However, no suicides occurred in the trials included in the meta-analysis by Bangs et al. 2008b

8.7.3 Clonidine

Pharmacodynamic characteristics	A non-psychostimulant that is not classified as schedule II drugs by the US CSA Clonidine is a central α_2-adrenenoceptor agonist with a high affinity for all three α_2-receptor subtypes α_{2A}, $\alpha_{2B,}$ and α_{2C}
Pharmacokinetic characteristics	For the extended-release formulation: mean $t_{max} = 6.8$ h (following a high fat meal), mean $t_{1/2} = 3.8$ h; protein binding and bioavailability, not known Following oral administration of an immediate-release formulation, about 40–60 % of the absorbed dose is recovered in the urine as unchanged drug in 24 h. About 50 % of the absorbed dose is metabolized in the liver
Indications	The extended-release formulation of clonidine is **US FDA-approved** for: The treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications in children and adolescent (aged 6–17 years) Treatment of hypertension in adults Clonidine formulations are **not approved** in **Europe** for the treatment of ADHD
Dosage	Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved. Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime Treatment with clonidine can cause dose-related decrease in blood pressure and heart rate. **Measure heart rate and blood pressure prior to initiation of therapy**, following dose increases, and periodically while on therapy. Uptitrate clonidine slowly in patients with a history of hypotension and those with underlying conditions that may be worsened by hypotension and bradycardia, e.g., heart block, bradycardia, cardiovascular disease, vascular disease, cerebrovascular disease, or chronic renal failure
ADRs	Common and drug-related ADRs (incidence at least 5 % and twice the rate of placebo) reported with the use of extended-release clonidine include somnolence, fatigue, upper respiratory tract infection (cough, rhinitis, sneezing), irritability, throat pain (sore throat), insomnia, nightmares, emotional disorder, constipation, nasal congestion, increased body temperature, dry mouth, and ear pain
Drug interactions	No drug interaction studies have been conducted with the extended-release formulation in children. The following have been reported with other oral immediate-release formulations of clonidine Sedating drugs: clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates, or other sedating drugs Tricyclic antidepressants: may reduce the hypotensive effect of clonidine **Drugs** known to **affect sinus node function** or AV nodal conduction: caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers, and β-blockers) due to a potential for additive effects such as bradycardia and AV block Antihypertensive drugs: use caution when coadministered with clonidine
Contraindications	Known hypersensitivity to clonidine Since clonidine is excreted in human milk, **caution** should be exercised when it is administered to a **nursing woman** Use caution in treating patients who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration. Use clonidine with caution in patients treated concomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope. Advise patients to avoid becoming dehydrated or overheated

8.7.4 Guanfacine

Pharmacodynamic characteristics	A non-psychostimulant that is not classified as schedule II drugs by the US CSA Central α_2-adrenenoceptor agonist, the most selective agonist for the α_{2A}-receptor subtype
Pharmacokinetic characteristics	For the extended-release formulation: t_{max} = approximately 5 h, mean $t_{1/2}$ = 18 h; protein binding 70 %, bioavailability 80 % (immediate-release formulation) In vitro studies with human liver microsomes and recombinant CYPs demonstrated that guanfacine was primarily metabolized by CYP3A4
Indications	The extended-release formulation is **US FDA approved** for the treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications in children and adolescent (aged 6–17 years) Guanfacine formulations are **not approved** in **Europe** for the treatment of ADHD
Dosage	It should be taken once daily, either in the morning or evening, at approximately the same time each day. Begin at a dose of 1 mg/day and adjust in increments of no more than 1 mg/week. Maintain the dose within the range of 1–4 mg once daily, depending on clinical response and tolerability, for both monotherapy and adjunctive therapy to a psychostimulant Clinically relevant improvements were observed beginning at doses in the range 0.05–0.08 mg/kg once daily in both mono- and adjunctive therapy. Efficacy increased with increasing weight-adjusted doses (mg/kg). If well tolerated, doses up to 0.12 mg/kg once daily may provide additional benefits
ADRs	Most common ADRs (≥ 5 % and at least twice placebo rate) in the monotherapy trials: somnolence, fatigue, nausea, lethargy, and hypotension Most common ADRs (≥5 % and at least twice placebo rate) in the adjunctive trial: somnolence, fatigue, insomnia, dizziness, and abdominal pain
Drug interactions	Guanfacine is primarily metabolized by CYP3A4, and its plasma concentrations can be affected significantly by CYP3A4 inhibitors or inducers Strong **CYP3A4 inhibitors** (e.g., ketoconazole): coadministration increases guanfacine exposure. The dose should be limited to no more than 2 mg/day. When discontinuing CYP3A4 inhibitors, the guanfacine dose should be doubled based on patient tolerability. The maximum dose should not exceed 4 mg/day Strong **CYP3A4 inducers** (e.g., rifampin): coadministration decreases guanfacine exposure. The dose may be titrated up to 8 mg/day. When discontinuing CYP3A4 inducers, the guanfacine dose should be decreased by half in 1–2 weeks based on patient tolerability. The maximum dose should not exceed 4 mg/day Guanfacine does not significantly affect exposures of methylphenidate and lisdexamfetamine when coadministered. Therefore, no dose adjustments in methylphenidate or lisdexamfetamine are necessaryy
Contraindications	Known hypersensitivity to guanfacine It is not known whether guanfacine is excreted in human milk; however, guanfacine is excreted in rat milk. Because many drugs are excreted in human milk, **caution** should be exercised when guanfacine is administered to a **nursing woman** Treatment with guanfacine can cause dose-related decreases in blood pressure and heart rate. Use guanfacine with **caution** in patients at risk for hypotension, bradycardia, heart block, or syncope (e.g., those taking antihypertensives). Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Advise patients to avoid becoming dehydrated or overheated

8.7.5 Methylphenidate

Pharmacodynamic characteristics	A psychostimulant classified as a schedule II drug by the US CSA
	Sympathomimetic amine. Inhibition of transport systems for the reuptake of dopamine and noradrenaline (to a lesser degree: serotonin); indirect agonist of peripheral and central dopamine and noradrenaline neuroreceptors
	D-*threo*-methylphenidate and L-*threo*-methylphenidate are only included in the currently available methylphenidate formulations. Available data suggest that many of the behavioral effects of methylphenidate are conferred by D-*threo*-methylphenidate, although most methylphenidate formulations are composed of a racemic mixture of D-*threo*-methylphenidate and L-*threo*-methylphenidate
Pharmacokinetic characteristics	Protein binding in plasma (57 %) and erythrocytes (43 %); bioavailability 22 ± 8 % for the D-enantiomer and 5 ± 3 % for the L-enantiomer.
	Methylphenidate is metabolized by the carboxylesterase CES1A1 to ritalinic acid. Therapeutic activity seems to be principally due to the parent compound
Immediate-release formulations	t_{max} = 1–2 h on average, the c_{max}, however, show considerable intersultrject variability: mean $t_{1/2}$ = 2 h.
Long-acting formulations	A number of long-acting formulations have been developed with the goal of providing once-daily dosing, employing various means to extend duration of action.
	Depending on technology, the mean t_{max} and $t_{1/2}$ are longer than those of the immediate-release formulations (t_{max} 3–7 h; $t_{1/2}$ 2.5–7 h). Some formulations produces a bi-modal plasma concentration-time profile (i.e., two distinct peaks approximately 4 h apart).
Indications	The US **FDA-approved** areas of application are:
	Treatment of ADHD in children from the age of 6 years and older, and adolescents
	Narcolepsy in adults
	Some methylphenidate products were also **approved** in many **European countries**
Dosage	Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose
	Immediate-release formulations
	Children (over 6 years of age): begin with 5 mg once or twice daily (e.g., at breakfast and lunch), increase the dose and frequency of administration if necessary by weekly increments of 5–10 mg in the daily dose. Doses above 60 mg daily are not recommended. The total daily dose should be administered in divided doses
	If the effect of the drug wears off too early in the evening, disturbed behavior and/or inability to go to sleep may recur. A small evening dose may help to solve this problem
	Long-acting formulations
	They usually administered orally once daily in the morning. The choice of methylphenidate-containing products will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effects. The appropriate dosages of methylphenidate products vary according to their pharmaceutical form (see Table 8.4)
ADRs	Very common ADRs (≥1/10) observed during clinical trials and post-market spontaneous reports with all methylphenidate formulations are headache, insomnia, and nervousness
	Careful follow-ups of weight and height in children aged 7–10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10–13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slower growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Drug interactions	**Pharmacokinetic interactions**
	Methylphenidate is not metabolized by CYP enzymes to a clinically relevant extent. Therefore, inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the D- and L- enantiomers of methylphenidate do not relevantly inhibit cytochrome P4501A2, -2C8, -2C9, -2C19, -2D6, -2E1, or -3A. It is not known how methylphenidate may affect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, especially those with narrow therapeutic window
	However, there are reports indicating that **methylphenidate** may **inhibit** the metabolism of coumarin anticoagulants, **anticonvulsants** (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclic **antidepressants** and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times)
	Pharmacodynamic interactions
	Methylphenidate may decrease the effectiveness of drugs used to treat hypertension
	Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure. Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with nonselective, irreversible MAO inhibitors
	Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment
	There is a risk of sudden blood pressure increase during surgery. If **surgery** is **planned**, methylphenidate treatment should not be used on the day of surgery
	Serious adverse events, including sudden death, have been reported in **concomitant** use with **clonidine**.
	Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when coadministered with direct and indirect dopamine agonists (including tricyclic antidepressants) or with dopamine antagonists including antipsychotics
Contraindications	Patients known to be hypersensitive to methylphenidate or other components of the product, pheochromocytoma, during treatment with nonselective, irreversible MAO inhibitors or within a minimum of 14 days of discontinuing those drugs, due to risk of hypertensive crisis, hyperthyroidism or thyrotoxicosis
	Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder, diagnosis or history of severe and episodic (type 1) bipolar (affective) disorder (that is not well controlled)
	Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some structural heart problems alone may carry an increased risk of sudden death, stimulant products generally should **not be used** in children or adolescents with **known structural cardiac abnormalities**, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug
	The US PI carries a FDA black box warning regarding a history of substance abuse/dependence, cardiac history, and psychotic suicidal ideation in children and adolescents

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Part III

Symptomatic and Symptom-Oriented Pharmacological Therapy of Psychiatric Disorders in Children and Adolescents

Aggressive and Autoaggressive Behavior, Impulse Control Disorder, and Conduct Disorder

9

Claudia Mehler-Wex, Marcel Romanos, and Andreas Warnke

Contents

C. Mehler-Wex, MD (✉)
Department of Child and Adolescent Psychiatry and Psychotherapy, University of Ulm, Steinhövelstr. 5, 89075 Ulm, Germany

HEMERA-Klinik, Schönbornstr. 16, 97688 Bad Kissingen, Germany
e-mail: mehler-wex@hemera.de

M. Romanos, MD • A. Warnke, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: romanos@kjp.uni-wuerzburg.de; warnke@kjp.uni-wuerzburg.de

9.1 Definition, Classification and Target Symptoms

Aggressive behavior can occur alone or as an accompanying symptom or consequence of various psychiatric disorders (Comai et al. 2012a; Siever 2008; Steiner et al. 2011) as classified in the International Classification of Diseases, 10th revision (ICD-10; World Health Organisation 1996) and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5; American Psychiatric Association 2013). Aggression can be directed against oneself (self-injury, suicidal thoughts, and acts) or against others. Aggressive behavior can be the symptom of the different kinds of disruptive behavior (e.g., oppositional defiant disorder, conduct disorder, antisocial personality disorder), of emotional dysregulation (e.g., borderline personality disorder), of disturbance of impulse control (attention deficit/hyperactivity disorder, ADHD), of cognitive deficiency (e.g., co-occurring with intellectual disabilities, pervasive developmental disorders, with psychosis or bipolar disorder), and of trauma or stress (e.g., post-traumatic stress disorder, adjustment disorders), and the aggressive behavior may be drug-induced. Thus each kind of behavioral and psychopharmacological treatment of the symptoms of aggression depends on the associated individual conditions of the aggression. Various subtypes will benefit differently from pharmacotherapy.

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Aggression is **not classified as** a **distinguished psychiatric disorder** in ICD-10 or DSM-5. Nevertheless, impulsive aggression could be identified as a valid diagnostic construct that occurs in consistent form across diagnostic category boundaries (Jensen et al. 2007).

9.2 Therapeutic Framework

The diagnostic prerequisite is a comprehensive pediatric/adolescent psychiatric examination in order to identify or exclude potential underlying disorders. A detailed discussion of the child's history with its various caregivers and other important contacts is of major importance in order to gain the most objective view of symptom frequency and of possible precipitating factors.

Psychotherapy in the sense of behavioral modification (instruction in problem-solving strategies and techniques for impulse control, development of behavioral plans with the use of reinforcement, cognitive restructuring) is **particularly appropriate** for impulsive aggression (in the context of ADHD, for instance); the choice of psychotherapeutic-educational measures as the primary treatment approach is, in fact, always to be recommended. For further information regarding the therapy of aggression, autoaggression, and impulse control disorders, the reader is referred to the reviews (Comai et al. 2012b; Ipser and Stein 2007; Jensen et al. 2007; Pappadopulos et al. 2006; Siever 2008; Tsiouris 2010).

Pharmacotherapy is indicated when structuring educational and behavioral therapeutic efforts have proved insufficient and an underlying psychiatric disorder that might explain symptomatic aggression has been identified. In the latter case, pharmacotherapy will principally be **directed** specifically at the **underlying disorder**. Otherwise, the treatment of aggression, autoaggression, and impulse control disorders is purely symptomatic; there is no specific medication.

9.3 Choice of Pharmacotherapy

The choice of psychopharmacological agent depends upon the underlying disorder, the severity, and character of the aggression. In use are antipsychotics, lithium salts and mood-stabilizing anticonvulsants, antidepressants, and benzodiazepines; in ADHD with aggressive behavior, psychostimulants may be indicated as first choice. All these drugs are described "off-label" because the regulatory drug agencies do not consider aggressive behavior as a distinct disease and standardized clinical national and international guidelines are still controversial (Comai et al. 2012b).

9.3.1 Antipsychotics

Antipsychotics (see Chap. 5) are of major importance and often the first choice medication in the symptomatic treatment of aggression and impulse control disorders. First-generation antipsychotics such as **haloperidol** have been used extensively to treat aggression in psychiatric patients. But there is weak evidence of efficacy for antipsychotic agents in the treatment of aggression in adults (Goedhard et al. 2006). There is only one double-blind placebo-controlled study (Campbell et al. 1984) in hospitalized children (age 5.2–12.9 years) with conduct disorder, aggressive type, showing the superiority of haloperidol (1.0–6.0 mg/day) to placebo in decreasing behavioral symptoms. According to the review of Pappadopulos et al. (2006), the effect size for haloperidol and thioridazine was found to be 0.8 and 0.35, respectively. As first-generation, high-potency antipsychotics more frequently elicit extrapyramidal motor ADRs (especially tardive dyskinesia, usually not reversible), in longer-term therapy second- and third-generation antipsychotics are preferred.

In contrast to first-generation antipsychotics, the efficacy of **second- and third-generation** antipsychotics is well **established** in children and adolescents with schizophrenia, bipolar I disorder, tic disorders, and irritability, agitation, and aggression associated with autistic disorder and other pervasive developmental disorders, as well as in youths with disruptive behavior disorders with and without mental retardation (see Chap. 5): there are several randomized, placebo-controlled antipsychotic trials showing that aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone were superior to placebo in children and

adolescents (mean effect size for second-generation antipsychotics in general 0.9; Pappadopulos et al. 2006). Risperidone is the only antipsychotic agent that is US Food and Drug Administration (FDA) approved for the treatment of irritability associated with autistic disorder including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods in children and adolescents (ages 10–17 years).

Several placebo-controlled studies were carried out with **risperidone** in children and adolescents (age range over all studies: 5–15 years) with aggressive behaviors associated with mental retardation/subaverage intelligence. All studies demonstrated that the antipsychotic was superior to placebo regarding the study-defined response measure (Aman et al. 2002, 2004; Buitelaar et al. 2001; Correll et al. 2011; Croonenberghs et al. 2005; Reyes et al. 2006; Snyder et al. 2002; Turgay et al. 2002). In addition, several randomized, placebo-controlled studies in children and adolescents with irritability/aggression associated with autism spectrum disorders have been reported that showed superior efficacy compared to placebo (McCracken et al. 2002; Nagaraj et al. 2006; Pandina et al. 2007; Parikh et al. 2008; Troost et al. 2005). Risperidone was also shown to be superior to placebo in the treatment of aggression in the context of an oppositional disorder (LeBlanc et al. 2005), conduct disorder (Aman and Lindsay 2002), and ADHD (Aman et al. 2004). Risperidone, by augmenting the effect of psychostimulants, also moderated aggressive behavior in ADHD and was well tolerated (Armenteros et al. 2007).

The anti-aggressive effect of **olanzapine** was confirmed by some double-blind, placebo-controlled studies in children and adolescents with pervasive developmental disorder (Hollander et al. 2006), with schizophrenia (Kryzhanovskaya et al. 2009), and bipolar mania (Tohen et al. 2007). The dose range in the studies was 2.5–20 mg/day. The marked weight gain was the main ADR.

Quetiapine appears to be effective against aggression in adolescents with co-occurring bipolar disorder (Barzman et al. 2006) and ADHD (Kronenberger et al. 2007). It is not significantly evaluated to be helpful in the treatment of conduct disorder in adolescents (Connor et al. 2008; Findling et al. 2007).

Aripiprazole was efficacious in adults with borderline personality disorder (daily dosage 15 mg) and has also been successfully employed in the treatment of the irritability of autistic children (average 7 mg) and in those with intellectual deficiency (average 10 mg) or aggressive symptoms in conduct disorder (1–10 mg; Marcus et al. 2011; Owen et al. 2009; Valicenti-McDermott and Demb 2006). Transitory sedation and weight gain were noted as ADRs. Lower starting doses reduced ADRs in youths (Findling et al. 2009).

Studies in adults (Volavka and Citrome 1999) and in youth with aggressive behavior in schizophrenia (Chalasani et al. 2001; Kranzler et al. 2005; Kryzhanovskaya et al. 2009; Tohen et al. 2007) suggest that **clozapine** may be helpful to reduce aggression in schizophrenic patients. According to a retrospective review by Beherec et al. (2011) and in accordance with the study of Hollander et al. (2006), clozapine also seems to reduce disruptive behavior in autism spectrum disorders. Effects were also seen in the treatment of aggression in children with Tourette syndrome and aggression (Stephens et al. 2004).

Pilot studies indicated the efficacy of **ziprasidone** in children with autism (daily dosage 20–160 mg; McDougle et al. 2002; Malone et al. 2007). A retrospective evaluation found that the efficacy of intramuscular-administered ziprasidone and olanzapine in the treatment of acute aggressive states in 100 children and adolescents was comparable (mean dosage of olanzapine 8.19 mg/day; ziprasidone 19.07 mg/day; Khan and Mican 2006). Compared to the sample treated with olanzapine and ziprasidone, subjects received significantly more doses of emergency medication during their hospital stay and significantly more doses of ziprasidone were administered with concomitant lorazepam or antihistamines.

9.3.2 Psychostimulants

Psychostimulants (see Chap. 8) are indicated for the treatment of aggressive symptoms associated with ADHD. They selectively improve attention and thus facilitate greater forward planning and

more structured activity; that is, improvement of impulse control disorders ensues as a secondary response. Numerous studies have confirmed the clinical efficacy of psychostimulants with regard to aggression and impulsivity in children with ADHD (Aman and Lindsay 2002; Bukstein and Kolko 1998; Connor et al. 2008; Hechtman and Greenfiled 2003; Ipser and Stein 2007; Pappadopulos et al. 2006; The MTA Cooperative Group 1999). Two double-blind, randomized studies demonstrated the efficacy of methylphenidate in the treatment of aggressive behavior in children with autism (review: Parikh et al. 2008).

NB: Aggression is not per se an indication for psychostimulant therapy.

Psychostimulants are possibly also effective in conduct disorders, but there have been only a few investigations in this regard, and they have yielded somewhat contradictory results (reviewed: Gerardin et al. 2002; Ipser and Stein 2007). At the moment, psychostimulants appear to be contraindicated in this difficult (with respect to compliance) patient group, particularly where a risk of substance misuse exists (sensation seeking through substance abuse).

9.3.3 Mood Stabilizers

Although studies regarding treatment of aggression with lithium salts and antiepileptic medications that act as mood stabilizers (e.g., carbamazepine, gabapentin, lamotrigine, oxcarbazepine, valproic acid, and topiramate) in children and adolescents are sparse (see Chap. 7), the results have been positive but are inconsistent with regard to effect size (overview in Kowatch and Bucci 1998; Ipser and Stein 2007). The overall **effect size** for mood stabilizers is **low** (0.4; Pappadopulos et al. 2006); it was found largest for lithium salts (0.9; Malone et al. 2000).

It was shown in double-blind and placebo-controlled as well as open-label studies that lithium salts are effective in the treatment of aggression (emotional explosiveness) in children and adolescents with comorbid ADHD, conduct, and oppositional defiant disorder (Campbell et al. 1995; Carlson et al. 1992; Nevels et al. 2010). Valproate products were shown to reduce explosive temper and mood liability (Donovan et al. 2000; Lindenmayer and Kotsaftis 2000; Saxena et al. 2006; Steiner et al. 2003). With regard to carbamazepine several studies showed a small but significant effect on aggressiveness in youths (overview: Pappadopulos et al. 2006). But there was no difference from placebo in the study of Cueva et al. (1996). The adjunctive treatment with a psychostimulant and valproate products may be helpful to reduce aggression in youth refractory to stimulant monotherapy (Blader et al. 2009, 2010)

Cave! Lithium salts should only be employed where compliance can be assured. Application in children under 12 years is generally inadvisable.

Lithium salts, carbamazepine, and valproic acid are second-choice medications in the symptomatic treatment of aggression.

9.3.4 Antidepressants

Antidepressants (see Chap. 4), especially selective serotonin reuptake inhibitors (**SSRIs**), are employed in cases of aggressive and impulsive disorder. They have exhibited unequivocally positive effects upon aggression, impulsivity, and suicidality in numerous studies of adult patients, mainly in those with affective disorders, but also in those with other psychiatric diagnoses (Hollander 1999; Walsh and Dinan 2001). In children and adolescents, however, the **efficacy** of SSRIs for the treatment of aggression has **not** yet been adequately **substantiated**. An open-label study found that citalopram was well tolerated and clinically effective in children and adolescents with impulsive aggression (Armenteros and Lewis 2002). In a series of studies, reboxetine exhibited positive effects upon the symptoms of ADHD and associated behaviors, such as aggression, anxiety, and depression (Mozes et al. 2005; Quintero et al.

2010; Ratner et al. 2005; Tehrani-Doost et al. 2008; Toren et al. 2007).

The average effect size with regard to the treatment of pediatric aggression was found to be 0.3. The greatest effect was seen for the tricyclic antidepressant desipramine (0.85; Biederman Baldessarini et al. 1989; reviewed by Pappadopulos et al. 2006).

9.3.5 Miscellaneous

The selective noradrenaline reuptake inhibitor **atomoxetine** approved for the indication ADHD in children and adolescents is suggested to have only a **minor** but significant **effect** upon (comorbid) aggressive behavior (Michelson et al. 2004; Newcorn et al. 2005; Pappadopulos et al. 2006; Weiss et al. 2005). This suggestion is supported by the randomized, placebo-controlled, double-blind study in youths with ADHD and co-occurrence of oppositional defiant disorder after 9 weeks of medication (Dittmann et al. 2011). But according to the meta-analysis of Polzer et al. (2007), atomoxetine compared to placebo was not significantly helpful to reduce aggressive symptoms. The study of Newcorn et al. (2005) suggested that higher dosages (1.8 mg/kg body weight) are possibly required by the subgroup of children with ADHD and comorbid oppositional disorder in order to achieve the same efficacy as in children without comorbid oppositional disorder (1.2 mg/kg body weight). To keep in mind is the black box warning for atomoxetine with regard to an increased risk of suicidal ideation in children and adolescents by the US FDA. Further details are found in Chap. 8.

With regard to the treatment of aggression, β-adrenoceptor antagonists (**β-blockers**), such as propranolol and pindolol, were **not evaluated by** randomized, controlled **studies** in children and adolescents. The pilot study of Connor et al. (1997) and the study of Buitelaar et al. (1996) support the suggestion that β-blockers (nadolol, pindolol) may reduce aggressive symptoms in individuals with aggression and developmental delay, and in children with conduct disorder and ADHD. But in the study of Buitelaar et al. (1996) during pindolol therapy, the decrease of the conduct problems was seen only at home, not at school, and there were some severe ADRs (paresthesias, hallucinations, sleep disorder).

Adrenergic α_2-agonists (such as **clonidine**, 0.025 up to 0.4 mg/day) are suggested to facilitate attention and inhibit impulsivity. Clonidine improved aggression in a small number of cases in children, particularly in those with ADHD (combination with psychostimulants; Connor et al. 2000; Hazell and Stuart 2003) and autistic syndromes (Frankenhauser et al. 1992; Jaselskis et al. 1992). According to the meta-analysis of 11 double-blind, placebo-controlled, randomized studies, clonidine was effective in the treatment of aggressive behavior in youth (Connor et al. 1999). The medium effect sizes were ranging from 0.5 to 1.1 (Pappadopulos et al. 2006). Clonidine remains controversial because of cardiovascular ADRs and reports of sudden deaths.

Guanfacine (0.5–4 mg/day) as well is suggested to be helpful in the treatment of oppositional behavior co-occurring with ADHD. In a double-blind, placebo-controlled trial in children aged 6–12 years with ADHD, the oppositional symptoms were significantly reduced within 9 weeks of treatment with guanfacine (Connor et al. 2010).

9.4 Treatment Strategy

There is no established algorithm for the pharmacological treatment of aggression in children and adolescents; the **choice of medication** generally **depends** on the **underlying symptoms** and if acute or chronic aggression should be treated (Nevels et al. 2010; Pappadopulos et al. 2003).

For example, if the child or adolescent has ADHD and the aggression stems from impulsivity, the use of psychostimulants (e.g., methylphenidate in its various formulations) can be helpful. If the aggression is the result of pediatric bipolar mania, it is appropriate to use mood stabilizers. Second- and third-generation

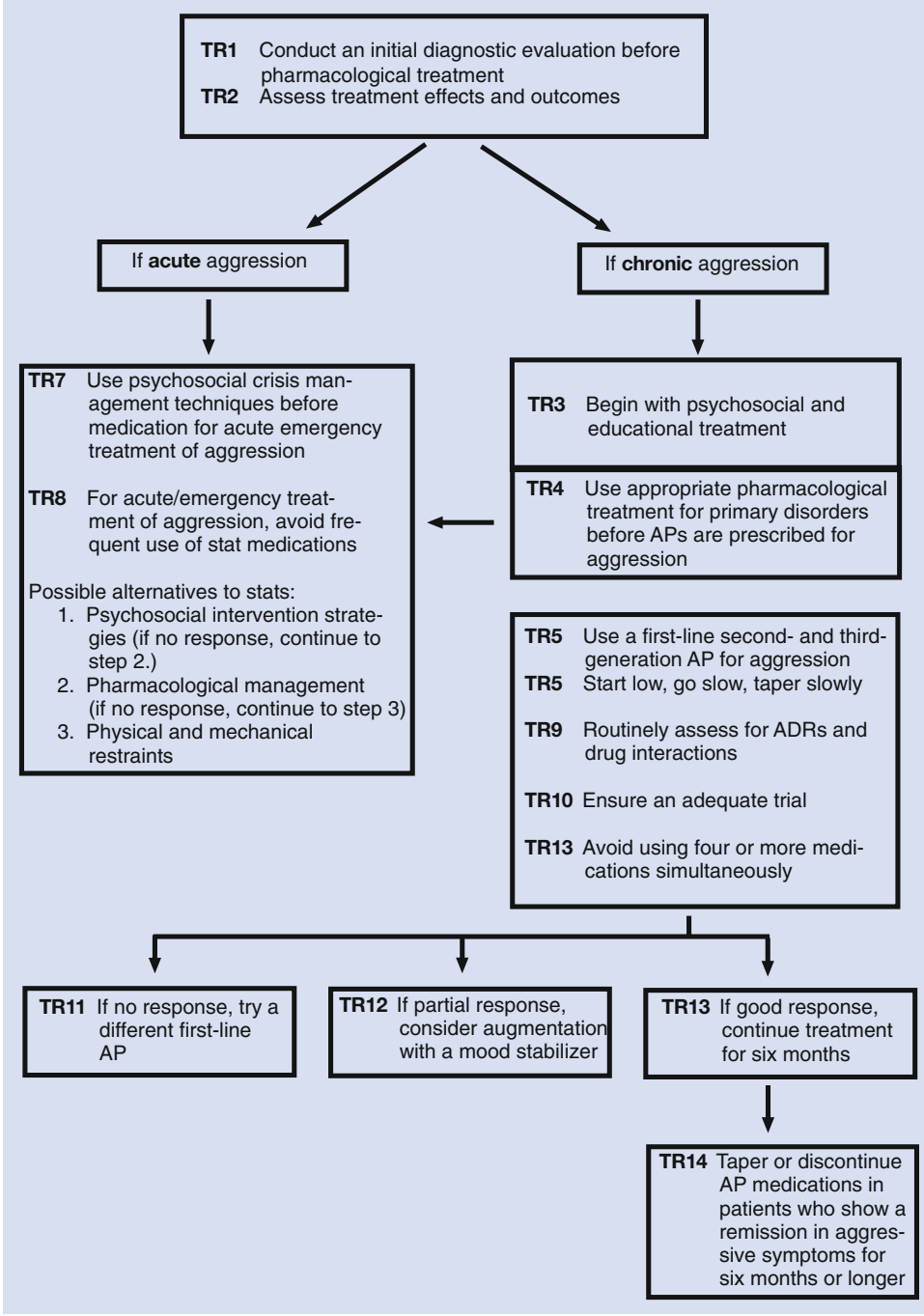

Fig. 9.1 Flow chart depicting the systematic application of the treatment recommendations (TR) for the use of antipsychotics (APs) for aggressive youths (TRAAY, according to Pappadopulos et al. 2003). *ADRs* adverse drug reactions, *stat* emergency pharmacological management

antipsychotics may be most appropriate if psychosis has emerged. Aggression in an emergency situation with violent and self-harming behavior may be treated, for example, with lorazepam and haloperidol. Figure 9.1 depicts the guideline for the psychopharmacological treatment of children and adolescents with serious psychiatric disorders and aggressive behavior.

Table 9.1 Second- and third-generation antipsychotics dosing strategies for children and adolescents

Antipsychotic	Starting daily dose (mg)	Titration dose (mg) (minimal days to antipsychotic dose)	Usual daily dose range for aggression (mg)[a]		Usual daily dose range for psychosis (mg)	
			Child	Adolescent	Child	Adolescent
Aripiprazole	2.5–15			1–15		In adults: 15–30
Clozapine	6.25–25	1–2× starting dose (18–20)	150–300	200–600	150–300	200–600
Olanzapine	2.5 for children 2.5 for adolescents	2.5 (9–16)	No data available	2.5–20	7.5–12.5	12.5–20
Quetiapine	12.5 for children 25 for adolescents	25–50 to 150, then 50–100 (18–33)	No data available	No data available	No data available	75–600
Risperidone	0.25 for children 0.50 for adolescents	0.5–1 (18–20)	1.5–2	2–4	3–4	3–6
Ziprasidone	10 for children 20 for adolescents	10–20	Mean dosage: 20	10–160	No data available	In adults: 40–160

Modified from Pappadopulos et al. (2006)

[a]There is little information to guide dosing strategies for aggression. However, for aggressive children treated with risperidone, doses are about half that of the used antipsychotic dose

When psychosocial and first-line medication treatments for primary nonpsychotic conditions have failed, physicians initially should use **first-line** second- and third-generation (rather than first-generation) **antipsychotic medications** to treat severe and persistent aggression because they have a safer acute ADRs profile than the traditional antipsychotics, i.e., likely lower risk for tardive dyskinesias, neuroleptic malignant syndrome, cognitive impairment, and extrapyramidal symptoms (Pappadopulos et al. 2003). Table 9.1 offers suggestions regarding medication-specific starting doses, titration schedules, and recommended daily dose ranges.

Lithium salts and **mood-stabilizing anticonvulsants** are agents of **second choice** after second- and third-generation antipsychotics. Lithium therapy may be given in the treatment of aggression comorbid with bipolar disorder. There is the necessity of frequent and highly reliable drug monitoring including the careful control of blood level (see Sect. 7.6). Dosage corresponds to that employed in the treatment for phase prophylaxis (see Sect. 7.4). Dosage is adjusted according to plasma levels (therapeutic range for lithium: 0.6–0.8 mmol/L; for aggression an increase to 1.–1.2 mmol/L can be considered if tolerated; dosage for valproate 500–2,100 mg/day).

Cave! The serious ADRs that are sometimes encountered should be considered when choosing a medication for the treatment of aggression (carbamazepine: hematological and cardiovascular effects; valproate products: hepatic effects in some cases, primarily in infants and preschool children, rarely in older children). Lithium ADRs include CNS and renal symptoms.

Methylphenidate is agent of first choice in the treatment of aggression in youths **comorbid** with **ADHD**. Only if these do not achieve a satisfactory effect should co-medication be initiated, primarily with medium- and low-potency antipsychotics or low doses of the second-generation antipsychotic risperidone (dosage: Table 9.1) or possibly with other second- and third-generation antipsychotics. Where response to methylphenidate is unsatisfactory, amphetamine or atomoxetine can be substituted (see Chap. 8).

Cave! Caution in prescribing psychostimulants to patients with heart illness/dysfunction and to patients with risk of substance misuse personally or within the family or peer group.

SSRIs are superior to other antidepressants in the treatment of aggressive symptoms in patients with an **affective disorder**. In the case of an affective disorder, SSRIs are the medication of first choice. Dosage and application are analogous to procedures for the specific therapy of depression (see Table 4.5). Anti-aggressive effects of antidepressants may be manifested no earlier than 2–3 months after initiation of therapy. Selecting an antidepressant for the symptomatic treatment of aggression or suicidality is therefore appropriate only for longer-term therapy, and combination with other more rapidly effective psychopharmacological agents (such as benzodiazepines, antipsychotics) is required until the effect of the antidepressant is manifested. In contrast to tricyclic antidepressants, SSRIs possess a more favorable ADRs profile, without anticholinergic or cardiovascular risks; further, overdosage in the context of attempted suicide involves only a minor danger of toxicity (see Chap. 4).

Following reports of increased frequency of suicidal ideation during medication with SSRIs for the treatment of depressive disorders, a corresponding warning was issued in the USA by the regulatory authority, the FDA. Meta-analyses of SSRI therapy in children and adolescents have not, however, identified an increase in the number of successfully executed suicide attempts (Gibbons et al. 2012; Kaizar et al. 2006; Schneeweiss et al. 2010; see also Sect. 4.4.1). Particular attention should nonetheless be given to potential suicidality during the employment of SSRIs, perhaps introducing the medication in an inpatient setting or under especially close supervision.

9.4.1 Therapy of the Acute Symptoms

Table 9.2 provides recommendations for the symptomatic treatment of acute aggression and autoaggression.

In an emergency situation with acute agitation and aggression, antipsychotics are the most appropriate agents (see Chap. 24). Particularly where additional symptoms of the schizophrenic type are presented, antipsychotics are combined with anxiolytics. For anxiety-related aggression and acute suicidality, benzodiazepine monotherapy is in use; for autoaggression (self-injury, self-mutilation) low- to mid-potency antipsychotics can be considered.

Antipsychotics possess the advantage of achieving rapid resolution of tension as well as sedation and can also be flexibly administered as required, within their therapeutic range, at short notice (Table 9.1). In acute severe aggression, and when the patient has no insight in the crucial danger associated, some antipsychotics can be administered parenterally (intramuscularly; intravenously). High-potency antipsychotics (such as haloperidol, ziprasidone) are agents of first choice usually only where there is a need for rapid easing of tension in acute agitation states (Table 9.2). Medium- and low-potency antipsychotics are particularly useful in managing impulse control disorders and aggressive tension.

Cave! Monitoring the ADRs following treatment with antipsychotics is crucial. See Sect. 5.6.

Benzodiazepines (see Chap. 6) are especially suitable for the acute treatment of aggressive restlessness and agitation states. In emergency conditions, because of violent or self-harming behavior of the patient, they are often combined with high-potency antipsychotics (Table 9.2).

Cave! One should be aware of the possibility of a paradoxical increase in aggression, particularly at lower dosages of benzodiazepines.

Table 9.2 Symptomatic treatment of acute aggression and autoaggression

Acute symptoms	Recommended medication (with examples)	Possible doses per day	Maximal daily dosage (mg)[a]
Severe aggression, restlessness, and marked psychotic symptoms	Haloperidol 10 mg i.v. + lorazepam 2 mg i.v. **NB**: lorazepam slowly injected (2 mg/min)!	2–3	Haloperidol 30 (−60) Lorazepam 6 (−7.5)
	Case reports of beneficial effects of ziprasidone 10 mg p.o. or i.m.	According to tolerability **NB**: cardiac effects!	P.o. administration similar to therapy of schizophrenia possible **NB**: individual i.m. dose >10 mg not advisable
Aggression, mild, or no psychotic symptoms	Medium-/low-potency antipsychotics		
	Levomepromazine 50 mg i.m./p.o.	2–3	150
Anxiety with aggression	Benzodiazepines		
	Lorazepam 2.5 mg p.o.	3	7.5
Suicidality	Benzodiazepines		
	Lorazepam 2.5 mg p.o.	3	7.5
Self-harming behavior, suicidal thoughts/acts, self-mutilation	Medium-/low-potency antipsychotics		
	Levomepromazine 50 mg i.m./p.o.	2–3	150
	Benzodiazepines		
	Lorazepam 2.5 mg p.o.	3	7.5

i.m. intramuscular, *i.v.* intravenous, *p.o.* per os

[a]Recommended maximal daily dosage for children <14 years: haloperidol (>3 years) p.o. 0.025 to max. 0.2 mg/kg body weight; chlorprothixene 0.5–1 mg/kg body weight; pipamperone and levomepromazine 1 mg/kg body weight; lorazepam 0.05 mg/kg body weight

Because of the risk of dependence, long-term therapy with benzodiazepines for this indication is obsolete. After a few days and no later than after 3 weeks, benzodiazepine medication should be gradually withdrawn and, if necessary, replaced by other psychopharmacological agents (such as second- and third-generation antipsychotics).

9.4.2 Long-Term Therapy

An overview of the typically employed psychopharmacological agents and their dosages is given in Table 9.3. Second- and third-generation **antipsychotics** are preferable to first-generation antipsychotics for long-term treatment because of their more favorable ADRs profiles. In longer-term treatment of aggressive behavior, these antipsychotics are generally employed at lower doses than for schizophrenic disorders and are therefore quite well tolerated. Depending upon the antipsychotic employed, however, ADRs can occur even at low dosages, including weight gain and elevated serum prolactin levels (see Sect. 5.4.4).

Lithium salts are mainly used for the treatment of severe emotional explosiveness in youth. Where regular monitoring of the medication cannot be assured, valproate or carbamazepine should be chosen. Dosage corresponds to that employed in the treatment for phase prophylaxis (see Chaps. 7 and 20). Dosage of lithium salts is adjusted according to plasma levels (therapeutic range: 0.6–0.8 mmol/L); for aggression an increase to 1.0–1.2 mmol/L can be considered if tolerated.

Intellectual deficiencies, if other treatment measures have failed, are **not contraindications** for lithium therapy, provided that satisfactory compliance and monitoring of therapeutic effect and ADRs are guaranteed. According to our clinical experience, the lack of compliance by a patient with conduct disorder can be problematic,

Table 9.3 Recommendations for longer-term therapy of aggression, impulsivity, and autoaggression

Associated symptoms	Recommended pharmacotherapy (with examples)[a]	See chapter/ table
ADHD	Psychostimulants Methylphenidate 0.5–1 mg/kg body weight Co-medication with risperidone if required	Chapter 8
Aggressive tension, low frustration tolerance, ADHD with less expansive behavioral manifestations	Second- and third-generation antipsychotics Risperidone 0.25–4.0 mg/day Low-potency antipsychotics Levomepromazine 4 × 25–50 mg/day	Chapter 5
Anxiety, suicidality	Benzodiazepines Lorazepam 3 × 1 mg/day Diazepam 3 × 2.5–5 mg/day **Short-term therapy only!**	Chapter 6
Depression, affective involvement, obsessive-compulsive components, anxiety	SSRIs Citalopram: initial dose 10–20 mg/day, standard dose 20–40 mg/day, maximum dose 60 mg/day (all cited doses are for adults), as single morning dose Fluoxetine: initial dose 10–20 mg/day, standard dose in children 20 mg, in adults 20–60 mg/day, maximum dose 80 mg for adults, as single morning dose Sertraline 50–100 mg/day **Note warnings with respect of suicidality (see the blue box on p. 101)**	Chapter 4
EEG abnormalities, epilepsy	Mood-stabilizing antiepileptics Carbamazepine (plasma level 4–10 µg/L) Valproic acid (plasma level 50–100 µg/L) Phenytoin (plasma level 4–15 µg/L)	Chapter 7
Emotionally unstable personality	Low-potency second- and third-generation antipsychotics (for tension resolution), see text Quetiapine 200–600 mg/day Aripiprazole 5–10 mg/day	Chapter 5
	SSRIs (with predominantly depressive mood) **Note FDA black box warnings with respect of suicidality**	Chapter 4
Impulsive conduct disorder, autism and mental deficiency, including cases with self-injurious behavior	High-potency second-generation antipsychotics Risperidone 0.25–0.75 mg evenings, >50 kg up to 1.5 mg evenings or as 2 doses/day Quetiapine 75–350 mg (1–2 doses/day)	Chapter 5
Phasic mood swings, mania, family history of bipolar disorder	Mood stabilizers Lithium salts (plasma level 0.6–1.2 mmol/L) Carbamazepine (plasma level 4–10 µg/L) Valproic acid (plasma level 50–100 µg/L)	Chapter 7
Pronounced autonomic involvement (tremor, tachycardia, hypertension), **organic brain disorders, mental retardation**	β-Adrenoceptor antagonists (β-blockers) Propranolol from 300 mg/day **NB**: vegetative ADRs!	Chapter 6

ADHD attention deficit/hyperactivity disorders, *ADRs* adverse drug reactions, *SSRIs* selective serotonin reuptake inhibitors
[a]Procedures for dosage adjustment, ADRs, interactions, and contraindications, see corresponding chapters

impeding adequate dose adjustment with regard to plasma levels. Variations in blood concentrations, however, lead not only to unreliable efficacy (resulting from the narrow therapeutic range of lithium salts) but also to the risk of severe ADRs (enuresis, weight gain, tremor, etc.) and the risk of intoxication. On the other hand our experience is that the necessity of intensive drug monitoring (see Sect. 7.6) reinforces the regular treatment control by the physician and helps the patient to be compliant also to nonmedical interventions.

Anti-aggressive **effects** of **antidepressants** are manifested **no earlier than 2–3 months** after initiation of therapy. Selecting an antidepressant for the symptomatic treatment of aggression or suicidality is therefore appropriate only for longer-term therapy. The combination with other, more rapidly effective psychopharmacological agents (such as benzodiazepines, antipsychotics) is required until the effect of the antidepressant is manifested.

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Alcohol-Related Disorders

10

Gerhard A. Wiesbeck and Rudolf Stohler

Contents

G.A. Wiesbeck, MD (✉)
University Hospital of Psychiatry,
University of Basel, Wilhelm-Klein-Str. 27,
4012 Basel, Switzerland
e-mail: gerhard.wiesbeck@upkbs.ch

R. Stohler, MD
Substance Use Disorders, Treatment and Research, Psychiatric University Hospital,
Selnaustr. 9, 8001 Zurich, Switzerland
e-mail: stohler@dgsp.uzh.ch

10.1 Definition, Classification, and Target Symptoms

The International Classification of Diseases, 10th revision (ICD-10; World Health Organization 1996) and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5; American Psychiatric Association 2013) classify disorders directly related to increased alcohol consumption as follows:

- **Acute intoxication** (F10.0; DSM-5 Alcohol Intoxication 303.00): this is characterized by loss of inhibitions, lability of mood, and aggression and can also involve attention deficits, reduced capacity for judgment, unsteady posture and gait, and disturbed consciousness.
- The **withdrawal state** (F10.3; DSM-5 Alcohol Withdrawal 291.81): a state arising following discontinuation or reduction of alcohol consumption, characterized by nausea, perspiration, restlessness, disturbed sleep, accelerated heart rate, shaking, fever, and general malaise. Hallucinations and seizures can also occur in severe cases. The most serious form of alcohol withdrawal is delirium tremens alcoholicum (F 10.4).
- **Harmful use** (F 10.1; DSM-5: Mild Alcohol Use Disorder 305.00): the diagnosis "harmful use" (abuse) presupposes that dependence has not yet developed, but that physical or psychological health has already sustained injury.
- The **dependence syndrome** (F10.2; DSM-5: Moderate and Severe Alcohol Use Disorder

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303.90): characterized by a strong desire or a form of compulsion to consume alcohol ("craving"), reduced ability to control the onset, termination, and the level of alcohol consumption, a physical withdrawal syndrome, evidence of tolerance, progressive neglect of other interests in favor of alcohol consumption as well as continuous use despite the fact that harmful consequences are already evident.

DSM-5 classifies "Alcohol-Related Disorders" under "Substance-Related and Addictive Disorders." The criteria for the dependence syndrome are similar in both ICD and DSM classification systems. However, in DSM-5 harmful use and dependence are summed up in one disorder: alcohol use disorder. The criteria "fit within overall groupings of impaired control, social impairment, risky use, and pharmacological criteria" (American Psychiatric Association 2013).

Other disorders related to alcohol abuse such as psychoses (alcohol hallucinosis, irrational jealousy) or the amnesic (Korsakow) syndrome are not important for child and adolescent psychiatry (Clark et al. 2002) and are therefore not discussed here.

The **primary objectives of pharmacotherapy** are to ensure survival and to prevent permanent harmful consequences. In addition, disorder-specific pharmacological treatment aims at the prevention or alleviation of symptoms of intoxication and withdrawal; with respect to alcohol dependence, on the other hand, its aim is the reduction of alcohol consumption and the prevention of relapse. There is no specific pharmacotherapy targeted at harmful use.

Harmful use and **alcohol dependence** may be **accompanied** in adolescents **by further psychiatric disturbances**. The occurrence with conduct disorder, antisocial and emotionally unstable personality development, aggression, impulsivity (including ADHD), suicidality as well as affective, anxiety, and eating disorders is frequent. The data regarding the incidence of these comorbidities varies considerably between studies; depending on disease and sample, the rate is between 20 and 40 %. These so-called comorbid disorders generally also require specific and, in some cases, combined pharmacotherapy, but this needs to be carefully assessed on a case-by-case basis. The reader is referred to the corresponding chapters of this book for further information.

The evidence underlying the pharmacotherapy of alcohol-related disorders in children and adolescents is based upon clinical experience and inferences drawn from the treatment of adults. There are no randomized, double-blind, placebo-controlled studies available on the syndromes discussed above in children or adolescents (Dawes and Johnson 2004).

10.2 Therapeutic Framework

Rather than seeing alcohol dependence as a weakness of will, a character deficiency, or a bad habit, the therapeutic **prerequisite** for any treatment should be a **medical disease concept**, which regards alcoholism as a chronic disorder in the medical sense. Therefore, an atmosphere of respect and empathy should be provided for as well as the opportunity for physical-neurological examinations, for clinical laboratory investigations, and the assessment of EEG and ECG. Brain imaging (positron emission tomography, magnetic resonance imaging) may also be indispensable in some cases. According to the diagnosis, assessment, and management of harmful drinking and alcohol dependence, the disorder-specific diagnosis includes not only interviewing the young patient but also the parents, gathering information from the school, and a pediatric and adolescent psychiatric history as well as psychopathological findings, including the results of a psychological testing (Baving and Bilke 2007; National Institute for Health and Clinical Excellence 2011).

Acute alcohol-related disorders require not only medical, primarily pharmacological treatment, but also psychotherapeutic motivational interventions aimed at promoting the patient's insight into his/her disease and the willingness to cooperate. The **basic principles of** "**motivational interviewing**" (Miller and Rollnick 1991) should therefore be part of the fundamental therapeutic framework, even when pharmacotherapy has priority. Where psychotherapeutic motivational

therapy and medical detoxification treatment are combined, one speaks of "qualified withdrawal," and, at least in German-speaking countries and in England, this approach is regarded as state of the art (Mann and Stetter 2002; National Institute for Health and Clinical Excellence 2011).

10.3 Choice of Pharmacotherapy

Pharmacotherapies of alcohol-related disorders include following stages of treatment: intoxication, withdrawal, or other methods of abstinence initiation, reduction of alcohol consumption or the danger of relapse, and maintenance or relapse prevention. Evidence-based guidelines for the pharmacological management of these treatments are published elsewhere (Lingford-Hughes et al. 2012; Ross and Peselow 2009).

10.3.1 Medications for Treatment of the Withdrawal Syndrome

Clonidine

As a centrally active adrenergic α_2-receptor agonist, clonidine inhibits noradrenergic neurons in the locus coeruleus, thereby primarily ameliorating noradrenaline-mediated withdrawal symptoms ("noradrenaline storm"), including tachycardia and hypertonia, but also to a certain degree tremor, restlessness, and anxiousness. As clonidine possesses neither anticonvulsive nor anti-delirium properties, it is at best suitable for mild to moderate withdrawal syndromes (monotherapy).

Clonidine itself is not addictive. It is commercially available as a hypertensive agent, but there is no approval for the indication "alcohol withdrawal syndrome." There are no specific dosage guidelines for immediate-release clonidine in children and adolescents, so that it is advisable to commence with 0.075 mg, then to cautiously increase the dosage and frequency of administration (up to three times daily) according to symptom severity. Clonidine should be administered orally and intravenously only in exceptional cases (slowly and diluted in NaCl 0.9 %). Subcutaneous or intramuscular injection is also possible. After withdrawal symptoms have subsided, clonidine can be gradually reduced over a period of 5 days. Reduced blood pressure, tiredness, dry mouth, obstipation, and sleep disturbances are common adverse drug reactions (ADRs).

Carbamazepine

Carbamazepine is used in child and adolescent psychiatry off label as a mood-stabilizing anticonvulsant (see Sect. 7.4.2). Carbamazepine is structurally similar to imipramine and clozapine, but its mechanism of action is more complex and not yet completely elucidated; there is evidence that in addition to its inhibition of voltage-gated Na^+ channels, it modulates receptor-mediated neurotransmission (GABAergic, glutamatergic, and monoaminergic) and intracellular signaling pathways (see Sect. 7.3). Carbamazepine possesses no addiction potential.

Carbamazepine is FDA approved for the treatment of epilepsy in children, adolescents, and adults, treatment of pain associated with true trigeminal neuralgia in adults, and treatment of acute manic or mixed episodes associated with bipolar I disorder in adults. Its effectiveness and safety has not been established in the indication "alcohol withdrawal syndrome." Therefore, it is advisable to employ carbamazepine exclusively for prevention of withdrawal-related epileptic seizures.

The recommended daily dosage is 10–20 mg/kg, divided into several doses. Once alcohol withdrawal symptoms have subsided, the medication can itself be slowly withdrawn over several days. Carbamazepine can cause, among other ADRs, vertigo, ataxia, nausea, and allergic skin reactions. More ominous are aplastic anemia and agranulocytosis, which occur only rarely but are very serious ADRs. A further rare but dangerous ADR is the Lyell syndrome (toxic epidermal necrolysis).

Where there is **evidence of liver damage** – for example, significantly elevated transaminase levels caused by ethanol, hepatitis, etc. – carbamazepine can be **replaced by oxcarbazepine**, well tolerated even in the presence of mild to moderate hepatic injury. Oxcarbazepine is also used off label in child and adolescent psychiatry as a

mood-stabilizing anticonvulsant (see Sect. 7.4.5). Treatment can commence with 8–10 mg/kg body weight per day, divided into two to three doses. As a rule of thumb, a conversion ratio of carbamazepine to oxcarbazepine dose of 1:1.5 may be applied for the rapid achievement of seizure prophylaxis.

Benzodiazepines

Benzodiazepines are used off label in child and adolescent psychiatry as anxiolytics (see Sect. 6.4.1) and can also be employed in the treatment of the alcohol withdrawal syndrome. They *reduce anxiety and restlessness in particular* and *also effectively reduce withdrawal-related seizures*. As there is usually no danger in children and adolescents of accumulation as the result of hepatic cirrhosis, even benzodiazepines with long half-lives (such as diazepam, chlordiazepoxide) can be employed. Good results have been reported for *lorazepam* and *oxazepam*, which are glucuronidated and therefore place no demands upon the parenchyma. In sum, benzodiazepines are safe medications with extensive and practical experience in the treatment of alcohol withdrawal syndrome. The main risk is the *dependence potential* (see Sect. 6.4.1). Benzodiazepine use should therefore be limited to the period of detoxification and distributed only under controlled conditions. For dosage, see Table 6.4.

Clomethiazole

Clomethiazole, a hypnotic drug, is approved in several European countries for the treatment of alcohol withdrawal and alcohol withdrawal delirium in adults but is not available in the USA. The advantages of clomethiazole include its low hepatotoxicity, its good tolerability, its **anticonvulsive properties**, and its sedative and anti-deliriant efficacy. Unfortunately, it depresses respiration, increases bronchial secretions, and possesses a considerable addiction potential.

Clomethiazole is highly effective against the entire symptomatic spectrum of alcohol withdrawal. It should be administered several times a day because of its short half-life and individually dosed, but is easily adjusted. Clomethiazole should not be prescribed according to a schedule but rather according to the degree of sedation. Commencing with two capsules, two tablets or 10 ml of the mixture is advisable. The dosage should then be increased according to the severity of withdrawal symptomatology.

10.3.2 Medications for Reducing Alcohol Consumption or Reducing the Danger of Relapse

Disulfiram

This stalwart of relapse prophylaxis **induces alcohol intolerance** by inhibiting acetaldehyde dehydrogenase, interrupting metabolism of ethanol at the level of acetaldehyde, so that alcohol consumption leads to an extremely unpleasant intolerance reaction (acetaldehyde syndrome). This can be life-threatening if further alcohol is consumed.

Although disulfiram has been prescribed for decades as relapse prophylaxis in alcohol dependence, there is no unambiguous evidence-based proof of its working mechanism. There are only a few, casuistic reports regarding its employment in adolescents (Myers et al. 1994). For this reason, but also because of significant ADRs (sedation, allergic reactions, disturbed vision, hepatotoxicity) and the availability of better alternatives, the agent should be **used** in adults only in exceptional cases, but **not in adolescents**.

Naltrexone

Naltrexone is *approved* in several countries including the USA for alcohol dependence relapse prevention in adults. However, there have been no controlled studies on the use in adolescents.

Naltrexone exerts its effects as a competitive antagonist at the μ-opioid receptor; it possesses no intrinsic receptor activity properties and thus neither dependence potential nor clinically significant effects of its own. Naltrexone is well tolerated and has a broad therapeutic range, and, in contrast to disulfiram, no dangerous effects arise

from concurrent alcohol consumption. Headache, tiredness, disturbed sleep, depression, and exanthemata are potential ADRs.

The recommended dosage for adults is 50 mg/day; treatment should be continued for at least 6–12 months. There are injectable forms of naltrexone, which have been designed to overcome poor adherence. An extended-release monthly injectable formulation of naltrexone (XR-NTX) is licensed in the USA.

In a meta-analysis of several controlled studies, the **efficacy** of naltrexone in alcohol dependence was **corroborated** (Kranzler and Van Krik 2001). According to this analysis, naltrexone reduces the number of days of heavy alcohol consumption and prolongs the period before the first serious relapse. The medication appears to reduce the subjective effect of alcohol ("high") and thereby the danger of major relapse. Naltrexone is most effective when combined with parallel cognitive psychotherapy (Kranzler and Van Krik 2001). It is therefore recommended to employ naltrexone when total abstinence is not possible (in the sense of relapse prevention or reduced consumption). In a more recent meta-analysis, naltrexone has been found to be slightly more efficacious than acamprosate in reducing heavy drinking and craving (Maisel et al. 2013). In addition, it was shown that requiring abstinence before the trial was associated with larger effect sizes for abstinence maintenance and reduced heavy drinking compared with placebo.

An **alternative** oral medication is **nalmefene**, which is an opioid antagonist with a differing pharmacological profile to naltrexone at the three opioid receptor subtypes (Lingford-Hughes et al. 2012). Nalmefene can be prescribed safely in alcohol dependence and can significantly prevent relapse to heavy drinking. It may have a better safety profile than naltrexone with a reduced risk of liver toxicity.

Acamprosate

Acamprosate is *FDA approved* for the maintenance of abstinence in patients with alcohol dependence who are abstinent at treatment initiation. Treatment with acamprosate should be part of a comprehensive management program that includes psychosocial support. The numerous controlled studies were all conducted in adults; the safety and good tolerability of acamprosate confirm that it should be the **first choice agent in adolescents** when pharmacological relapse prophylaxis is necessary. Advice regarding dosage is found in the Prescribing Information. The recommended dose is two 333 mg tablets (each dose should total 666 mg) taken three times daily.

Table 10.1 Clinical advantages of acamprosate

No psychotropic effect of its own (therefore no potential for dependence)
Well tolerated (transitory initial diarrhea in approximately 10 % of patients as most frequent ADR)
No increases of hepatic enzymes
No interactions between acamprosate and alcohol
No interactions with disulfiram, diazepam, or imipramine reported
Discontinuation of acamprosate therapy is not necessary in case of relapse

The precise mechanism of action of acamprosate has not yet been completely elucidated. A major role must (Littleton 1995), however, be attributed to its indirect antagonism of the NMDA receptor (see Sect. 1.3.3.1). Acamprosate is well tolerated, possesses no dependence potential, and has a broad therapeutic range. Concurrent alcohol consumption leads to no clinically relevant interactions (Table 10.1).

The **relapse prophylactic effect** of acamprosate has been impressively **documented** (Mann et al. 2004). In comparison with placebo, acamprosate significantly increased both the probability of abstinence and the proportion of alcohol-free days after a relapse. In a meta-analysis of all European studies, the relative risk of relapse during acamprosate treatment was only 62 % (Mann et al. 2004). A more recent meta-analysis demonstrated that acamprosate is slightly more efficacious in promoting abstinence than naltrexone (Maisel et al. 2013). In addition, it was found that detoxification can be associated with better abstinence outcomes as compared to placebo.

10.4 Treatment Strategies

10.4.1 Intoxication

The transition from inebriation to intoxication is faster in children and adolescents than in adults (Lamminpää 1994). Mild to moderate intoxication can be treated on an outpatient basis and usually does not require pharmacological intervention. In contrast, severe alcohol intoxication is a life-threatening condition that can involve CNS depression and impaired consciousness ranging to coma and therefore necessitates hospitalization as a medical emergency.

There is currently no specific "antidote" that antagonizes acute effects of alcohol, nor is there a medication available that accelerates alcohol metabolism and elimination. The effectiveness of naloxone ("arousal reaction") in heavily intoxicated, comatose patients has not yet been adequately corroborated.

Psychomotor agitation can be treated with a high-potency antipsychotic (such as haloperidol).

NB: Reduced seizure threshold! Medications that can enhance alcohol-induced respiratory depression (benzodiazepines, clomethiazole) should be avoided.

10.4.2 Withdrawal Syndrome

As the severity of the withdrawal syndrome is closely correlated with the duration of consumption, alcohol withdrawal symptoms are **much milder in adolescents than in adults**. For the same reason, the classic delirium tremens alcoholicum is rarely encountered in adolescents (Stewart and Brown 1995). On the other hand, adolescents react to withdrawal-related changes with greater anxiety than adults, which can lead to aggravation of symptoms, depressive attacks, and suicidal crises.

The need for medication can vary widely between patients, so that pharmacotherapy of the withdrawal syndrome should always be individually adjusted and symptom oriented. The application of generalized dosage schedules should be rejected.

Pharmacotherapy is not required for milder forms of dependence. Patients should, however, be informed that during withdrawal they might feel nervous and increasingly anxious for several days and that sleep disturbances may occur.

Clonidine and **carbamazepine** are appropriate for the treatment of moderate withdrawal syndromes. Clonidine is particularly useful for ameliorating vegetative hyperactivity, while carbamazepine has the advantage of providing seizure prophylaxis. If withdrawal seizures have been identified in the patient's prior history, carbamazepine should be employed, regardless of the severity of the withdrawal syndrome. As the danger of seizures is greatest during the first days of withdrawal, the dosage of normal release formulation carbamazepine should be carefully but quickly increased to achieve an effective serum level (see also Sect. 7.4.2). Clonidine and carbamazepine have no effects upon delirium; however, both medications are suitable for a combination treatment with benzodiazepines or clomethiazole.

Benzodiazepines (see Sect. 6.4.1) are highly effective in the treatment of alcohol withdrawal syndrome. They can ameliorate withdrawal symptoms, reduce the risk of delirium, and also possess significant antiepileptic properties. Benzodiazepines with short half-lives (oxazepam, lorazepam) accumulate to a lesser degree and less commonly lead to excessive sedation; those with longer half-lives (diazepam, chlordiazepoxide), on the other hand, are particularly effective in the prophylaxis of withdrawal seizures.

Clomethiazole is the first choice medication for severe withdrawal syndromes as well as for delirium with or without withdrawal seizures. For this reason and because of its high addiction potential, clomethiazole should **only be prescribed for hospitalized patients**. The initial dosage should be such as to clearly dampen withdrawal symptomatology, but the patient should

still be in a position to be roused. In order to avoid the danger of the additive cardiovascular and respiratory depressive effects of ethanol and clomethiazole, the latter should not be administered, if clinically possible, until the breath alcohol level falls to c. 0.10 % by volume.

10.4.3 Relapse Prevention

Currently, three medications are available for pharmacological relapse prevention: **disulfiram**, **naltrexone**, and **acamprosate** – disulfiram mainly for reasons of tradition; naltrexone and acamprosate, however, have shown effectiveness in a number of evidence-based trials. There are no results from controlled studies for any of the substances in children and adolescents.

For these reasons and because of its favorable clinical properties (Table 10.1), **acamprosate** should be the **first choice** where pharmacological relapse prevention in adolescents is required. As its efficacy has thus far been documented only in the ideal case – the detoxified adult alcoholic committed to abstinence – it is not suitable as pharmacological relapse prophylaxis in adolescents who still drink and are unwilling to stay abstinent. The treatment of adolescents lacking insight into their condition thus remains the task of motivational psychotherapy.

Treatment with acamprosate should commence immediately after detoxification, ideally as early as the end phase of alcohol withdrawal. Studies to date justify a treatment duration of 12 months, but in individual cases there is no reason why administration should not be continued. The dosage should be adjusted according to body weight and can, because of its good tolerability, be guided by recommendations for adults (body weight <60 kg: 2–1–1 tablets/day, >60 kg: 2–2–2 tablets/day). Initial gastrointestinal ADRs in about 10 % of patients mean that the drug should be introduced gradually.

As with any pharmacotherapy, treatment errors can be avoided and compliance improved by comprehensively informing patients. Patients often cease to take the medication after drinking alcohol again. Each patient must therefore be aware that acamprosate can minimize the duration and severity of a relapse if they continue to take the medication.

If treatment with acamprosate does not achieve the desired success of treatment, a **combination with naltrexone** can be tested. The actions of the two medications complement each other in a useful manner, and there is evidence that the acamprosate-plus-naltrexone combination is more efficacious (Kiefer et al. 2003).

In addition to appropriate pharmacological relapse prevention, utilizing laboratory diagnostic procedures for **abstinence monitoring** is recommended. Apart from breath and blood alcohol assessment, the determination of ethyl glucuronide and carbohydrate-deficient transferrin is possible; the assay of ethyl glucuronide in 10 ml spot urine provides evidence of alcohol consumption in the previous 40–78 h.

The determination of carbohydrate-deficient transferrin in 1 ml serum provides evidence of increased alcohol consumption during the previous 3 weeks. Increased values are to be expected for a daily consumption of more than 50–80 g alcohol.

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Anxiety Disorders and Phobias

11

Andreas Warnke

Contents

A. Warnke, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr.15, 97080 Würzburg, Germany
e-mail: warnke@kjp.uni-wuerzburg.de

11.1 Definition, Classification, and Target Symptoms

11.1.1 Anxiety Disorders

According to the International Classification of Diseases, 10th revision (ICD-10) classification (World Health Organization 1996), anxiety disorders are characterized by excessive or dysfunctional anxiety reactions. With the exception of separation anxiety disorder, anxiety is not limited to certain objects or situations, as is the case for phobias. Anxiety may be accompanied by less developed depressive or compulsive symptoms, as well as elements of phobic anxiety.

The **ICD-10** classification **differentiates**:

- Panic disorder (F41.0; DSM-5: 300.01)
- Generalized anxiety disorder (F41.1; DSM-5: 300.02)
- Mixed anxiety and depressive disorder (F41.2)
- Other mixed anxiety disorders (F41.3)
- Other specified anxiety disorder (F41.8; DSM-5: 300.09)
- Unspecified anxiety disorder (F41.9; DSM-5: 300.00)
- Separation anxiety of childhood (F93.0; DSM-5: separation anxiety disorder 309.21)

The anxiety disorders in children and adolescents included in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5; American Psychiatric Association 2013) are mainly identical to those in ICD-10. In **DSM-5**, **two subtypes** are included in the chapter of

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generalized anxiety disorder: "Substance/Medication-Induced Anxiety Disorder" (corresponds to ICD-10 F10.180/280/980 up to F19.180/280/980: "Mental and Behavioral Disorders Due to Psychoactive Substance Use") and "Anxiety Disorder Due to Another Medical Condition" (93.84; corresponds to F 06.4 "Organic Anxiety Disorder"). In DSM-5, the Phobic Disorders (F 40, F 93.1, F93.2) and Selective Mutism (312.23; F 94.0) are classified under "Anxiety disorders."

11.1.2 Phobic Disorders

The feature common to phobias is that those affected experience great anxiety in the presence of certain objects or in particular situations that normally do not cause fear in persons without a phobic disorder. Those afflicted at least sometimes recognize that their anxiety is exaggerated or unjustified. One of the principle features of all phobias is the avoidance of the object or situation that arouses anxiety in the phobic person. The avoidance behavior thereby frequently determines the degree of functional impairment. Anxiety can be accompanied by vegetative symptoms such as tachycardia, paroxysmal sweating, tremor, dry mouth, respiratory difficulties, tightness of the chest, thoracic pain, nausea, and vomiting.

The **ICD-10** classification **distinguishes**:

- Agoraphobia (F40.0; DSM-5: 300.22)
- Social phobias (F40.1; DSM-5: Social anxiety disorder 300.23)
- Specific (isolated) phobias (F40.2; DSM-5: 300.29)
- Phobic anxiety disorder of childhood (F93.1)
- Social anxiety disorder of childhood (F93.2)

In DSM-5, there is no correspondence to F93.1 and F93.2 (included in separation anxiety disorder, 309.21).

Constitutional, life history, and current living circumstances – organic and sociocultural – are intermingled with factors of social interaction in the etiology of these disorders (Connolly and Bernstein 2007; Figueroa et al. 2012; Möhler 2012, Rapee 2012; Strawn et al. 2012). The symptomatology includes subjective psychological (such as the feeling of anxiety) features, vegetative symptoms (including tachycardia, sudden sweating) as well as objectively observable reactions and behavioral patterns (such as avoidance and flight behavior). This explains the essentially multimodal treatment approach, in which pharmacotherapy is generally subordinated to psychotherapeutic and social therapeutic interventions but which nevertheless plays a quite important role in individual cases, as well as in specific anxiety disorders.

Anxiety is also a component of a number of other psychiatric conditions such as weight phobia in anorexia nervosa, fear of pollution in obsessive-compulsive disorders, social anxiety in depression, and the paranoid or hallucination-related anxieties of schizophrenia. The pharmacotherapy of these disorder-inherent anxiety states is discussed in the chapters on disorder in this volume.

11.2 Therapeutic Framework

Both outpatient and partially or fully inpatient therapy of anxiety disorders and phobias generally involve **disorder-specific multimodal treatment approaches** (AACAP Official Action 2007; Rapee 2012). This includes comprehensive education of the patient and his or her relatives with respect to the nature of the disorder (psychoeducation) and general measures for the stabilization of autonomic reactions and circadian rhythms (including sleep hygiene, daily programs, physical activities, relaxation techniques).

Cognitive-behavioral therapeutic (CBT) **procedures** are of **central importance** in psychotherapy. Controlled studies of therapeutic efficacy in anxiety disorders in children and adolescents have thus far been reported only for cognitive behavioral therapy (Albon and Schneider 2007; Figueroa et al. 2012; Mohr and Schneider 2013; Rapee 2012), partly in combination with family therapy. A differentiated assessment for the individual clinical conditions is, however, lacking. Important procedural techniques include systematic desensitization, imitation and model learning,

cognitive restructuring, self-control techniques as well as imagination and intention formation. These can be supplemented as required by family therapeutic, psychodynamic, and psychopharmacological measures. In the treatment of social phobias and generalized anxiety disorders, behavioral therapy also aims to remedy deficits in social competence, in problem-solving behavior as well as in the perception of self and others. Anxiety disorders tend to chronification if not treated; the earlier treatment begins, the better the prognosis.

Therapy with psychopharmacological agents as one component of an overall treatment strategy is usually a preparatory and/or parallel symptomatic treatment measure that is particularly appropriate where symptomatology is severe, for crisis intervention and for cases with a chronic course (AACAP Official Action 2007; Bandelow et al. 2008; Muris 2012).

11.3 Choice of Pharmacotherapy

Psychopharmacological agents that can be employed, in principle, are those that improve the target symptoms agitation and anxiety (see Chap. 6). These include:

- **Antidepressants** with serotonergic and/or antihistaminergic properties, primarily preparations from the selective serotonin reuptake inhibitor (SSRI) group (such as fluoxetine, citalopram, fluvoxamine, paroxetine, sertraline). Venlafaxine, a serotonin and noradrenaline reuptake inhibitor, is also employed, as are tricyclic antidepressants, particularly imipramine and clomipramine.
- **Benzodiazepines** as classical representatives of the anxiolytic class. Examples include alprazolam, clonazepam, and lorazepam. In order to reduce dependence risk to a minimum, benzodiazepines should only be prescribed following careful deliberation with regard to the indication (e.g., when rapid symptomatic relief is necessary) and then taken for as short a period as possible (no longer than 6 weeks), until the anxiolytic effect of an SSRI has reached an adequate level, for instance. Whether further treatment with a benzodiazepine is necessary must be regularly reconsidered.
- Low-potency (such as thioridazine, sulpiride, fluspirilene) and second- and third-generation high-potency **antipsychotics** (such as risperidone, aripiprazole, olanzapine). High-potency antipsychotics are employed at low dosages (beneath the neuroleptic threshold) for the treatment of anxiety and anxious-depressive conditions as well as of anxiety in the context of other primary psychiatric disorders (such as schizophrenia).
- Buspirone and opipramol
- β-Adrenoceptor antagonists (β-blockers), such as atenolol and propranolol
- Antihistamines, particularly promethazine
- Certain antiepileptics such as gabapentin

In child and adolescent psychiatry, **SSRIs** have become the agents of **first choice** for the pharmacological treatment of anxiety disorders and phobias (AACAP Official Action 2007; Strawn et al. 2012), although only few SSRIs have thus far been approved for these indications in children and adolescents; **tricyclic antidepressants** were recommended only as medications of **second choice** because of the lack of positive results and the higher probability of adverse drug reactions (ADRs). Their use is associated with greater success when employed in the treatment of comorbid depressive episodes.

The current guidelines for the diagnosis and therapy of children and adolescents with anxiety disorders (AACAP Official Action 2007) recommend **benzodiazepines** as an adjunct short-term treatment with SSRIs to achieve rapid reduction in severe anxiety symptoms that may permit initiation of the exposure phase of CBT (e.g., panic disorder, school refusal behavior).

The current guidelines for the assessment and therapy of children and adolescents with anxiety disorders do not recommend low-potency antipsychotics, opipramol, β-blockers, as well as antihistamines such as doxylamine and diphenhydramine for the pharmacological treatment (AACAP Official Action 2007; Strawn et al. 2012). Buspirone is suggested as an alternative to be used alone or in combination with SSRIs.

Pregabalin (see Chap. 6) is an important **treatment alternative** in the therapy of generalized

anxiety disorder, approved for this indication in adults. Pregabalin rapidly reduced anxiety symptoms in four randomized, placebo-controlled studies, and this reduction was sustained. It was associated with fewer ADRs and was better tolerated than venlafaxine, with a positive influence on both physical and emotional symptoms (Montgomery et al. 2006). There have thus far been, however, no clinical studies in children and adolescents, and therefore, it is also not recommended for the treatment of anxiety disorders and phobias.

11.3.1 Panic Disorders/Agoraphobia and School Anxiety and Phobia (School Refusal/ Separation Anxiety)

SSRIs are regarded as the **first-choice** medications for the therapy of these anxiety disorders (Figueroa et al. 2012). Only after trials with different SSRIs have failed to provide symptomatic improvement is an attempt with a tricyclic antidepressant appropriate, with careful monitoring of cardiac function indicated (Birmaher et al. 1994; Masi et al. 2001). The same applies to all these anxiety disorders: any medication is only justified when the procedures that are always indicated in the first instance – psychoeducational, psychotherapeutic (CBT), and social therapeutic measures (e.g., change of school in case of excessive academic demands) – prove insufficient (e.g., to enable reintegration into school).

11.3.2 Social Phobias

SSRIs, such as paroxetine, sertraline, escitalopram, fluoxetine, and fluvoxamine, are regarded as the medications of **first choice** in the treatment of social phobic disorders on the basis of randomized, controlled studies (Beidel et al. 2007; Correll et al. 2011; Davidson 2006; Muller et al. 2005; Segool and Carlson 2007).

In an open-label study of mirtazapine in children and adolescents, more than half of the participants responded well, although significant weight gain was also reported; socio-phobic symptoms improved significantly during the observation period, as did coexisting depressive and other anxiety symptoms (Mrakotsky et al. 2008). In a placebo-controlled study, slow-release venlafaxine (a selective serotonin and noradrenaline reuptake inhibitor) was effective in disorders with social anxiety in adults (Liebowitz et al. 2005). It was also reported to be effective in socially anxious youths (March et al. 2007).

For patients with social phobia who do not respond to SSRI therapy or develop ADRs during such therapy, the MAO-A inhibitor moclobemide is seen as a treatment alternative (second-choice medication; Muller et al. 2005). In order to minimize the risk of a serotonin syndrome (see Chap. 4), the combination of moclobemide with another serotonergic agents (SSRIs, St John's wort) should be strictly avoided.

In cases where pronounced **vegetative symptoms** accompany social phobia (nervousness, shaking, muscular tension, sweating, palpitations, difficulties with swallowing, vertiginous feelings) or for "stage fright," the supplementary use of **β-blockers**, such as atenolol or propranolol, is recommended.

For the acute management of anxiety-laden social situations, the short-term use ad hoc of benzodiazepines, such as alprazolam, lorazepam, or clonazepam, can be helpful.

> Significant symptom reduction in social phobias, as in other phobias, can only be achieved in combination with behavioral therapeutic measures!

11.3.3 Generalized Anxiety Disorders

Dieleman and Ferdinand (2008) evaluated nine randomized, double-blind studies of the pharmacotherapy of generalized anxiety disorder, separation anxiety disorder, and social phobia with antidepressants and benzodiazepines in children and adolescents and concluded that neither tricyclic antidepressants nor benzodiazepines were superior to placebo. **SSRIs**, in contrast, were superior to placebo, so that these could be regarded as **first-choice medications** in the

treatment of generalized anxiety disorder and of separation anxiety. Two placebo-controlled, double-blind studies have also found that a slow-release formulation of venlafaxine represented a safe and effective treatment of generalized anxiety disorder in children and adolescents (Rynn et al. 2007).

For the therapy of **acute anxiety states**, the short-term employment of **benzodiazepines** such as diazepam, alprazolam, clonazepam, and lorazepam is preferable, as a broad spectrum of different anxiety symptoms can be favorably influenced (AACAP Official Action 2007; Simeon and Ferguson 1987; Simeon et al. 1992a; Strawn et al. 2012). In patients for whom benzodiazepines are contraindicated – for example, because of a history of drug or alcohol abuse or because of the danger of respiratory depression – the less sedative **buspirone** is a pharmacological alternative for the therapy of generalized anxiety states, having been found in open pediatric and adolescent psychiatric studies to be effective as an anxiolytic (Kranzler 1988; Simeon et al. 1992b). Because its onset of action is subject to a 1–2-week latency, buspirone is not suitable as an emergency medication or for administration on an ad hoc basis.

11.3.4 Post-traumatic Stress Disorder (PTSD)

The selection of medication for post-traumatic stress disorder should be primarily based upon the most prominent clinical symptom patterns such as "panic" or "depression." Various **SSRIs** are applied (including sertraline, approved in the USA for the use in children and adolescents with post-traumatic stress disorder).

Alternatives for symptomatic treatment of excessive agitation include **clonidine** (Harmon and Riggs 1996) and **propranolol** (Famularo et al. 1988), particularly in cases involving tachycardia and intrusions (involuntary recapitulation of traumatizing experiences), employed for about 7 days, and then slowly discontinued. For intrusions, irritability, or sleep disturbances, mood stabilizers (see Chap. 7) can also be appropriate. Treatment with anxiolytics should continue for a sufficient duration, at least 12–24 months for chronic post-traumatic stress disorders.

11.3.5 Simple Phobias

The efficacy of psychopharmacological agents in isolated phobias is controversial. In individual cases the limited and targeted administration of **benzodiazepines** appears to support attempts to approach the object of the phobia in the context of behavioral therapeutic treatment, the primary treatment option for phobias. The use of medications is otherwise limited to treatment of comorbid panic attacks or other anxiety symptoms.

11.4 Treatment Strategies

11.4.1 General Therapeutic Measures

A **multimodal therapeutic strategy** is indicated for the treatment of anxiety disorders in children and adolescents. A therapeutic program consists of primarily symptom-oriented, specific CBT, complemented by psychoeducative elements and generally stabilizing adjuvant measures as well as by family and socio-therapeutic methods (see Sect. 11.2).

Indications for a purely symptomatic and not causal **pharmacological** (parallel) **therapy** are:

- Severe and/or chronic disease course.
- Pronounced symptomatology in context of acute treatment as crisis intervention.
- Clear impairment of everyday living, combined with the threat of a long-term disorder of psychosocial development (for example, if school attendance is not possible).
- Absence of symptomatic improvement achieved by the previously mentioned non-pharmacological treatment strategies within 4–6 weeks.

Explanation of the effects and ADRs of pharmacological therapy is particularly important in order to make clear the absolute necessity of

psychotherapeutic treatment measures for treatment success and to neutralize the danger of unrealistic "expectations of a cure" through pharmacological therapy alone.

> The use of psychopharmacological agents for anxiety disorders and phobia disorders in children and adolescents should be the exception; their employment should only be temporary, as support for other measures. Treatment with psychotropic drugs alone is not to be undertaken (AACAP Official Action 2007; Ipser et al. 2009).

11.4.2 Selection of Medication and Dosage

The selection of the medication should be determined by the type and duration of the anxiety disorder as well as by any comorbid disorders and the age of the patient. Table 11.1 presents an overview of the indications spectrum and the dosages of these psychopharmacological agents.

It is recommended that the drugs employed be introduced in a gradual manner, with slow titration of dosage.

SSRIs

- are administered daily usually in the morning.
- Clinical improvement begins within 2–4 weeks.
- If there is no benefit at all after week 8, an alternative SSRI should be applied. After 4–6 months, depending upon symptomatic course, withdrawal of the SSRI may be attempted, reducing dosage by small steps.
- If there is a significant return of the symptoms, the former effective medication and dosage should be restarted.

Benzodiazepine

- may be employed at the commencement of pharmacotherapy of generalized anxiety disorders in the case of acute, well-defined symptoms and when a rapid solution is needed.
- **Discontinuation** of pharmacotherapy with benzodiazepines should commence after **no later than 4–6 weeks**, given the danger of dependence.
- As a guideline, a weekly dosage reduction of 25 % of the dosage at commencement of withdrawal is recommended.
- One has to take into account the relevant prescribing criteria (discussing possible ADRs and the risk of dependence with the patient and his or her family, use to be as short term as possible, tapering discontinuation of medication after regular administration for more than a week; **NB**: withdrawal syndrome!).
- Where a more extended delay prior to the onset of efficacy is acceptable, antidepressants (SSRIs) and, as an alternative, buspirone are primarily indicated.
- Where longer pharmacological treatment is necessary (more than 4–6 weeks), initial treatment with benzodiazepines should be followed by a switch – after a "washout period" if at all possible – to antidepressants or buspirone.

Cave!

- For the therapy of **acute panic disorders** with marked symptoms, **benzodiazepines** are generally employed. In case of high-frequency panic attacks, benzodiazepine therapy may be provisionally continued for a longer period (4–6 weeks), whereby dividing the daily dosage into two or three individual doses is advisable. **At the same time**, pharmacotherapy with an SSRI or **antidepressant** from the group of tricyclic antidepressants with predominantly serotonergic actions (such as imipramine, clomipramine) should be **initiated**. After an adequate dose has been reached, the benzodiazepine can be gradually reduced and then discontinued. The high risk of relapse means that a maintenance phase of several months (longer in some cases) is appropriate for anxiolytic medication. It should then be slowly, stepwise discontinued. β-Blockers may be used for excessive vegetative activity.
- Psychopharmacological treatment in phobic disorders is only justified for more severe manifestations. The choice of medication

Table 11.1 Guidelines for pharmacological treatment of anxiety disorders and phobias

Psychopharmacological group or medication	**Initial dosage** (mg)	**Dosage increase** (mg)	**Target dosage** (mg/day)	**Indication**	**Comments**
SSRIs				Panic disorders, generalized anxiety disorders, social phobia	ADRs: libido loss, erection disorder, withdrawal syndrome In detail, see Chap. 4
Citalopram	10	Every 5–7 days (10)	20–40, max. 60		
Escitalopram	5	Every 5–7 days (5)	5–20, max. 20		
Fluoxetine	5–10	Every 5–7 days (5–10)	up to 40, max. 60		
Fluvoxamine	25	Every 5–7 days (25)	up to 200		
Paroxetine	5–10	Every 5–7 days (5–10)	up to 50		
Sertraline	25	Every 5–10 days (5–10)	up to 200		
Other antidepressants					
Mirtazapine	7.5–15	Every 5–7 days (7.5)	30, max. 45	Social phobia	See Chap. 4
Reboxetine	2	Every 5–7 days (2)	4–8, max. 12	Panic disorder	See Chap. 4
Venlafaxine	37.5	Every 3 days	75–150, max. 375	Generalized anxiety disorder, social phobia	See Chap. 4
Tricyclic antidepressants				Panic disorder, generalized anxiety disorder; medication of second choice	See Chap. 4
Imipramine	10–25	Every 5–7 days (5)	25–200		
Clomipramine	10–25	Every 5–7 days (5)	max. 50		
Benzodiazepines				Panic disorders, school anxiety/ phobia	Short-term use recommended! Gradual discontinuance to avoid withdrawal symptoms See Chap. 6 NB: respiratory depression
Alprazolam	0.125–0,25	Every 3–4 days	2, max. 4		
Diazepam	2–4	Daily	5, max. 10		
Lorazepam	0.5–1	Daily	3–4, max. 6		

(continued)

Table 11.1 (continued)

Psychopharmacological group or medication	Initial dosage (mg)	Dosage increase (mg)	Target dosage (mg/day)	Indication	Comments
Buspirone	2.5–5	Weekly	15	Generalized anxiety disorder	Gradual dose increase over 4–6 weeks See Chap. 6
β-Adrenoceptor antagonists (β-blockers)				Post-traumatic stress disorder, examination anxiety	Short-term administration, rebound phenomena, latency of effect See Chap. 6
Atenolol	12.5–25	Weekly	100		
Propanolol	10	Every 2–5 days (10)	60–100		
Certain antiepileptics Pregabalin	150	Every 7 days	300, max. 600	Generalized anxiety disorder	

Modified from Kutcher (2002)

Cave: The use of psychopharmacological agents for anxiety disorders and phobia disorders in children and adolescents should be the exception; their employment should only be temporary and as support for other measures. Treatment with psychotropic drugs alone is not to be undertaken

ADRs adverse drug reactions, *SSRIs* selective serotonin reuptake inhibitors

must consider in particular the specific causes or triggers of the phobia. **Clomipramine** should be considered for depressive or compulsive-neurotic children and adolescents with phobic disorders. For phobias with predominantly anxiety components, therapy with **SSRI** antidepressants is preferable.

- In refractory cases – that is, when appropriate psychotherapeutic measures and the initially prescribed pharmacotherapy have not achieved a satisfactory improvement of anxiety symptoms – **supplementary augmentative treatment** with a **second- or third-generation antipsychotic** can be considered. The adjuvant employment of low-dosage risperidone in adult patients with generalized anxiety disorder and panic disorder has proved effective in open-label and controlled studies (Brawman-Mintzer et al. 2005; Simon et al. 2006). Supplementary medication with olanzapine in refractory panic disorder (Sepede et al. 2006) and with aripiprazole in panic and generalized anxiety disorder was found to be helpful (Hoge et al. 2008).

To Sum Up

- The use of psychopharmacological agents for anxiety disorders and phobic disorders in children and adolescents should be the exception.
- Preparations should be introduced in a gradual manner, with slow titration of dosage.
- SSRI medication: clinical improvement begins within 2–4 weeks. ADRs: libido loss, erection disorder, and withdrawal syndrome. In detail, see Chap. 4.
- Benzodiazepines may be employed in the case of acute, well-defined symptoms and when a rapid solution is needed (e.g., acute panic disorder). NB: benzodiazepines respiratory depression; see Chap. 6. Discontinuation of pharmacotherapy with benzodiazepines should commence after no later than 4–6 weeks, given the danger of dependence. NB: withdrawal syndrome! For prevention: weekly dosage reduction of 25 % of the dosage of the benzodiazepine.

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Attention-Deficit/Hyperactivity Disorders

12

Susanne Walitza, Marcel Romanos,
Laurence Greenhill, and Tobias Banaschewski

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S. Walitza, MD (✉)
Department of Child and Adolescent Psychiatry,
University of Zurich, Neumuensterallee 9,
P.O. Box 1482, 8032 Zurich, Switzerland
e-mail: susanne.walitza@kjpdzh.ch

M. Romanos, MD
Department of Child and Adolescent Psychiatry,
Psychosomatics and Psychotherapy,
University of Würzburg, Füchsleinstr.15,
97080 Würzburg, Germany
e-mail: romanos@kjp.uni-wuerzburg.de

L. Greenhill, MD
NYS Psychiatric Institute,
New York Presbyterian Hospital,
Riverside Drive 1051, New York, NY 10032, USA
e-mail: llg2@columbia.edu

T. Banaschewski, MD
Department of Child and Adolescent Psychiatry,
Psychosomatics and Psychotherapy,
University of Mannheim, J5, 68159 Mannheim, Germany
e-mail: tobias.banaschewski@zi-mannheim.de

12.1 Definition, Classification, and Target Symptoms

Attention-deficit/hyperactivity disorder (ADHD) is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, has persisted for at least 6 months to a degree that is inconsistent with expected developmental levels and that negatively impacts directly on social and academic/occupational activities. Manifestations of the disorder must be present in more than one setting (e.g., home, school, or work). Typically, symptoms vary depending within a given setting.

According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (**DSM-5**) criteria, several inattentive or hyperactive-impulsive symptoms must have been present prior to the age of 12 years (American Psychiatric Association 2013).

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DSM-5 distinguishes three different presentations, a predominantly inattentive presentation, a predominantly hyperactive/impulsive presentation, and a combined presentation, if criteria for both inattention and hyperactivity-impulsivity are met. Although the lists of 18 symptoms from the DSM-5 and the International Classification of Diseases, 10th revision (**ICD-10**; World Health Organization 1996), for ADHD are similar, ICD-10 is more restrictive as some symptoms must be present in all of the three dimensions (inattention, hyperactivity, and impulsivity), and hyperkinetic disorder (the nomenclature used in the ICD-10 that correspond to ADHD in the DSM-5) is excluded if depression and/or anxiety disorders are also identified.

The **targets** of pharmacotherapy are the **core symptoms** of ADHD, **associated symptoms** (such as aggression), and any **comorbid disorder** (including anxiety, tics, and developmental disorders). As many as 70–80 % of ADHD patients (children and adolescents as well as adults) present comorbid psychiatric disorders (Levy et al. 2013; Taurines et al. 2010). The most frequent (>50 %) are "externalizing" disorders (Angold et al. 1999; Groenman et al. 2013) such as oppositional defiant disorder or conduct disorder, which occur more often with the combined presentation of ADHD. Specific learning disorder commonly co-occurs with ADHD (Czamara et al. 2013; Levy et al. 2013), but also internalizing disorders (such as anxiety and depressive disorders) are more often comorbid with ADHD than in the general population (Angold et al. 1999; MTA Cooperation Group 1999b).

12.2 Therapeutic Framework

12.2.1 Diagnostic Requirements

ADHD has a complex pathogenesis, in which multiple genetic and environmental factors interact during early development and which is associated with alterations and maturational delays within different neural networks and deficits in the neuropsychological functions. Certain behavioral symptoms, however, can also be mimicked by symptoms of somatic disorders, e.g., hyperthyreosis and absence epilepsy, or other psychiatric disorders, e.g., oppositional defiant disorder, conduct disorder, and pervasive developmental disorders. Therefore, a careful assessment of each symptom in the child's history and consideration of a range of differential diagnoses and coexisting conditions are always necessary for the diagnosis of ADHD.

Several guidelines for assessment and treatment have been published over the last 10 years (American Association of Child and Adolescent Psychiatry: AACAP 2007, Canadian Attention Deficit Hyperactivity Disorder Resource Alliance: CADDRA 2011; European Society for Child and Adolescent Psychiatry: Taylor et al. 2004; National Institute for Health and Clinical Excellence: NICE 2008) not only for clinicians but also for patients and caregivers. All of the guidelines use **multidisciplinary assessments** including, e.g., standardized clinical interviews with the child, parents, and if possible, with teachers; observations of the behavior; psychological testing; and physical examinations. For the differential diagnosis, investigations should not be routine but guided by history and physical examination (Taylor et al. 2004).

12.2.2 Therapeutic Requirements

The **multimodal treatment approach** includes:

- Family- or school-related education and interventions
  - Instruction and counseling (psychoeducation) of parents, teachers, and other caregivers (preschool, school)
  - Parent training
- Child-related educations and interventions
  - Instruction and counseling (psychoeducation)
  - Psychotherapy (particularly cognitive behavioral therapy)
  - Pharmacotherapy

Psychoeducation alone or in combination with pharmacotherapy is usually the standard of care in Europe, and behavioral treatment is often provided to sustain success of

pharmacotherapy and to modify conduct problems. In the context of **non-pharmacological interventions**, cognitive treatment, neurofeedback training, and dietary measures can be regarded as potential, but to date not fully evidence-based treatment options. A recent review and meta-analysis of non-pharmacological interventions for ADHD has concluded that better evidence for efficacy from blinded assessments is required for behavioral interventions, neurofeedback, cognitive training, and restricted elimination diets before they can be supported as treatments for core ADHD symptom (Sonuga-Barke et al. 2013). Although not effective for ADHD symptoms themselves, behavioral interventions may result in other positive effects (e.g., reducing comorbidity or psychosocial difficulties).

12.2.3 Indication for Pharmacotherapy

Psychoeducation forms the cornerstone of treatment and should be offered to all affected families. **North American guidelines** recommend pharmacological and/or behavioral therapy (AACAP 2007; Greenhill et al. 2002a). **European guidelines** differ from those of North America in that psychoeducational and behavioral interventions are generally recommended as first-line treatments for children with moderate impairment (Taylor et al. 2004) although a recent meta-analysis suggests limitations in the efficacy of non-pharmacological treatments (Sonuga-Barke et al. 2013). In Europe, pharmacological treatment as a first-line treatment is generally reserved for those children with severe pervasive and functionally impairing symptomatology or those with less severe ADHD for whom nondrug interventions are either unavailable or have been found to be inadequate (Taylor et al. 2004). The **Canadian guidelines** recommend an individual treatment approach ("to treat each patient as a unique being"), which can start with different options (CADDRA 2011). If medication are used, then long-acting formulations of psychostimulants and atomoxetine are the first choice. Comorbid disorders may necessitate alternations to the treatment plan or additional treatment.

12.3 Selection of Pharmacotherapy

ADHD is the **primary indication** for therapy with **psychostimulants** (see Sect. 8.4.1), which have large effects on the child's symptoms of overactivity and inattention, regardless of whether combined with behavioral therapy or not (Swanson et al. 2001). In the National Institute of Mental Health (NIMH) Collaborative Multimodal Treatment Study of Children with ADHD (MTA study), the effects of both pharmacological therapy (methylphenidate and intensive counseling) and of multimodal therapy (methylphenidate and intensive behavioral therapy) were significantly more effective after 14 months than behavioral therapy alone or the "standard" (treatment as usual in the community) therapy of the control group. The multimodal therapy was not significantly better than pharmacological therapy alone but produced significant improvements of ADHD symptoms at a lower dosage of methylphenidate (MTA Cooperation Group 1999a, b, 2004).

For further details regarding the medications discussed here, such as clinical effects and efficacy, recommended dosages, adverse drug reactions (ADRs), interactions with other medications, and contraindications, the reader is referred to the relevant special Chap. 8.

12.3.1 First-Choice Medications

The psychostimulants methylphenidate and amphetamine are the most effective agents for the reduction of core ADHD symptoms (see Sect. 8.4.1). According to randomized, placebo-controlled trials in children and adolescents, 65–75 % of the patients with ADHD have been positive responders to psychostimulants compared to 4–30 % of patients treated with placebo (AACAP 2007; Greenhill 2002). **Methylphenidate** is the **best-investigated medication** employed in child and adolescent psychiatry. In 2000, already more

than 40 review articles and meta-analyses had been published; more than 5,000 ADHD patients had participated in methylphenidate efficacy studies. More than ten meta-analyses and systematic reviews comparing different formulations of long-acting methylphenidate preparations have been published between 2000 and 2012.

Amphetamine preparations have proved highly efficient in the treatment of the core symptoms of ADHD and associated functional impairments (Banaschewski et al. 2013; Coghill et al. 2013 and possess a favorable efficacy/ADR profile that is comparable with that of methylphenidate (Ahmann et al. 2001; Pelham et al. 1999).

The AACAP guidelines recommend psychostimulants as the first-line treatment for ADHD, particularly when no comorbidity is present. The effects of immediate-release formulations of methylphenidate and amphetamine develop rapidly, and dosage can be flexibly adjusted. A disadvantage is that immediate formulations have to be taken two or three times to manage ADHD symptoms through the respective time. Table 8.4 summarizes drugs for the treatment of ADHD and the US FDA approval status.

A number of **long-acting formulations** of amphetamine and methylphenidate have been developed with the goal of providing once-daily dosing, employing various means to extend duration of action (Table 8.4), including a transdermal delivery system, an osmotic-release oral system, capsules with a mixture of immediate- and delayed-release beads, and prodrug technology (lisdexamfetamine). According to the Canadian guidelines, long-acting formulations of methylphenidate and amphetamine are both equally first-choice agents (CADDRA 2011; Hosenbocus and Chahal 2009); if symptom reduction for 24 h is needed, also atomoxetine can be the first-line treatment. In Europe, methylphenidate is the preferred psychostimulant in pharmacological treatment (Taylor et al. 2004).

The use of long-acting formulations of methylphenidate and amphetamine has very much increased in importance in recent years. Long-acting formulations can assure continuous benefit throughout the day, which may contribute to maintaining compliance (regarding indications for the use of or switch to short or long-acting preparations, see Sect. 12.4.7). Each preparation has different characteristics with respect to bioavailability, duration of action, and practical application (see Sect. 8.4.1), so that an individual choice needs to be made for each patient according to his or her needs (Banaschewski et al. 2006). Long-acting formulations of methylphenidate and amphetamine often require somewhat higher dosages than immediate-release products (Wilens et al. 2006); treatment with higher doses is permissible in an individual trial therapy if close monitoring of pulse, blood pressure, and other ADRs is undertaken (see also Sect. 8.4.1).

The different **guidelines** summarize the **recommended dosages** for children and adolescents. But there are differences regarding the highest dosages, particularly with the use of long-acting psychostimulants where higher dosages are possible. Administration of more than 60 mg/day (or greater than 1 mg/kg body weight per day) methylphenidate (immediate-release formulations) or of more than 40 mg amphetamine/day (or >0.5 mg/kg body weight per day) is not generally recommended; enhanced efficacy has not been clearly demonstrated for higher doses but rather an increased frequency of significant physical and mental ADRs. In individual cases and especially using long-acting formulations, however, even higher doses may be beneficial (CADDRA 2011; Wilens et al. 2006). The absolute and relative contraindications discussed in Sect. 8.4.1 must be taken into account.

Atomoxetine is **not generally** the medication of **first choice** but may nevertheless be employed as such, both according to the AACAP (2007) and the European treatment guidelines (Taylor et al. 2004), if there exist a danger of drug abuse by the patient or their contacts, and compliance problems in the case of methylphenidate or if continuous efficacy around the clock is required (CADDRA 2011). It can also be the first-choice medication for patients with comorbid anxiety or tic disorders (NICE 2008; Taylor et al. 2004). Atomoxetine is also preferred, if the patient experiences severe ADRs to psychostimulants (AACAP 2007).

In comparison with methylphenidate and amphetamine, full effects of atomoxetine on reducing ADHD symptoms might require 3–7 weeks of administration before becoming apparent (see Sect. 8.4.2). Atomoxetine is not a controlled substance and the medication is licensed in the USA and in various European countries for treatment of ADHD in children above age of 6 years, adolescents, and adults in the USA and various European countries. It has been shown to be effective in decreasing ADHD core symptoms with an effect size of around 0.7 which is somewhat lower than the effect size for methylphenidate (around 1.0; see Chap. 8). Together with psychoeducation, atomoxetine can also reach effect sizes over 1.0 level (Svanborg et al. 2009).

Atomoxetine is preferably initiated as a twice-daily dose for at least 1 week before it can be administered as a single morning dose to reduce the risk of ADRs such as nausea or sedation. Then it can also be given in the evening or broken into two doses if required. The recommended daily dosage is 0.5 mg/kg body weight in the first week and 1.2 mg/kg body weight from the second week.

12.3.2 Second- and Third-Choice Medications

Extended-release formulations of **clonidine** and **guanfacine**, which are α_2-adrenoceptor agonists, are FDA approved as monotherapy or as adjunctive therapy for the treatment in pediatric patients aged 6–17 years. To date, a number of studies have shown that clonidine and guanfacine improve the clinical course of ADHD in children and adolescents (Sallee et al. 2013). The efficacy and safety of clonidine and guanfacine have also been evaluated in combination with psychostimulants (see Sect. 8.4.3). Data suggest that they may be helpful in treating symptoms of impulsivity, conduct disorder, and disorganization, while amphetamine and methylphenidate appear to have a greater overall effect (see Arnsten et al. 2007 for a review). However, so far there are only few double-blinded, placebo-controlled studies so far.

The safety of all guanfacine and clonidine formulations is generally consistent with what might be expected of α_2-adrenoceptor agonists, and as centrally active antihypertensive agents, these drugs produce small but consistent decreases in pulse and blood pressure, both systolic and diastolic, within the dose range used for clinical effects in ADHD (Sallee et al. 2013).

The **past experience** of clonidine used as an adjunct to psychostimulants has **raised questions** regarding the **cardiovascular safety** of this augmentation strategy (Sallee et al. 2013). Potentially harmful interactions of clonidine and psychostimulants were hypothesized as a result of reports of untoward cardiac events such as syncope and catastrophic events, including three case reports of sudden death in children. However, an FDA report documenting these cases concluded that there was no reason to postulate a drug interaction; any cardiovascular effects exerted by clonidine and methylphenidate were deemed independent of each other, and the causes of death in those cases were either determined to be unknown or not attributable to the medication (Popper 1995). In addition, recent studies have uniformly not supported the presence of harmful interactions (summarized in Sallee et al. 2013). Similarly, studies of guanfacine formulations have not found harmful interactions between guanfacine and psychostimulants.

12.4 Treatment Strategies

Prior to initiation of pharmacological treatment, a physical-neurological examination (height, weight, heart rate, blood pressure) should be undertaken. If clinically indicated by family history of sudden cardiac death, exercise intolerance, evidence of fainting, or a history of cardiac structural defects or physical anomalies at birth, patients should be referred for consultation with a cardiologist for

ECG and echocardiography. If psychostimulants are initiated, the patients should be also followed by the cardiologist during the treatment (AACAP 2007). When taking the patients' history, they should be questioned about their physical condition, particularly with regard to episodes of tiredness, exhaustion, or chest pains during exercise or physical activity, heart disease, and any indications of seizure-type disorders (see also Sect. 8.6).

12.4.1 Preschool Children

Psychostimulant therapy should only be initiated in preschool children if the symptoms severely impair the social integration of the child (e.g., danger of exclusion from the family, social isolation), and prevent age-appropriate development, and behavioral therapeutic interventions have not been satisfactorily effective (Taylor et al. 2004). The Canadian guidelines (CADDRA et al. 2011) recommend that treatment before the age of six, if necessary, should be only done by a specialist. A multisite study randomizing 160 preschool children (3–5½ years) to placebo or immediate-release methylphenidate (1.25, 2.5, 5, or 7.5 mg three times daily) found that the overall effect size was lower (0.4–0.8) than for school-aged children and that the ADRs generally were more marked than in older children (Greenhill et al. 2006). Also in systematic reviews, psychostimulant medication was found to be efficacious and well tolerated across the age range, but preschoolers appear to have a less beneficial response and more ADRs (Charach et al. 2011; Cornforth et al. 2010). Up to now there is far more evidence for the safety and efficacy of methylphenidate than for amphetamine and atomoxetine.

In preschoolers, the use of immediate-release formulations of methylphenidate is commonly recommended, if medication is indicated, as they have the advantage of better handling (titration in small steps).

Methylphenidate dosage titration should be particularly gradual in preschool children, beginning with, for example, 2.5 mg of an immediate-release formulation, then increased to 5 mg for 8 days (at breakfast), followed by individual titration, possibly in 2.5 mg increments (¼ tablet with 10 mg methylphenidate or ½ tablet with 5 mg methylphenidate).

12.4.2 School-Aged Children

Methylphenidate and amphetamine are the first-line treatments. For example, methylphenidate should be administered at a daily dosage of 0.3–1 mg/kg body weight (immediate-release formulations), divided across the day into one to three doses (generally 2/3 in the morning, 1/3 at midday). Treatment generally begins with 5 mg methylphenidate in the morning and, if required, a further 5 mg at midday. The daily dosage can be increased after a week by 5–10 mg.

Further titration should be discussed again after about 8 days and afterwards at approximately monthly intervals. In the MTA study (Jensen et al. 2001), an average dosage of 32 mg (range 15–50 mg) immediate-release methylphenidate (broken into three doses/day) was effective in the therapy of ADHD symptoms. Crucially important is an individual titration of the dosage of up to a maximum of 60 mg methylphenidate per day, although in certain cases an even higher dosage may be desirable (Sect. 12.3.1).

In order to avoid a prolonged sleep latency, the last dose of a respective day should not be administered after 4 p.m. In individual cases, however, a small third dose or fourth around 6–7 p.m. can be helpful in a child who requires maintenance of attention to complete homework. If more than one or two individual doses are necessary, switching to a long-acting product of methylphenidate/

amphetamine or to atomoxetine should be considered (dosages for long-acting psychostimulants products and atomoxetine: see Table 8.4).

Immediate-release products of amphetamine should be administered at 0.1–0.5 mg/kg body weight as one or two doses. Long-acting medications should be started with a once-daily morning dosage of 5–10 mg. Lisdexamfetamine should be started with a once-daily morning dosage of 20–30 mg (30 mg corresponding to 8.9 mg (S)-amphetamine). Titration should be done weekly to the most effective and best tolerable dose while carefully measuring both response to medication and any ADRs.

12.4.3 Therapy of ADHD with Comorbid Disorders

12.4.3.1 ADHD with Conduct Disorder

In the first instance, psychostimulant treatment is similarly indicated here for treatment of the ADHD symptomatology, with dosages according to the usual recommendations (see above and Sect. 8.4.1). Psychotherapy alone (without any medication) has been described as being inadequate in this patient group (Jensen et al. 2001).

Methylphenidate and amphetamine are effective medications in the treatment of impulsive aggressive behavior (Sinzig et al. 2007). Spencer et al. (2006) and Findling et al. (2007) recommend that a **higher dosage** of the psychostimulant should be **initially administered**. In rare cases aggressive behavior can be increased by treatment. If aggressive behavior is only manifested at the time point when the medication effect is wearing off, it probably reflects a rebound phenomenon, so that an alternative daily dosage pattern should be considered. Prior to this step, however, intensified behavioral therapeutic measures should be implemented; the **supplementary use** of second- or third-generation **antipsychotics** should be considered only in case of severe and **persistent aggressive behavior** (Aman et al. 2004; Pliszka et al. 2006). If antipsychotics and psychostimulants are administered together, an abrupt withdrawal of psychostimulants might cause acute dystonias (Benjamin and Salek 2005).

If the impact of risperidone is insufficient, treatment with quetiapine or aripiprazole can be discussed (Findling et al. 2007). However, according to a Cochrane analysis (Loy et al. 2012), there is only limited evidence of efficacy of risperidone in reducing aggression and conduct problems in children aged 5–18 in the short term. There is currently no evidence to support the use of quetiapine for disruptive behavior disorders in children and adolescents (Loy et al. 2012).

Mood stabilizers, such as lithium salts, valproic acid, and carbamazepine (Chap. 7), are second- and third-choice treatment options for ADHD with conduct disorders, and there is no sufficient database and no randomized placebo-controlled trials to provide a good evidence (after methylphenidate and amphetamine); mood stabilizers necessitate close monitoring, especially if they are combined with psychostimulants.

12.4.3.2 ADHD with Depressive Symptoms

The best treatment effects were achieved in most patients with ADHD and **anxiety disorders** by a combination of methylphenidate and accompanying behavioral therapy (Jensen et al. 2001). Among the patients with comorbid anxiety disorders, there appears to be a subgroup that responded adequately to behavioral therapy alone; in another subgroup (7/32), methylphenidate monotherapy also reduced anxiety symptoms (Abikoff et al. 2005). In this study, the addition of fluoxetine to methylphenidate (15/32) did not provide any further symptomatic relief beyond that of methylphenidate plus placebo (Abikoff et al. 2005).

Where methylphenidate accompanied by behavioral therapy does not improve anxiety, treatment with atomoxetine should be considered, which can then be the first-choice medication. Atomoxetine was reported to both improve ADHD core symptoms and to diminish anxiety (Geller et al. 2007; Kratochvil et al. 2006).

Supplementary medication with selective serotonin reuptake inhibitors (SSRIs), the first-choice

medications for anxiety and obsessive-compulsive disorders, would in this case be a second-choice treatment, as monotherapies are preferable. There are no positive study results regarding the impact of SSRIs on ADHD symptoms.

In cases of ADHD with **comorbid depression**, treatment generally begins with methylphenidate monotherapy. After dosage titration of methylphenidate for the primary treatment of ADHD is completed, **combination with an antidepressant** may be appropriate (see also Chap. 4). Potential interactions between methylphenidate and SSRIs are discussed in Sect. 4.4.1 and Table 4.9.

12.4.3.3 ADHD and Comorbid Tic Disorders

ADHD is also frequently associated with comorbid tic disorders. Psychostimulant therapy can initially exacerbate existing tics, but this is often only transient (see Sect. 8.4.1). Should tic symptoms persist or further increase, a reduction in psychostimulant dosage should initially be implemented while giving due consideration to the severity of ADHD. If this is not successful, withdrawal of the medication or a switch to another should be considered.

Atomoxetine can be the first-choice medication in such cases (NICE 2008; Taylor et al. 2004). An alternative would be co-medication with psychostimulants and second-generation antipsychotics such as risperidone and in German-speaking countries tiapride (see Chap. 27). In the USA, a combination of psychostimulants with **clonidine** or **guanfacine** rather than with second-generation antipsychotics is used (Scahill et al. 2001; Weisman et al. 2013). Combination therapy of ADHD with tic disorders has generally proved effective and well tolerated in a few studies as well as according to our own clinical experience (Eggers et al. 1988; Weisman et al. 2013). With these combinations, however, cardiovascular ADRs must be carefully monitored. Interactions between methylphenidate and clonidine have been discussed in detail in Sect. 8.4.3.

The combination of psychostimulants with antipsychotics, such as risperidone (0.5–1.5 mg/day), olanzapine, aripiprazole, or quetiapine, can be used for refractory comorbid tics. Haloperidol and pimozide are effective in the treatment of comorbid tics; because of the ADRs they are only third-choice medications (Pliszka et al. 2006). They should be employed conservatively, as their ADR profiles may in turn require the introduction of further medications (such as biperiden and benztropine for extrapyramidal motor ADRs; see also Chaps. 5 and 25), the antidopaminergic effects of which can reduce that of the psychostimulant (Markowitz and Patrick 2001).

12.4.3.4 ADHD and Epilepsy

In patients with well-controlled epilepsy and even with infrequent seizures, methylphenidate is effective and associated with a low seizure risk (Koneski et al. 2011), while for atomoxetine, both efficacy and short-term safety have yet to be established.

12.4.3.5 ADHD and Intellectual Disability

Santosh and Taylor (2000) reported significant effects of methylphenidate in patients with ADHD and low intelligence. Accordingly, Simonoff et al. (2013) reported moderate effect sizes for methylphenidate in reducing ADHD symptoms in children with intellectual disability (0.4–0.6). According to Pearson and colleagues (2003), a dosage of 0.6 mg/kg body weight per day is ideal for an optimal effect upon core symptoms. The probability of ADRs during psychostimulant therapy is higher in children with mental retardation and ADHD than for children without mental retardation (Handen et al. 1999; see also Chap. 23). **Competent monitoring of therapeutic effects and ADRs** by caregivers is particularly important, if children with ADHD and mental retardation are treated with medication because these children are less able to report drug effects and ADRs (see also Chap. 23 and Simonoff et al. 2013).

12.4.4 Adolescents with ADHD and Substance Abuse

Psychostimulant medication prescribed for the treatment of ADHD can be diverted by patients or families toward abuse (Wilens et al. 2008). Thus, history of substance abuse or the presence of current substance abuse in the family can,

depending on the precise situation, be seen either as a relative contraindication for psychostimulant prescription, especially in the immediate-release preparation, or as a reason for extremely close monitoring of a patient's psychostimulant use. The **long-acting formulations** of psychostimulants are less prone to diversion because some preparations cannot be easily crushed into powder for injection or snorting and also because the once-a-day administration makes parental supervision easier. **Atomoxetine** is another option for these patients. If an adolescent is misusing their prescribed psychostimulants, or is selling them to third parties, methylphenidate and amphetamine should not be prescribed.

12.4.5 Duration of Treatment and Withdrawal of Medication

Drug treatment for ADHD should be continued as long as clinically necessary and effective. This should be reviewed at least annually. However, little empirical evidence is available to guide clinicians on questions such as the optimal duration of treatment and when it is appropriate to consider drug discontinuation. As ADHD can persist into adulthood, decisions on treatment discontinuation need to be taken on a case-by-case basis (CADDRA 2011; Jacob et al. 2007).

12.4.6 Management Strategies of Adverse Drug Reactions

Strategies for dealing with ADRs include monitoring, dose adjustment of the psychostimulant, switching medication, and adjunctive pharmacotherapy to treat ADRs (Cortese et al. 2013). Among the most frequent ADRs of psychostimulant therapy is **reduced appetite**. Appetite reduction following treatment initiation with an ADHD drug often attenuates with time. Reduced appetite at mealtimes can be reduced by taking the medication after meals rather than before. Should a clinically significant lack of appetite persist, dosage reduction (by ¼ or ½ tablet methylphenidate), discontinuation (rarely necessary), or switching to a different formulation or medication are possible solutions.

Increased blood pressure and heart rate can be observed at the start of therapy with short-acting and long-acting psychostimulants as well as with atomoxetine, especially if dosage is increased too rapidly or is too high. If these ADRs occur, it is recommended that dosage be reduced.

If **sleep disorders** develop, it may be necessary to move the afternoon dose to an earlier time point or to reduce its level or, in exceptional cases, to dispense with an afternoon dose altogether. In severe cases combination therapy with low dose of clonidine (see above) is possible.

With respect to **depressive mood and social withdrawal**, one must distinguish between disease-related symptoms and ADRs. Overdosage is frequently associated with a depressed state, so that dosage reduction is indicated.

Psychotic reactions are very rare ADRs if psychotic symptoms occur with therapeutic doses of ADHD drugs, dose reduction or discontinuation is necessary; they are completely reversible following reduction or discontinuation of the medication.

If psychostimulants trigger or increase **tic disorders** (see above) and pharmacological therapy is essential, decreasing, briefly discontinuing, and then slowly restarting the psychostimulant could be considered. Alternatively, treatment could be switched to atomoxetine, monotherapy, or combination therapy with a second-choice medication such as clonidine or guanfacine (see above).

12.4.7 Recommendations on Switching from Immediate-Release to Long-Acting Formulations

If a child has responded well to an immediate-release psychostimulant, there may still be reasons to shift to a long-acting psychostimulant, for example, to avoid the stigma or inconvenience of repeated dosing or to increase privacy, where compliance needs to be addressed or to reduce

the risk of diversion. A long-acting preparation of methylphenidate or amphetamine will then be preferred (Banaschewski et al. 2006). According to the CADDRA (2011), the use of long-acting medication should be preferred in most patients because of the presumably better compliance of the patients and an increase of quality of life (see also Sect. 8.4.1).

The change to a long-acting formulation or the use of these medications must always be adapted to the individual patient, and take place under close medical monitoring. Which long-acting product is chosen will depend on the desired profile of action required across the day (see AACAP 2007; Banaschewski et al. 2006; CADDRA 2011; Taylor et al. 2004 for further information).

12.4.8 Changing Medication in Nonresponders

Where there is a failure to respond to a particular treatment or when a patient is unable to tolerate a treatment due to ADRs, it is necessary to consider either adjusting or switching treatment. Recommendations for switching treatments vary depending on the current and past treatment history and the reasons for switching. If there is a failure to respond to psychostimulants as a first-line treatment, medication might be switched either to another psychostimulant or to atomoxetine. If one psychostimulant has led to intolerable ADRs, switching to another or to atomoxetine is appropriate (Banaschewski et al. 2006; NICE 2008).

12.4.9 Precautionary Measures During Co-medication

Interactions between psychostimulants and other medications are described in Sect. 8.4.1. Dosage reductions may be required, for example, for combination with antiepileptics or antidepressants. The medications commonly employed in child and adolescent psychiatry can, according to the current state of knowledge, generally be coadministered with methylphenidate and amphetamine. Caution is necessary with regard to other sympathomimetic medications, whereby blood pressure and heart rate, in particular, must be monitored. Therapeutic drug monitoring (TDM, see Sect. 2.3) may be appropriate when combining medications, but close clinical monitoring is always required.

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Autism Spectrum Disorders

13

Christine M. Freitag and Tomasz A. Jarczok

Contents

C.M. Freitag, MD, MA (✉) • T.A. Jarczok, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Goethe-Universität Frankfurt am Main, Deutschordenstraße 50, 60528 Frankfurt, Germany
e-mail: c.freitag@em.uni-frankfurt.de; tomasz.jarzok@kgu.de

13.1 Definition and Classification

Autism spectrum disorders (ASD) comprise autism/autistic disorder (ICD-10: F84.0; DSM-IV TR: 299.00), Asperger syndrome/disorder (ICD-10: F84.5; DSM-IV TR: 299.80), and atypical autism (ICD-10: F84.1)/pervasive developmental disorder – not otherwise specified (PDD-nos; DSM-IV TR: 299.80). In addition, some authors also subsume childhood disintegrative disorder (ICD-10: F84.3; DSM-IV TR: 299.10) under ASD. In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5; American Psychiatric Association 2013), they are combined into one diagnosis of autism spectrum disorder (DSM-5: 299.00) with varying levels of symptom severity and additional specifiers for intellectual and language impairment, medical condition, and catatonia.

The three **core defining symptom clusters** of the disorders according to ICD-10 and DSM-IV TR are:

- Difficulties in reciprocal social interaction
- Difficulties in communication (especially pragmatic language difficulties and impaired nonverbal communication abilities, language delay in autism or atypical autism/PDD-nos)
- Repetitive and stereotyped behaviors and special interests

Varying symptoms across ASD underlie the respective ICD-10 or DSM-IV TR diagnoses, such as (ab)normal language development, presence or absence of developmental (including

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language) regression, different age of onset, and different core symptom patterns. In DSM-5, only two areas of impairments are mentioned: (1) deficits in social communication and interaction and (2) restricted repetitive behaviors, interests, and activities. Both components are required for a diagnosis of ASD. In contrast to ICD-10 or DSM-IV TR, individuals with impairments in social interaction and communication, but no history of repetitive behavior are not diagnosed with ASD in DSM-5, but with the new category "social communication disorder." In ICD-10, these children are diagnosed with "atypical autism"; in DSM-IV TR, these children receive a diagnosis of "PDD-nos." This **shift in diagnostic criteria** has to be reflected when interpreting psychopharmacological studies. In addition, inclusion criteria of these studies also need to be kept in mind, as they can vary considerably. In general, children and adolescents with "atypical autism" or "PDD-nos" and "childhood disintegrative disorder" are under-researched, as are adults with any kind of autism spectrum disorder.

Psychopharmacological research in ASD in the past has – as a rule – **focused on specific behavioral targets**, which are often better classified as comorbid disorders or behaviors that are currently not covered by diagnostic criteria (neither in ICD-10/DSM-IV TR nor DSM-5). Published randomized controlled trials (RCTs) with psychopharmacological agents have rarely chosen language abilities or impairments in communication or social interaction as primary outcome measures to date. Of the core ASD symptoms, improvement of repetitive and stereotyped behavior has been studied repeatedly by RCTs.

The prevalence of ASD is around 1 % in children, adolescents, and adults. Approximately 50 % are also affected by intellectual disability (Baird et al. 2006; Baron-Cohen et al. 2009; Brugha et al. 2011). ASD etiology is mainly genetically based (Berg and Geschwind 2012; Freitag et al. 2010). Still, some environmental risk factors have also been proven, especially viral infections (e.g., rubella), exposure to medication (e.g., valproic acid, thalidomide), or other substances/compounds affecting neural development during pregnancy (Freitag 2012). In addition, maternal and child specific immunological mechanisms have been discussed to lead to ASD (Rapin and Tuchman 2008).

13.2 Therapeutic Framework

13.2.1 Psychiatric and Neurological Comorbid Disorders

ASD show a high rate of psychiatric and neurological comorbid disorders besides intellectual disability (ID). The most frequent comorbid disorders with a higher than chance association with ASD are shown in Table 13.1. Where possible, data from population-based studies are reported. Additional frequent comorbid disorders are genetic syndromes and monogenetic disorders, cerebral palsy, and hearing and vision impairments (Kielinen et al. 2004; Mouridsen et al. 2011a, b). This puts an emphasis on a **thorough** psychiatric, neurological, hearing, vision, and genetic **assessment** of all children and adolescents with ASD. Especially medically treatable comorbid disorders such as epilepsies need to be treated by the respective antiepileptic medication (see textbooks on pediatric neurology) before behavioral symptoms and psychiatric comorbid disorders are treated by psychotherapy or psychopharmacotherapy.

13.2.2 Behavioral Therapy Approaches

A diagnosis of ASD currently does not imply that psychopharmacological therapy per se is necessary for the respective child/adolescent. The **method of choice** to improve core ASD symptoms as well as an associated ID is (early) **behavioral therapy** and **ongoing training** of a broad range of language, social, and cognitive abilities on an individual-, group-, family-, and nursery-/kindergarten-/school-based level. The respective behavioral therapy method is chosen according to the (developmental) age and cognitive and social abilities of the child, and the resources of the

Table 13.1 Prevalence of frequent psychiatric and neurological comorbid disorders in children with ASD

Psychiatric/neurological disorder	Prevalence/incidence N/100 (95 % CI) **or frequency** in %	Reference
Emotional disorder[a]	44 (30–59)[c]	Simonoff et al. (2008)
Social phobia	29 (13–45)[c]	Simonoff et al. (2008)
Attention-deficit/hyperactivity disorder[b]	28 (13–43)[c] 2/3 inattentive subtype	Leyfer et al. (2006), Simonoff et al. (2008)
Oppositional defiant disorder	28 (14–42)[c]	Simonoff et al. (2008)
Obsessive-compulsive disorder	8 (3–13)[c]	Simonoff et al. (2008)
Enuresis	11 (4–18)[c]	Simonoff et al. (2008)
Encopresis	7 (2–11)[c]	Simonoff et al. (2008)
Obstipation	34 (ASD) vs. 18 (controls)[d]	Ibrahim et al. (2009)
Selective eating/eating disorder	25 (ASD) vs. 16 (controls)[d]	Ibrahim et al. (2009)
Any sleeping disorder	53 (ASD) vs. 32 (controls)[e]	Krakowiak et al. (2008)
Epilepsy	10 % of $N=68$ children with ASD[c]	Williams et al. (2008)
	25 % of $N=118$ individuals with autism[e]	Mouridsen et al. (2011a)
	4 % of $N=4{,}180$ individuals with Asperger syndrome[e]	Mouridsen et al. (2013)

CI confidence interval
[a]Anxiety and depressive disorders according to DSM-IV TR
[b]All DSM-IV TR subtypes
[c]3-month prevalence
[d]Cumulative incidence
[e]Lifetime prevalence

family (Freitag et al. 2013; Ospina et al. 2008). In addition, several recent RCTs in children, adolescents, or adults with ASD without ID have shown the efficacy of individual and/or group-based cognitive behavioral therapy on comorbid anxiety and obsessive-compulsive disorder (OCD) in children, adolescents, and adults with ASD (Russell et al. 2013; Storch et al. 2013; White et al. 2010). Also, comorbid enuresis, functional urinary incontinence, and encopresis should be treated primarily by the respective disorder-specific behavioral therapy approaches. If constipation is present in encopresis, additionally Macrogol3350/4000 can be of use (see Chap. 18).

13.2.3 Indication for Pharmacotherapy

Currently, the indication for psychopharmacotherapy is the **presence of a comorbid disorder** or comorbid behavioral symptoms which are regularly treated by pharmacotherapy also in children without ASD. This is the case for symptoms or presence of attention-deficit/hyperactivity disorder (ADHD), tic disorders, or major depressive disorder (MDD). The following behavioral symptoms or comorbid disorders should first be treated by the respective targeted behavioral therapy; if results are not satisfying within a reasonable time frame (2–3 months), pharmacotherapy needs to be added, or a full switch to pharmacotherapy may be necessary: oppositional and (auto)aggressive behavior, OCD, anxiety disorders, and sleep disorders (see Chaps. 9, 11, and 26).

In clinical practice, a **combination of behaviorally based and pharmacological therapeutic approaches** is common and effective in many children and adolescents (evidence level II–IV, see below), but has rarely been systematically studied (Aman et al. 2009; Cortesi et al. 2012). In addition, the availability of symptom- and disorder-specific behavioral therapy varies considerably across different countries, so in practice, in countries where behavioral therapy is not publicly available, pharmacotherapy is often the first choice when some behavioral symptoms, especially irritability, aggression, or severe stereotyped behavior, cause impairment for a child/adolescent with ASD (Mandell et al. 2008; Murray et al. 2013).

13.3 Choice of Pharmacotherapy

Table 13.2 provides an overview of studied psychopharmacological agents for the treatment of core ASD symptoms and/or comorbid behavioral symptoms and disorders in ASD. For more detailed pharmacological information on the psychopharmacological substances shown here, the reader is referred to the corresponding special Chaps. 4, 5, 6, 7, and 8. The **level of evidence** has been chosen between I and V according to the National Service Framework on Mental Health as reported in Cooper (2003). Briefly, level I is the highest level of evidence; level V carries the lowest evidence, but may also be a clinically relevant information if no other studies have been performed on a specific kind of medication or therapy.

In Table 13.2, only studies which are supporting the highest level of evidence for the respective medication are cited. In addition, only such intervention or observational studies with at least 20 individuals in the therapy and in the control group have been included when levels I–III are reported. For level IV and V-information, any kind of study with clearly defined in- and exclusion criteria for ASD and theoretically proven outcome measures are included. Also, information on replication of findings by an independent research group as well as study quality, rated as "strong," "adequate," or "weak" (Reichow et al. 2008; Siegel 2012), are taken into account. Only studies with at least an adequate study quality are shown in Table 13.2 when levels I–III are reported.

Unfortunately, only a limited number of RCTs have been performed on ASD and comorbid disorders/symptoms, predominantly with a focus on aggressive, irritable, stereotyped, and hyperactive behavior. Most RCTs have been performed using antipsychotics, psychostimulants, and selective serotonin reuptake inhibitors (SSRIs, see Table 13.2). Studies on **combined** psychotherapeutic and pharmacotherapeutic **approaches** have been very **rare**, but promising (Aman et al. 2009). Especially, such combined studies need to be done far more often in the future to achieve optimal treatment and care for children and adolescents with ASD. Studies on combined psychopharmacotherapy are also scarce. In clinical practice, monotherapy should always be given preference over pharmacological combination therapy due to the reduced adverse drug reactions (ADRs) in monotherapy and the increased rate of interaction and ADRs in combined psychopharmacotherapy. The studies reported in Table 13.2 are monotherapeutic (level I–IV) or add-on (level III–IV) studies.

In addition, some **new medication developments** are under way which may show efficacy on core ASD symptoms in future RCTs. Given the involvement of the glutamatergic system in ASD, several studies have been performed with the *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonists amantadine (Hosenbocus and Chahal 2013a; King et al. 2001) and memantine (Hosenbocus and Chahal 2013b), the partial NMDA agonist D-cycloserine (Posey et al. 2004), and *N*-acetylcysteine (Hardan et al. 2012). In addition, galantamine, an acetylcholinesterase inhibitor and nicotinic receptor modulator, has been studied for its effect on social withdrawal, hyperactivity, and irritability due to findings of reduced nicotinic receptor binding in postmortem brains of ASD individuals (Nicolson et al. 2006; Niederhofer et al. 2002). These agents have been studied only in small samples and rarely by RCTs; therefore, results have to be viewed with caution.

Currently, several RCTs on **memantine** with different primary outcome measures are under way. Also, preliminary results on **oxytocin** treatment in adults with ASD have been reported from RCTs, but no such studies have been performed in children and adolescents with ASD to date (Anagnostou et al. 2012). In addition, behavioral ratings did not show improvement by oxytocin therapy in adolescents and adults with ASD (Anagnostou et al. 2012; Tachibana et al. 2013). Therefore, the value of oxytocin as future treatment option for core ASD symptoms also needs to be viewed with strong caution.

Carriers of specific copy number variations or single-gene mutations may benefit from specific **medication targeted at** the respective **genetic finding**. This, e.g., has been shown in a single case study on aggressive behavior in a carrier of a 15q13.3 deletion for pharmacotherapy

Table 13.2 Symptomatic pharmacotherapy of ASD: effective or likely effective substances

Indication	Substance	Dosage range[b]	Adverse drug reactions (ADRs)[a]	Evidence-based level	Reference
Core ASD symptoms					
Social interaction	D-Cycloserine (add-on therapy)	1.0–2.6 mg/kg × day	Motor tic, echolalia	III–IV (NR)	Posey et al. (2004)
	Memantine (add-on therapy)	2.5–20 mg/day	Irritability, seizures	IV–V (NR)	Erickson et al. (2007)
	Galantamine (monotherapy)	12–24 mg/day	Headaches, gastrointestinal problems	III (R)	Nicolson et al. (2006), Niederhofer et al. (2002)
Communication and language	Memantine (add-on therapy)	2.5–30 mg/day	Behavior aggravation	IV (NR)	Chez et al. (2007)
Stereotyped and repetitive behavior	Risperidone (monotherapy)	0.5–3.5 mg/day	Weight gain, prolactin increase, somnolence, enuresis, extrapyramidal symptoms	I (NR)	McDougle et al. (2005)
	Aripiprazole (monotherapy)	5–15 mg/day	Weight gain, vomiting, somnolence, extrapyramidal symptoms	II (NR)	Owen et al. (2009)
Comorbid psychiatric symptoms/disorders					
Hyperactive behavior	Methylphenidate (monotherapy)	0.3–1.5 mg/kg × day; medium dose best	Irritability, decreased appetite, social withdrawal (especially with high doses)	I (R-RCT)	Reichow et al. (2013)
	Atomoxetine (monotherapy)	1.2 mg/kg × day	Nausea, fatigue, decreased appetite	II (R-RCT)	Arnold et al. (2006), Harfterkamp et al. (2012)
	Risperidone (monotherapy)	0.5–3.5 mg/day	Weight gain, prolactin increase, somnolence, enuresis, extrapyramidal symptoms	I (R-RCT)	Jesner et al. (2007), Sharma and Shaw (2012)
	Aripiprazole (monotherapy)	5–15 mg/day	Weight gain, vomiting, somnolence, extrapyramidal symptoms	II (NR)	Marcus et al. (2009), Owen et al. (2009)
	Ziprasidone (add-on and monotherapy)	20–160 mg/day	QTc prolongation (ECG), sedation, extrapyramidal symptoms	IV (NR)	Malone et al. (2007), McDougle et al. (2002)
	Haloperidol (monotherapy)	0.25–4 mg/day	Sedation, high rate of extrapyramidal symptoms	II (NR)	Anderson et al. (1989)
	Amantadine (add-on therapy)	5 mg/kg × day	Insomnia	II (NR)	King et al. (2001)
	Memantine (add-on therapy)	2.5–20 mg/day	Behavior aggravation	IV (R)	Erickson et al. (2007), Owley et al. (2006)
	Naltrexone (monotherapy)	0.5–1 mg/kg × day	Decreased appetite, vomiting, sedation	II (NR)	Campbell et al. (1990, 1993)

(continued)

Table 13.2 (continued)

Indication	Substance	Dosage range[b]	Adverse drug reactions (ADRs)[a]	Evidence-based level	Reference
Inattention	Methylphenidate (monotherapy)	0.3–1.5 mg/kg × day; medium dose best	Irritability, decreased appetite, social withdrawal (especially with high doses)	II (NR)	Posey et al. (2007), Research Units on Pediatric Psychopharmacology Autism Network (2005)
	Memantine	2.5–20 mg/day	Irritability, seizures	IV (NR)	Erickson et al. (2007)
Aggressive behavior/ irritability	Risperidone (monotherapy)	0.5–3.5 mg/day	Weight gain, prolactin increase, somnolence, enuresis, extrapyramidal symptoms	I (R-RCT)	Jesner et al. (2007), Sharma and Shaw (2012)
	Aripiprazole (monotherapy)	5–15 mg/day	Weight gain, vomiting, somnolence, extrapyramidal symptoms	II (NR)	Marcus et al. (2009), Owen et al. (2009)
	Ziprasidone (add-on and monotherapy)	20–160 mg/day	QTc prolongation (ECG), sedation, extrapyramidal symptoms	III–IV (NR)	Malone et al. (2007), McDougle et al. (2002)
	Haloperidol (monotherapy)	0.25–4 mg/day	Sedation, extrapyramidal symptoms	II (NR)	Anderson et al. (1989)
	Pipamperone (add-on and monotherapy)	20 mg/kg × day	Sedation, weight gain	V (NR)	Renynghe et al. (1976)
	Valproic acid (monotherapy)	20 mg/kg × day or 500–1,000 mg/day	Rash, weight gain	II–III (NR)	Hellings et al. (2005), Hollander et al. (2010)
	Memantine (add-on therapy)	0.4 mg/kg × day	Worsened behavior	III–IV (NR)	Owley et al. (2006)
	Galantamine (add-on and monotherapy)	8–24 mg/day	Headaches, gastrointestinal problems	IV (R)	Nicolson et al. (2006), Niederhofer et al. (2002)
	N-acetylcysteine (add-on therapy)	900–2,700 mg/day	Nausea, vomiting, diarrhea, change in appetite	II (NR)	Hardan et al. (2012)
Comorbid ADHD	See hyperactive behavior and inattention				
Comorbid OCD	See also stereotyped and repetitive behavior: risperidone, aripiprazole				
	Fluoxetine (add-on therapy)	20–40 mg/day	Agitation, aggressiveness, headaches	IV (NR)	Mehlinger et al. (1990)
Comorbid AD	Citalopram (add-on therapy)	17 (12) mg/day	Agitation, aggressiveness, headaches	IV (NR)	Namerow et al. (2003)
	Sertraline (add-on and monotherapy)	25–50 mg/day	Abdominal pain	IV (NR)	Steingard et al. (1997)
Comorbid MDD	Mirtazapine (add-on therapy)	7.5–45 mg/day	Increased appetite, irritability, transient sedation	IV (NR)	Posey et al. (2001)
	Fluoxetine (add-on therapy)	10–20 mg/day	Irritability, abdominal pain, headaches	IV (NR)	Ghaziuddin et al. (1991)
	Reboxetine (monotherapy)	4 mg/day	Irritability, insomnia, decrease in appetite, abdominal pain, headaches	IV (NR)	Golubchik et al. (2013)

Comorbid TD	Aripiprazole (add-on therapy)	5–15 mg/day	Akathisia, insomnia	IV (NR)	Kim et al. (2010)
Comorbid sleeping problems	Melatonin (monotherapy)	2.5–10 mg	none	I (R-RCT)	Rossignol and Frye (2011)
Other behavioral problems					
Excessive masturbation	Mirtazapine (add-on therapy)	15–30 mg/day	Increased appetite, irritability, transient sedation	IV (R)	Albertini et al. (2006), Coskun et al. (2009), Nguyen and Murphy (2001)

Evidence level I, at least one good systematic review, including at least one randomized controlled trial; level II, at least one good randomized, controlled trial; level III, at least one well-designed intervention study without randomization; level IV, at least one well-designed observational study; level V, expert opinion, including the opinion of service users and carers

NR R (not) replicated by an independent research group, *R-RCT* replicated by randomized controlled trial in an independent research group, *AD* anxiety disorder, *ADHD* attention-deficit/hyperactivity disorder, *ASD* autism spectrum disorder, *MDD* major depressive disorder, *OCD* obsessive-compulsive disorder, *TD* tic disorder

[a]Only the most frequent and/or most adverse drug reactions (ADRs) are reported. Please, refer to Chaps. 4, 5, 6, 7, and 8 for more details

[b]Dosage range refers to the dosage implemented in the respective studies. In clinical practise, the optimal dosage should be titrated, which is the lowest effective dosage

with galantamine (Cubells et al. 2011). In addition, several studies, including one large RCT, on different metabotropic glutamate receptor 5 (mGluR5) antagonists are currently performed in children, adolescents, and adults with fragile X syndrome, a monogenetic disorder strongly associated with ASD (Hagerman et al. 2009). Other substances, which have shown efficacy in a single, not yet replicated RCT (level of evidence II) especially on anxiety-related behaviors in children and adolescents with fragile X syndrome, are minocycline (Leigh et al. 2013) and arbaclofen (Berry-Kravis et al. 2012). Hyperactivity in children with fragile X syndrome was positively influenced by L-carnitine in one RCT (Torrioli et al. 2008). For any other ASD-associated genetic risk factors, as, e.g., mutations in TSC1/TSC2, an indication of a specific pharmacotherapy is currently only given by the additional medical findings present in the disorder (e.g., infantile spasms in tuberous sclerosis). Still, in the future, psychopharmacotherapy in ASD may more often be chosen according to the underlying genetic findings in the respective affected individual.

Due to the above-shown criteria, the following **medications** can be considered as **inefficient** for ASD and/or comorbid psychiatric symptoms and disorders (evidence level I or II): **secretin** (Krishnaswami et al. 2011), **lamotrigine** (Belsito et al. 2001), and **levetiracetam** (Wasserman et al. 2006). **Citalopram** and **fluoxetine** were inefficient in reducing stereotyped and repetitive behavior symptoms as measured by the Children's Yale-Brown Obsessive Compulsive Scale modified for pervasive developmental disorder (CY-BOCS-PDD) in RCTs (Doyle and McDougle 2012; King et al. 2009). Still, citalopram may be of use for the treatment of comorbid anxiety disorder and fluoxetine for comorbid MDD in ASD (see below). Also, hardly any studies on comorbid OCD in ASD have been performed to date, so the value of SSRIs in treating comorbid OCD in ASD cannot be judged from the current studies. **Clomipramine** has also not shown sufficient evidence to reduce repetitive behavior in a meta-analysis and should not be used due the disadvantageous cost to benefit ratio (Hurwitz et al. 2012). Also, **olanzapine** shows a disadvantageous cost to benefit ratio, and given the efficacy of risperidone and aripiprazole to reduce irritability, aggressive, and stereotyped behavior, it should not be used as first-line therapy in ASD (Hollander et al. 2006; Siegel 2012). **Quetiapine** also was not efficient in reducing hyperactive and aggressive behavior (level III) and showed a high rate of ADRs (Corson et al. 2004; Hardan et al. 2005). Therefore, it should not be used for pharmacotherapy in ASD.

Vitamin, **fatty acids**, and **mineral supplements** may be helpful, especially for children who show selective eating behavior (Zimmer et al. 2012), but the studies which have been performed using different formulations of vitamins, fatty acid, and mineral supplements (e.g., Adams et al. 2011; Amminger et al. 2007; Nye and Brice 2005; Rueda et al. 2011) lack many aspects of well-planned and well-conducted medication studies (as, e.g., lack of definition of a primary outcome measure, no valid and reliable measurement scales, no intention-to-treat analysis, in- and exclusion criteria not properly defined), so that no firm conclusions can be drawn from these studies. Thus, they were not included in Table 13.2 and are not further discussed in this chapter.

13.3.1 Communication and Social Interaction Abilities

To date, hardly any psychopharmacological agent has been shown to improve communication and social interaction abilities in ASD. The best studied substances risperidone (Jesner et al. 2007; Sharma and Shaw 2012), aripiprazole (Marcus et al. 2009; Owen et al. 2009), methylphenidate (Posey et al. 2007), atomoxetine (Harfterkamp et al. 2012), fluoxetine (Hollander et al. 2005), and citalopram (King et al. 2009) have either not been assessed for their effect on or did not improve these core ASD symptoms in RCTs. The new NMDA receptor partial agonist D-cycloserine, which acts at the NMDA receptor-associated glycine modulatory site and at high doses acts as a functional NMDA receptor antagonist, the low

to moderate affinity NMDA receptor antagonist memantine as well galantamine, an acetylcholinesterase inhibitor, may be promising new substances to improve social interaction, communication, and language abilities even in younger children with ASD, but no RCTs have been published to date. Previously, also several smaller case or pre-post observational studies had shown improvement, e.g., stereotyped behavior by fluoxetine, but subsequent large RCTs did not find this effect (Doyle and McDougle 2012). Thus, the following study results have to be viewed with caution.

D-Cycloserine was prospectively studied in 12 children (Posey et al. 2004), adolescents, and adults with autism with increasing doses from 0.7 to 2.8 mg/kg × day over 8 weeks (level III–IV evidence). Outcome measures were the Clinical Global Impression Scale (CGI), the Social Responsiveness Scale (SRS), different subscales of the Aberrant Behavior Checklist (ABC), and the CY-BOCS modified for pervasive developmental disorder. Improvements were shown at medium and high doses for CGI and the ABC social withdrawal subscale (effect sizes not reported). The study states that in 40 % of the individuals, the improvement was clinically meaningful. Only few ADRs (motor tics, increased echolalia) were observed.

Memantine was reported to show beneficial effects on social interaction in one retrospective and on communication abilities in one prospective study. A retrospective chart review (level IV–V) of 18 6–19-year-old individuals with pervasive developmental disorder who received open-label add-on memantine therapy (ranging from 2.5–20 mg/day) over 1.5–56 weeks showed improvement of social withdrawal by CGI and hyperactivity by ABC. ADRs, especially increased irritability, occurred in 40 % of the patients (Erickson et al. 2007). A larger open-label prospective study on 151 individuals with autism or PDD-nos aged 3–26 years old (level IV) reported positive effects of add-on memantine therapy (ranging from 2.5 to 30 mg/day) over 1–20 months on language development and also some positive effects on social interaction. As ADR, worsening of behavior was reported in a few individuals (Chez et al. 2007). Both studies are of rather weak quality.

Galantamine has been studied in one small RCT ($N=20$) and one pre-post open-label study ($N=13$; level III). Both studies showed positive effects on ABC-derived scales irritability and social withdrawal after 12 weeks of therapy with 12–24 mg/day in 7–17-year-old individuals with autism (Nicolson et al. 2006; Niederhofer et al. 2002). One of these studies additionally reported 8/13 individuals as responders defined by CGI (Nicolson et al. 2006). ADRs were reported to be rather minimal.

Taken together, these new pharmacological agents have **not** been studied to the extent that they can be **recommended** for standard clinical practice. Memantine currently is studied by several large RCTs in the USA and in Europe. Still, from previous studies, the most promising substance seems to be galantamine, which may currently be tried as off-label therapy approach in children who do not show sufficient improvement in social interaction by behavioral therapy alone.

13.3.2 Stereotyped, Repetitive Behavior and Comorbid OCD

Pharmacological studies of stereotyped, repetitive, and rigid behavior have primarily focused on the use of **SSRIs**. Repetitive behavior in ASD bears some resemblance with symptoms of OCD, which is treated with SSRIs (see Chap. 21). Furthermore, neurobiological studies pointed toward alterations in the serotonergic system in subgroups of ASD individuals and their first-degree relatives (Abramson et al. 1989; Anderson et al. 1987). Still, from a psychopathological point of view, stereotyped and rigid behavior in ASD does strongly differ from OCD, which was also shown by studies on comorbid disorders in ASD (Simonoff et al. 2008) or comparative psychopathological studies (Caamano et al. 2013; Cath et al. 2008). In addition, the underlying neurobiological mechanisms of OCD and ASD show a more distinct than overlapping pattern (Anagnostou and Taylor 2011; Arnsten and

Rubia 2012; Brennan et al. 2013). The pervasive developmental disorders modified CY-BOCS as well as the ABC-stereotyped behavior scores are the most frequently used primary or secondary outcome measures in pharmacological studies on repetitive and stereotyped behavior in ASD. These measures were not designed to diagnose OCD in children and adolescents with ASD. Therefore, negative study results with regard to these outcome measures do not necessarily preclude an effect of the respective substances in ASD comorbid with OCD.

Citalopram was studied in a large RCT including 147 children and adolescents aged 5–17 years. Participants met criteria for autistic disorder, Asperger disorder, or PDD-nos with or without intellectual disability. They were assigned to a 12-week trial of either citalopram (average dose 16.5 mg/day, maximum dose 20 mg/day) or placebo. The responder rate as determined by the CGI-Improvement subscale did not differ between the citalopram group (32.9 %) and the placebo group (34.2 %). Also, no difference was found between groups in the secondary outcome parameter reduction of repetitive behavior measured with the CY-BOCS modified for pervasive developmental disorders. Citalopram was associated with a high rate of ADRs including hyperactivity, impulsiveness, stereotypic behavior, insomnia, dry skin, and pruritus (King et al. 2009).

Despite small positive results of a smaller RCT (Hollander et al. 2005) and positive findings in a smaller study in adults with ASD (Hollander et al. 2012), the large, as yet unpublished SOFIA study, has not found an effect of **fluoxetine** on repetitive and stereotyped behavior in children and adolescents with ASD. SOFIA is an industry-sponsored trial of fluoxetine in ASD, which included a total of 158 patients between 5 and 17 years. According to a press release, a novel melt in mouth formulation of fluoxetine was found to be not more effective than placebo in reducing repetitive behaviors during a 14-week treatment course (Doyle and McDougle 2012).

A **Cochrane review** that included a series of studies on SSRIs (fluoxetine, fluvoxamine, fenfluramine, citalopram) in both pediatric and adult populations with ASD (but not the negative SOFIA study mentioned above) came to the conclusion that there is currently **no evidence** that **SSRIs are effective** as a treatment for repetitive and stereotyped behavior in children and adolescents with ASD but that there is emerging evidence that they may cause harm (Williams et al. 2013).

Tricyclic antidepressants have been only studied in trials with small sample sizes. **Clomipramine** was reported to be superior to desipramine and placebo in the reduction of autistic symptoms including stereotypies in a small crossover study ($N=30$). There were relevant ADRs including grand mal seizures, increased QTc interval, and tachycardia (Gordon et al. 1993). Another small crossover study ($N=36$) comparing haloperidol, clomipramine, and placebo reported a very high dropout rate of 62.5 % for clomipramine due to ADRs, lack of efficacy, or behavioral problems. Clomipramine was not superior to baseline in the intent-to-treat sample (Remington et al. 2001). Given the insufficient evidence for efficacy and the high probability for ADRs, tricyclic antidepressants **cannot be recommended** as a treatment of stereotyped behavior in pediatric populations with autism.

Several trials of **antipsychotics** used measures of repetitive and stereotypical behavior as secondary outcome parameters. Both large and sufficiently powered RCTs of risperidone (level I) (Sharma and Shaw 2012) and aripiprazole (level II) (Owen et al. 2009) showed a greater reduction of repetitive behavior than placebo in children and adolescents with ASD in doses of 0.5–3.5 mg/day (risperidone), respectively, 5–15 mg/day (aripiprazole) by 8-week treatment. To improve stereotyped and repetitive behavior, **risperidone** and **aripiprazole** therefore are currently the only two substances which **should be chosen**. Risperidone shows a higher effect size than aripiprazole with regard to repetitive and stereotyped behavior, so it is to be recommended as first-line psychopharmacotherapy for these symptoms, especially in children without obesity (level I).

There is a significantly increased rate of OCD in children with autism (Simonoff et al. 2008), and children and adolescents with **comorbid ASD and OCD** as a rule are strongly impaired

in everyday life and often unable to leave the house. While an RCT on cognitive behavioral therapy and anxiety management for comorbid OCD in adolescent and adult ASD individuals without ID showed positive effects on OCD symptoms (Russell et al. 2013), systematic and randomized controlled psychopharmacological trials on symptoms or the diagnosis of OCD in ASD have not been performed. A case study has reported improvement of OCD symptoms in children and adolescents with ASD by fluoxetine (Mehlinger et al. 1990). From a clinical point of view (level V), the combination of risperidone or aripiprazole with an SSRI (cave: interaction) is strongly recommended in individuals with ASD comorbid with OCD, when risperidone or aripiprazole alone has not lead to clinically sufficient improvement.

13.3.3 Hyperactivity, Inattentiveness, and Comorbid ADHD

Trials on the primary outcome measures hyperactivity, inattentiveness, and comorbid ADHD symptoms in ASD patients have primarily focused on drugs used in the treatment of ADHD without comorbid ASD. In addition, studies on other medications, especially antipsychotics, have often studied hyperactivity as secondary outcome measure.

The stimulant **methylphenidate** is first line in the pharmacotherapy of ADHD (see Chap. 12). One sufficiently powered double-blind placebo-controlled crossover trial conducted by the RUPP Autism Network studied methylphenidate in children with pervasive developmental disorder and moderate to severe hyperactivity (Research Units on Pediatric Psychopharmacology Autism Network 2005). The trial included 72 patients with autistic disorder, Asperger syndrome, or PDD-nos with at least moderate symptoms of hyperactivity and/or impulsiveness with onset prior to the age of 7 years. During the crossover phase, participants received three different doses of methylphenidate and placebo for 1 week, each in random order. The maximum daily dose was approximately 1.25 mg/kg divided into three separate doses. Methylphenidate, especially at a medium dose of <1 mg/kg × day, was consistently **superior to placebo** in reducing ADHD symptoms as measured by the parent-rated ABC hyperactivity subscale with small to medium effect sizes. Forty-nine percent of participants were classified as responders ("much improved" or "very much improved" on the CGI-Improvement scale). The study included patients with and without ID, but no influence of IQ on the primary outcome measure was found. A dropout rate of 18 % due to ADRs was observed, with irritability being the most common reason for dropout. In summary, the responder rate appeared to be smaller, and ADRs were more frequently compared to rates reported in children with ADHD without pervasive developmental disorder (Jensen et al. 2001). Secondary outcome measure analysis showed that methylphenidate also improved inattentiveness; however, the effect was smaller than for hyperactivity (Posey et al. 2007). A recent meta-analysis has reported an effect size of 0.66 on hyperactivity in children and adolescents with pervasive developmental disorder based on four RCTs on methylphenidate (Reichow et al. 2013). Also, ADRs were combined across studies and showed increased rates of decreased appetite, insomnia, depressive symptoms, irritability, and social withdrawal with methylphenidate compared to placebo. No increase in stereotyped and repetitive behavior, in contrast, a slight improvement of these behaviors was observed.

Atomoxetine is a noradrenaline reuptake inhibitor used as second-line treatment in ADHD (see Chap. 12). One small (Arnold et al. 2006) and one adequately powered RCT examined the efficacy and safety of atomoxetine in ASD (Harfterkamp et al. 2012). The latter study included 97 patients aged 6–17 years with ASD and concomitant ADHD symptoms. Children included were required to have an IQ above 60. Medication was titrated to a fixed dose of atomoxetine of 1.2 mg/kg × day within 3 weeks. After 8 weeks there was a significantly greater **improvement** of symptoms on the investigator-administered **ADHD Rating Scale** (ADHD-RS). The ADHD-RS change from baseline for atomoxetine was 8.2 ± 8.8 vs. 1.2 ± 7.3 for placebo.

However, there was no statistically significant difference in the number of participants who improved much or very much according to the CGI-Improvement subscale between atomoxetine (20.9 %) and placebo (8.7 %). Atomoxetine improved both hyperactive-impulsive symptoms and inattentiveness with larger improvements on measures of hyperactivity-impulsivity. The effect of atomoxetine appeared to be smaller than the effects reported in studies in children with ADHD without comorbid ASD. Common ADRs were nausea, decrease in appetite, fatigue, and early-morning awakening. An open-label extension of this study (Harfterkamp et al. 2013) for a period of 20 weeks found that ADHD symptoms further decreased with continued treatment. However, as this extension had no control group, it is possible that the natural course of symptoms contributed to this effect. ADRs were mild, and there was a tendency for the adverse events, especially nausea and fatigue, to subside during the course of treatment.

In summary, there is **strong evidence** supporting the **use of methylphenidate** (level I) and **atomoxetine** (level II) in children with ASD and comorbid hyperactivity, but less so for inattentiveness (methylphenidate, level II). As ADHD cannot be diagnosed as comorbid disorder in the DSM-IV TR/ICD-10 classification systems, ADHD was not diagnosed in addition to ASD in the abovementioned studies. Because ADHD usually is diagnosed by behavioral parent and teacher ratings of hyperactivity-impulsivity and inattentiveness, with an onset before the age of 7 years, the results of the above-reported studies can easily be extrapolated to children with comorbid ASD and ADHD (according to DSM-5). Treatment effects of methylphenidate and atomoxetine seen in ASD with ADHD symptoms appear to be smaller than in patients with ADHD without ASD. Clinicians need to be aware of higher rates of ADRs in ASD patients. As there are currently no direct comparison studies of atomoxetine and methylphenidate, no conclusive statement can be made about differences in efficacy and tolerability.

Hyperactivity has also been studied as a secondary outcome measure in trials of second- and third-generation **antipsychotics**. In these studies, a diagnosis of comorbid ADHD or increased ADHD was not established, but hyperactive behavior was assessed dimensionally using the ABC hyperactivity subscale. Both risperidone (McCracken et al. 2002; Shea et al. 2004) and aripiprazole (Marcus et al. 2009; Owen et al. 2009) lead to a greater reduction in the ABC hyperactivity subscale than placebo. The effect size of 0.6–1.0 was slightly higher than the effect size in the methylphenidate and atomoxetine studies, especially for risperidone (level I) with an effect size of 1.0 in the ABC hyperactivity scale (McCracken et al. 2002). Ziprasidone has also been shown to reduce ABC-rated hyperactivity in a small open-label study in 12 adolescents (level IV), with doses from 60–160 mg/day. It was weight neutral, but QTc increased by a mean of 14.7 ms, and extrapyramidal symptoms were observed. Cholesterol levels decreased, and no effect on prolactin level was observed (Malone et al. 2007). Haloperidol also was effective (level II) for hyperactivity in ASD (Anderson et al. 1989), but the high rate of extrapyramidal symptoms especially in male adolescents advises against its use as first- or second-line substance for hyperactivity in ASD.

When **choosing pharmacotherapy for hyperactivity** in *ASD*, the clinician should therefore first **assess** the broad range of possible psychopathology in ASD. If only **hyperactivity** (with or without inattention) is present in a child or adolescent with Asperger syndrome or PDD-nos (mild ASD), and neither aggressive nor stereotyped and repetitive behavior are of clinical concern, methylphenidate or atomoxetine may be chosen as first-line treatments. In **depressed** and **socially withdrawn children**, atomoxetine should be first-line psychopharmacotherapy over methylphenidate, due to the increased rate of ADRs by methylphenidate treatment, especially with regard to anxious and depressed symptoms. When **irritable and aggressive behavior** is present in addition to hyperactivity (with or without inattention) (see below) or when stereotyped and repetitive behavior are additionally of clinical concern, risperidone should be first-line treatment for hyperactive behavior, because it will also improve aggressive or stereotyped

behavior. Aripiprazole (or – as third line – ziprasidone) may be chosen in children with (severe) **obesity**. If **inattention** is of strongest concern (and no other behavior problems are present), behavioral therapy may be chosen first. If this shows no improvement within 2–3 months, additionally, low to medium-dose methylphenidate should be added.

A few **new agents** have also been studied with regard to hyperactivity and inattention as primary or secondary outcome measures. Of the NMDA receptor antagonists, amantadine and memantine were assessed in studies of differing quality. **Amantadine** in a small double-blind RCT ($N=39$ randomized) in individuals with autism, aged 5–15 years old, showed reduction in investigator-rated hyperactivity, but not in parent-rated hyperactivity (King et al. 2001). Inattentive behavior was not specifically addressed. Interestingly, a high placebo response for hyperactivity ratings by parents was observed in this and another study (Belsito et al. 2001).

Three studies on **memantine** have been performed to date. One retrospective open-label add-on study (level IV) in 3–12-year-old individuals ($N=14$) with pervasive developmental disorder reported positive effects on parent-rated (ABC) hyperactivity and irritability (Owley et al. 2006). Another retrospective open-label add-on study (level IV) in $N=18$ 6–19-year-old individuals with pervasive developmental disorder reported positive effects on parent-rated (ABC) hyperactivity and clinician-rated inattention by memantine doses from 2.5–20 mg/day, i.e., 0.4 mg/kg × day (Erickson et al. 2007). The third and largest study did not assess hyperactivity as outcome measure (Chez et al. 2007).

In addition, the opioid receptor antagonist **naltrexone** has been studied in five RCTs with mostly weak quality (Siegel 2012). The largest RCT (level II) with adequate quality included 41 children (2–7 years) with autism who received 1 mg/kg × day naltrexone over 3 weeks after a wash-out phase of 2 weeks (Campbell et al. 1993). In the blind clinician rating by the Children's Psychiatric Rating Scale (CPRS), the children showed improvement in hyperactive behavior. Parent ratings were not assessed, and results have not been replicated by an independent research group to date (Siegel 2012).

Taken together, as several well-researched substances (risperidone, methylphenidate, atomoxetine, aripiprazole) do exist for the treatment of hyperactivity, inattention, and comorbid ADHD in children and adolescents, these should be the first-line treatments, and naltrexone may be used (off label) in children and adolescents who did not respond to these substances or showed a high rate of ADRs.

13.3.4 Irritability, Aggressive and Self-Injurious Behavior

Aggressive behavior, self-injuries, and tantrums are common comorbid symptoms in children and adolescents with ASD. Their pharmacological treatment has primarily been studied in clinical trials evaluating **antipsychotics**. Studies have focused on irritability, with the ABC irritability subscale commonly used as the primary outcome measure. Dysfunctional behaviors on this subscale include self-injurious behavior, aggressive behavior, and tantrums. The antipsychotics most intensively studied in ASD are risperidone and aripiprazole.

The first large RCT of **risperidone** in autism was conducted by the RUPP Autism Network (McCracken et al. 2002) and included 101 children and adolescents from 5–17 years with autistic disorder (with or without ID) and tantrums, aggression, or self-injurious behavior. The risperidone group received an average of 1.8 mg daily (range 0.5–3.5 mg, with a maximum dose of 2.5 mg for children with less than 45 kg body weight). There was a significantly greater decrease on the ABC irritability subscale of 56.9 % in the treatment group vs. 14.1 % in the placebo group. Sixty-nine percent of the subjects in the risperidone group and only 12 % in the placebo group were classified as responders. Analysis of secondary outcome measures also suggested positive effects of risperidone on the ABC stereotypy and hyperactivity subscales. ADRs included increased appetite, weight gain,

and fatigue. However, most ADRs observed in the study were mild and self-limited. Weight gain in the risperidone group was significantly higher with 2.7 ± 2.9 vs. 0.8 ± 2.2 kg in the placebo group. Further analysis of secondary measures showed improvements on the CY-BOCS and the Ritvo-Freeman Real-Life Rating Scale under risperidone. However, risperidone did not improve the autistic core symptoms social interaction and communication (McDougle et al. 2005). A subgroup of subjects in the study performed a series of cognitive tasks before and after administration of medication. No negative, but also no positive effects of risperidone on cognitive performance were found (Aman et al. 2008).

Another study of risperidone included 79 children aged 5–12 with a diagnosis of pervasive developmental disorder with or without ID (Shea et al. 2004). The primary efficacy parameter was again the reduction of the ABC irritability subscale. Risperidone treatment, which was applied in a mean dosage of 0.04 mg/kg × day or 1.17 mg/day, resulted in a significantly higher decrease of irritability than placebo. Risperidone-treated subjects experienced improvement of 64 % over baseline irritability scores, while the placebo group only improved by 31 %. 69.2 % in the risperidone group vs. 39.5 % in the placebo group were classified as responders. The risperidone group also experienced greater decline in the other ABC subscales hyperactivity, inappropriate speech, social withdrawal, and stereotypy, with the largest difference between groups on the ABC hyperactivity subscale. Two recent meta-analyses have corroborated the **large effect size** of **risperidone** on ABC irritability and hyperactivity in ASD (Jesner et al. 2007; Sharma and Shaw 2012).

Aripiprazole has been studied in autism in two industry-sponsored trials that were published in the same year and conducted by partially the same authors. The first study included 212 children and adolescents with a diagnosis of autism and behaviors such as tantrums, aggression, and self-injurious behavior (Marcus et al. 2009). Subjects were randomly assigned to either fixed doses of either 5, 10, or 15 mg of aripiprazole or placebo. Aripiprazole was superior in reducing the ABC irritability subscale score in all doses. All treatment arms showed greater improvement compared with placebo already during week 2 at a dose of 5 mg. The responder rate was numerically higher in all aripiprazole arms; however, the difference of drug vs. placebo only reached statistical difference for the 5 mg dose. The ABC hyperactivity and stereotypy subscales scores, which were used as secondary outcome measures, also showed greater improvement in all aripiprazole doses than in the placebo group.

A second RCT on aripiprazole was done in 98 children and adolescents with autism (Owen et al. 2009). The subjects also demonstrated behaviors like tantrums, aggression, and self-injurious behavior with a minimum score of 18 in the ABC irritability subscale as inclusion criterion. Aripiprazole was found to be superior compared to placebo in the reduction of irritability. The ABC irritability subscale score decreased by 12.9 in the treatment group, while the reduction in the placebo group was 5.0. There was a significantly higher responder rate of 52.2 % for aripiprazole vs. 14.3 % for placebo. Again, secondary outcome measures suggested effects of aripiprazole on hyperactivity and stereotyped behavior.

On the basis of the studies reported above, there is established **evidence** that **risperidone** (level I) and **aripiprazole** (level II) are **efficient** in the **treatment of irritability** (aggressive and self-injurious behavior, tantrums) in children and adolescents with ASD, with risperidone showing a somewhat larger effect size than aripiprazole.

Other antipsychotics, as olanzapine, quetiapine, ziprasidone, paliperidone, and clozapine, have not been studied in trials with sufficiently large sample sizes (Doyle and McDougle 2012; Siegel 2012). The evidence regarding the efficacy of these psychotropic agents in ASD is currently insufficient. One older study of the first-generation antipsychotic haloperidol (Anderson et al. 1989) in children (2–7 years) with autism reported a reduction of a variety of behavioral symptoms including temper tantrums. However, given its ADRs haloperidol should not be considered as first- or second-line treatment in autism.

The antipsychotic **pipamperone** is used in clinical practice due to its **sedating properties** in patients with aggressive or self-injurious behavior

(see Chap. 9). However, there are no RCTs regarding the efficacy of pipamperone in ASD. Based on clinical experience the use of pipamperone (2–4 mg/kg × day) in ASD can be beneficial if sedation is necessary.

Some smaller studies have investigated the use of psychopharmacological agents other than antipsychotics in the treatment of irritability and aggression. **Valproate** has been studied by two small RCTs in children and adolescents with autistic disorder (Hellings et al. 2005; Hollander et al. 2010): the first ($N=30$) showing no effect, the second ($N=27$) showing a medium effect for the parent ABC irritability score (effect size of $d=0.44$) and by clinician-rated CGI-I for irritability. The second study included more severely affected children with autistic disorder (versus pervasive developmental disorders) who also showed an increased rate of irritability at baseline.

The RCT on **amantadine** (King et al. 2001) yielded conflicting results regarding irritability (see also Sect. 13.3.3); therefore amantadine currently **cannot be recommended** in the treatment of behavioral symptoms including irritability in autistic disorder. Similarly, **memantine** and **galantamine**, despite showing more positive effects, have not been studied by sufficiently powered RCTs and therefore cannot be recommended at the current state for the treatment of (auto)aggressive behavior and irritability in ASD (Nicolson et al. 2006; Niederhofer et al. 2002; Owley et al. 2006).

One RCT on **naltrexone** has shown a trend for improvement of self-injurious behavior (Campbell et al. 1993), but again, this needs to specifically be studied by sufficiently powered RCTs in children with ASD and self-injurious behavior. *N*-**Acetylcysteine** has been proposed as another new substance with impact on the glutamatergic system and simultaneous antioxidant effects. An RCT pilot study in 31 3–12-year-old individuals with autism showed a large effect on the parent-rated ABC irritability scale with *N*-acetylcysteine doses between 900 and 2,700 mg/day (Hardan et al. 2012). As the study showed some methodological limitations and was an add-on study, *N*-acetylcysteine needs to be studied in sufficiently powered, independent RCTs, before firm conclusions can be drawn.

13.3.5 Comorbid Anxiety Disorder

No RCTs on any psychopharmacological agent have been done in children with ASD and comorbid anxiety disorder, despite the high prevalence of comorbid anxiety disorder in ASD (see Table 13.1). The treatment of choice in individuals with ASD without ID are the respective disorder-specific behavioral therapy approaches (cognitive, exposition) to improve different kinds of comorbid anxiety disorder in ASD (Storch et al. 2013). Still, clinically some children and adolescents do not improve sufficiently by this approach. For these children, low to medium-dose treatment with SSRIs such as citalopram (5–20 mg/day) or sertraline (25–50 mg/day) can be effective as reported by case reports, open-label pre-post observational studies, and clinical experience (Namerow et al. 2003; Steingard et al. 1997). There is a strong need for more psychopharmacological studies on ASD comorbid with anxiety disorders in children and adolescents.

13.3.6 Comorbid Major Depressive Disorder

Similar to comorbid anxiety disorders, comorbid MDD is under-researched in ASD, despite a high rate of MDD especially in adolescents with ASD (Simonoff et al. 2012). Only a single case report study exists which reports on the use of fluoxetine in comorbid MDD in ASD (Ghaziuddin et al. 1991). Other SSRIs have not specifically been studied for their effect on comorbid depression in ASD. Clinically, SSRIs show an insufficient effect on adolescent depression in ASD (level V), which is less than the antidepressant effect of SSRI in adolescents without ASD. Also, SSRIs show an increased rate of ADRs in ASD (Williams et al. 2013).

Mirtazapine and, even more so, **reboxetine** seem to be more useful as psychopharmacotherapy for MDD in ASD. Mirtazapine has been studied by one open-label add-on study in a very mixed sample of 26 children, adolescents, and young adults with pervasive developmental disorders (Posey et al. 2001). Improved depressive symptoms by clinician-rated CGI are mentioned

in the text. Reboxetine has been studied by a more recent and qualitatively stronger open-label monotherapeutic study in 11 adolescents with ASD. Treatment duration was 12 weeks with a dose of 4 mg/day (Golubchik et al. 2013). Especially in individuals with a high CDRS score at baseline, a strong clinician-rated improvement in this scale was observed.

13.3.7 Comorbid Tic Disorders

Comorbid tic disorders have been studied even more rarely in ASD, despite their increased prevalence in ASD (see Table 13.1). In a retrospective study on aripiprazole augmentation, two of four ASD children with tic disorders showed clinical improvement (Kim et al. 2010). Clinically, also risperidone may be recommended (level V), but there are no systematic studies on the efficacy of risperidone in comorbid tic disorders in ASD.

13.3.8 Comorbid Sleep Disorders

Just recently, a practice pathway (level III–IV) has been published on the identification, evaluation, and management of insomnia in children and adolescents with ASD (Malow et al. 2012). It has been recommended that underlying medical causes should first be excluded in a child or an adolescent with insomnia and ASD. If a need for intervention does exist, parent education and behavioral therapy approaches should be used first, before psychopharmacological therapy is started.

The best studied substance for sleep disorder in ASD is **melatonin**, a nutritional substance and over-the-counter medication. A recent meta-analysis has shown an effect on sleep duration, number of nighttime awakenings, and sleep onset latency with very limited adverse effects, as morning drowsiness, increased enuresis, headache, diarrhea, and worsening of behavior in few children. Children and adolescents aged 2–18 years were included in the reported RCT, and doses ranged from 2.5–10 mg, given approximately ½–1 h before bedtime (Rossignol and Frye 2011).

In addition to melatonin, especially risperidone, pipamperone, and mirtazapine are sedating and can also improve sleeping in children with ASD. These drugs have not been studied in detail for their effect on sleep disorders, but effects on insomnia were reported by a study analyzing side effects of an RCT on **risperidone** (Aman et al. 2005) and in a small observational add-on study for mirtazapine (Posey et al. 2001).

The **choice of psychopharmacotherapy** in children and adolescents with insomnia or other sleep disorders should therefore reflect the pattern of comorbid disorders. If a child is receiving risperidone because of irritability, this may be sufficient to improve insomnia. In children and adolescents who need additional pharmacotherapy or who do not receive any other psychopharmacotherapy, melatonin is a safe and efficient psychopharmacological option and can likely be used on an ongoing basis (longest follow-up: 4 years). However, longer-term safety studies have not yet been performed.

13.3.9 Other Comorbid Behavioral Problems

A few low-quality observational studies on the use of mirtazapine in excessive masturbation have been published (see Table 13.2). Given that these behavioral problems are not well studied, and behavioral therapy approaches were not systematically evaluated, no scientific basis for any kind of recommendation can be given with regard to these behaviors.

13.4 Combined Pharmaco- and Behavioral Therapy as an Essential Treatment Strategy

In summary, there is good evidence (level I–II) for pharmacotherapy for externalizing problems in ASD. The scientific basis for the treatment of internalizing problems is less well established (level IV), despite the high co-occurrence of these comorbid disorders in ASD. Generally, the lowest effective dosage should be used for any kind of long-term psychopharmacotherapy. Individual titration needs to be done with all substances.

In clinical practise, often a combination of behaviorally based psychotherapy and psychopharmacotherapy is chosen for treatment of different behavioral problems in ASD. This is especially true for countries, where public services for behaviorally based psychotherapy are available. Given the existing small evidence of just a few studies on maladaptive behavior (Aman et al. 2009) and sleeping problems (Cortesi et al. 2012) showing an improved effect by combined therapy and the positive effect of cognitive behavioral therapy in adolescents with ASD without ID and comorbid anxiety disorders (Storch et al. 2013), combined treatment approaches need to be studied more often by RCTs.

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Depressive Disorders

14

Regina Taurines and Christoph Wewetzer

Contents

R. Taurines, MD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: taurines_r@ukw.de

C. Wewetzer, MD
Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Florentine-Eichler-Str. 1, 51067 Köln, Germany
e-mail: wewetzerc@kliniken-koeln.de

14.1 Definition, Classification, and Target Symptoms

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), the common feature of depressive disorders is "sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function" (American Psychiatric Association 2013). The International Classification of Diseases, 10th revision (**ICD-10**), characterizes **depressive episodes** (ICD-10 F32.0–F32.3; DSM-5: Major depressive disorder 296.20–296.26) by a dejected state of mind and anhedonia, which includes loss of interests, lack of joy, and reduced energy and spontaneity (World Health Organization 1996). Further symptoms include reduced concentration and attention, a decline in self-confidence, feelings of worthlessness, and negative thoughts. Reduced performance at school and in the workplace are the result of the depressive mood, reduced ability to concentrate, increased anxiousness, and the feelings of inferiority. The symptoms of a depressive episode persist for most days, most of the time for at least 2 weeks; they are age dependent but only situation related to a minor degree. Somatic and psychotic symptoms may also be presented.

Recurrent depressive disorders (ICD-10 F33.0–F33.3, F33.9, F33.41, F33.42; DSM-5: 296.30–296.36) are characterized by repeated depressive episodes without any history of independent episodes of mood elevation and overactivity

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that fulfill the criteria of mania. The individual episodes last between 3 and 12 months and are frequently initiated by stressful life events.

In **DSM-5** the diagnosis of **major depressive disorder** requires the presence of at least five of nine symptom criteria for at least 2 weeks, one of which is depressed mood or loss of interest. These symptoms must cause significant subjective distress or clinically significant impairment at school or work, in social life, or other important areas of functioning almost every day. In children and adolescents also an irritable mood can be observed and, due to reduced appetite, a loss of weight or failure to gain weight. The term "major depression" is used to distinguish discrete episodes of depression from mild, chronic (1 year or longer) low mood, or irritability, which is known from DSM-IV as "dysthymia" (according to DSM-5 persistent depressive disorder 300.4 [ICD 10: F34.1]). In dysthymia the depressed mood for most of the day may be continuously present for at least 2 years. According to DSM-5, persistent depressive disorder in children and adolescents mood can be irritable, and the duration must be at least 1 year. In the mood disorders category, patients with fewer than five depressive symptoms, or with symptoms that were not present every day or nearly every day for a minimum of 2 weeks, would be diagnosed with **depressive disorder not otherwise specified**, if the development of the symptoms was not attributable to a stressful event. If the symptoms occurred in the context of a stressful event, the diagnosis would be **adjustment disorder**.

The **target symptom** of the **pharmacotherapy** of depressive disorders in children and adolescents is the sad, dejected, and disconsolate mood, combined with joylessness, disinterest in play, apathy, and social withdrawal. Common symptoms are marked mood swings, reduced initiative, lack of energy, and psychomotor inhibition, which require treatment. On the other hand, constant irritability and agitation can also dominate the clinical picture, particularly in children and adolescents. Delusional depressive symptoms, especially delusions of sinfulness and guilt, are absent in children and very rare in adolescents. There is frequently a tendency to brooding and vegetative symptoms such as lack of appetite and somatic complaints, including abdominal pain and headache (Findling et al. 1999). All these symptoms might be therapeutic targets. Additional target symptoms of therapy are disturbances of the sleep-wake cycle (especially early morning waking), and in older adolescents disturbances of libido. Significant target symptoms are suicidal thoughts and actions.

14.2 Therapeutic Framework

Prior to the commencement of therapy, the **diagnosis must be secured**. Organic causes such as an endocrinological or chronic disease, infections, and organic brain disorders as well as intoxications must be excluded (by physical-neurological examination, clinical chemistry investigation, EEG, etc.). Effects of medication and of drug or alcohol abuse, which can similarly induce depressive symptoms (DSM-5: substance-/medication-induced depressive disorder), as well as other psychiatric differential diagnoses must be part of examination. Depression in children and adolescents is frequently not detected or treated, as the disorder in this age group initially often manifests with behavioral or physical complaints, what may obscure the typical depressive symptoms presented in adulthood.

Diagnosis of a depressive episode and titration of an antidepressive medication can be undertaken on an outpatient or on a partly or fully inpatient basis, depending upon the severity of the disorder. In cases of acute suicidality, treatment in a closed child and adolescent psychiatric ward is required.

Psychoeducation, including the comprehensive explanation of the disease and therapeutic options as well as supportive management and ongoing involvement of family and school, is the **basis of the treatment**. Thereby the way of involvement will certainly depend on the patient's age, stage of development, the familial

circumstances, and cultural background. Antidepressant treatment also includes relief from overtaxing stresses and burdens such as conflicts and excessive demands at school.

Prior to antidepressant medication, the indication for the drug, the status of approval, and potential ADRs should be explained. The delayed effect of antidepressants should be mentioned as well as the necessity to take medication as prescribed.

For the **assessment** of **drug response** and adverse drug recations (**ADRs**) and for further supportive interventions, weekly contacts (personally or over the phone) during the first month of antidepressant therapy are recommended. Given the reported small association of some antidepressants with an increase in suicidal thoughts and behavior and the activating effect of some agents (see also Sect. 4.4), especially during the first weeks of treatment with an antidepressant, suicidal thoughts and suicide-related behavior should be carefully monitored as well as ADRs believed to be associated with an increase of suicidality, increased agitation, irritability, sleep disruption, and induction of mixed states (AACAP Official Action 2009; Birmaher et al. 2007; Rey et al. 2012).

In children and adolescents presenting uncomplicated **mild or brief depressive episodes** or mild psychosocial impairment, "**watchful waiting**" (an arrangement of a further assessment within about 2 weeks) and supportive management strategies might be appropriate. Antidepressants take some time to have an effect. So it should be considered whether the observation period is worth any disadvantage caused by further delaying an antidepressant effect. In mild to moderate depression, specific psychotherapeutic treatment approaches, particularly cognitive behavior therapy and interpersonal psychotherapy, are advisable.

In case of a **moderate to severe depressive disorder**, chronic or recurrent depression, considerable psychosocial impairment, suicidality, agitation, and psychotic symptomatology, the combination of specific psychotherapeutic and psychopharmacological treatment might be required. Antidepressant pharmacotherapy may follow a first-line treatment of psychotherapy, but it may also antecede to make the child and adolescent amenable for psychotherapy (Birmaher et al. 2007; National Institute for Health and Care Excellence 2005; Rey et al. 2012).

For further information regarding the diagnosis and therapy of depressive disorders, the reader is referred to current reviews (Birmaher et al. 2007; Bujoreanu et al. 2011; Clark et al. 2012; Taurines et al. 2011).

14.3 Choice of Pharmacotherapy

The choice of pharmacotherapy should be guided by these considerations: effectiveness and safety and the subtype of depression. There is little research evidence on the efficacy of antidepressant medication for the young child in the age of 5–11 years; however, some antidepressants were used in the treatment of anxiety disorders from the age of 7 years on (Ginsburg et al. 2011; Walkup et al. 2008). Thus, the following treatment recommendations are mainly based upon the evidence in children and adolescents of 12–18 years (National Institute for Health and Care Excellence 2005).

For more detailed information regarding the psychopharmacological agents discussed in this chapter (indications, indication- and age-specific aspects of approval status, recommended dosages, ADRs, interactions with other medications, restrictions on use, and special cautions), the reader is referred to Chap. 4.

14.3.1 Antidepressants in Monotherapy

Selective serotonin reuptake inhibitors (**SSRIs**) have become the **cornerstone of pharmacotherapy** for depression in this age group since the FDA approval of fluoxetine for the treatment of major depression in children with 8 years of age and older and escitalopram starting with the age of 12 years. SSRIs are first- and second-choice antidepressants in treating depression in children and adolescents as they are effective in all forms of depressive episodes, in inhibited and restless-agitated depressions (Ambrosini 2000; Edwarts and Anderson 1999; Hazell 2009). SSRIs are preferred to tricyclic antidepressants because of their more favorable risk-benefit relationship. Further FDA approval exists for the SSRIs fluvoxamine and sertraline, however not for the indication depression but for obsessive-compulsive disorder.

Fluoxetine and escitalopram (approved for acute and maintenance treatment of major depressive disorder in youths: fluoxetine 8–17 years, escitalopram 12–17 years) are **first-choice** antidepressants in the treatment of depression in children and adolescents, due to their efficacy in numerous controlled trials (including Emslie et al. 1997, 2002, 2008, 2009; Gibbons et al. 2012; Wagner et al. 2006; Yang and Scott 2010) and the FDA approval. According to the meta-analysis by the FDA (2004), beside fluoxetine, sertraline and citalopram possess the lowest relative risks of all the SSRIs for an increase in suicidal thoughts and para-suicidal acts. Therefore and because of their effectiveness (Wagner et al. 2003, 2004; Wagner 2005), **sertraline and citalopram** can be employed as **second-choice** antidepressants. For citalopram in 2011 the FDA issued a drug safety "MedWatch" communication regarding potential abnormal heart rhythms (QT interval prolongation and torsade de pointes) associated with doses above 40 mg/day. In a recent evaluation of this topic, however, no elevated risk of ventricular arrhythmia or all-cause, cardiac, or noncardiac mortality associated with daily citalopram dosages above 40 mg was found (Zivin et al. 2013).

Few randomized controlled trials have evaluated the effects of other classes of antidepressants in children and adolescents (see Chap. 4). In summary, these studies on tricyclic antidepressants and the selective serotonin and noradrenalin reuptake inhibitors duloxetin and venlafaxine showed no general superiority to placebo and venlafaxine being better only in adolescents, not in children. This lack of evidence regarding efficacy, however, may be explained by the methodological limitations of such studies (see Sect. 4.4). For these reasons, a recommendation for an antidepressive medication can only be given for SSRIs as first- and second-choice agents. As there might be reasons to choose an alternative antidepressant due to availability or patient and family preference, in this chapter also further antidepressants, not of first or second choice, are discussed.

Tricyclic antidepressants should be **avoided** in children and adolescents because of their unfavorable ADR profile and low intoxication threshold. In meta-analyses on the treatment of depressed children and adolescents, no difference in the efficacy of tricyclic antidepressants and placebo was found (Papanikolaou et al. 2006, see also Sect. 4.4.1.1).

As above mentioned, the serotonin and noradrenaline reuptake inhibitor **venlafaxine** was not found to possess a general efficacy in controlled studies of the treatment of depressive disorders in children and adolescents (Courtney 2004; Emslie et al. 2007a, b; Review: Mandoki et al. 1997). However, in two randomized controlled trials, a clearly greater improvement according to the Children's Depression Rating Scale-Revised was observed with the agent than with placebo in adolescents aged 12–17 years, but not in the younger children (Emslie et al. 2007). As a result of a controversy regarding a possible increase in suicidal ideation and parasuicidal acts (see Sect. 4.4.1.3), the manufacturer has warned since 2003 against using venlafaxine in patients younger than 18 years.

As **alternative agents**, but also not of first or second choice, the α_2-adrenoceptor antagonists mianserin and mirtazapine might be employed in anxious-agitated depression with restlessness

and sleep disturbances. A positive impact upon depressive symptoms, including sleep disturbances, in children and adolescents has been reported in non-placebo-controlled studies (Dugas et al. 1985; Haapasalo-Pesu et al. 2004).

St. John's wort (*Hypericum perforatum L.*) preparations are popular herbal remedies used worldwide to treat a variety of medical illnesses including depression. In certain areas of Europe, St John's wort has been a commonly prescribed treatment for depression in children and adolescents, but in the USA, various formulations (e.g., extracts, crude drug in tablets or capsules, tinctures, teas) in several doses are available either as over-the-counter drugs or dietary supplements. Standardization and quality are an issue of note with St. John's wort, as extracts show variability of efficacy potentially due to different constituent profiles (Kasper et al. 2010). Therefore, results of high quality European pharmaceutical grade extracts for which efficacy has been shown in adults in randomized, placebo-controlled studies (Sarris et al. 2011) cannot be generalized to inferior extracts.

There is **insufficient evidence** to support the use of St. John's wort in the treatment of depression **in children and adolescents** (Hazell 2009). No controlled studies of St John's wort therapy of depression in children and adolescents have thus far been published. However, in open-label studies, an antidepressive effect of St. John's wort has been reported in children and adolescents (Findling et al. 2003; Simeon et al. 2005).

14.3.2 Psychopharmacological Agents as Co-medications

The treatment of depressive episodes occasionally demands co-medication with sedating agents.

14.3.2.1 Benzodiazepines

In cases involving suicidal ideation and actions, it is advisable to temporarily supplement antidepressive medication with an anxiolytic benzodiazepine (see Chap. 6 and Sect. 14.4.3). Benzodiazepines are suitable due to their sedative, hypnotic, and anxiolytic effects. They show a low toxicity and weak ADRs – beside their risk of abuse, dependence, and withdrawal symptoms upon discontinuation (Lader and Petursson 1981). Data on adults with major depression reveal a favorable effect of the combination of antidepressants and benzodiazepines on dropout rates due to ADRs, and the improvement of depressive symptoms during the first weeks of treatment (Furukawa et al. 2001). Data on such co-medications in minors lacks.

14.3.2.2 Low-Potency Antipsychotics

Where motor restlessness or mental agitation are marked and in cases including sleep disturbances, co-medication with a low-potency antipsychotic (see Chap. 5) might be considered (see Sect. 14.4.3). Antipsychotics provide a range of potential ADRs, depending on their individual receptor-binding profile (see Sect. 5.4.4 and Table 5.6); therefore close monitoring is necessary. In long-term treatment of adult psychiatric patients, medications such as melperone did not generate reports of serious ADRs (Christensen et al. 1986). However, there are no data on the use of co-medication with antipsychotics in depressed children and adolescents.

14.4 Treatment Strategies

Considering the above discussed aspects on safety, efficacy, and status of approval, the following **aspects** might be **helpful to select an antidepressant**:

- How severe are the depressive symptoms?
- Does the patient report suicidal thoughts and impulses? If he or she does, immediate sedation and anxiolysis (benzodiazepine) as well as close monitoring of the titration of antidepressant dosage may be indicated. This should be done in an inpatient hospitalization.
- Does the patient exhibit either inhibition or elevation of drive? In cases of anxious-agitated depression, more sedative antidepressants are advisable such as mirtazapine or sertraline (because of its relatively minor activating properties).

- What are the specific profiles of effects and ADRs of the individual psychopharmacological agent?
- What other medications are also being employed? Which potential medication interactions might appear?
- Has the patient previously been successfully treated with an antidepressant? If this is the case, this preparation should again be employed.

14.4.1 SSRIs as First- and Second-Choice Medication

Titration of SSRI dosage should be quite gradual in order to avoid a pharmacogenic delirium. Particularly at the beginning of therapy and during dosage increases, one should watch – as above mentioned – for the occurrence of increased restlessness, irritability, and impulsive suicidal ideation, anxiety states, and insomnia, in addition to other ADRs. It may be necessary to reduce SSRI dosage, to introduce a co-medication or to gradually withdraw the SSRI altogether.

An antidepressive effect is generally evident after 2–4 weeks.

Before starting antidepressant medication with an SSRI, the assessment of blood count, electrolytes, liver and kidney parameters, and heart rate and pulse are recommended. These parameters should be controlled in the treatment course. Prior to SSRI therapy also an EEG is recommended. Increases in dosage should continue until steady-state plasma levels are reached and monitored by therapeutic drug monitoring (TDM; Sect. 2.3).

A single morning dose is sufficient for most SSRIs. As the elimination half-life for fluvoxamine is 10–22 h, two daily doses are appropriate for this SSRI. Fluvoxamine and sertraline should be taken with meals, whereby grapefruit juice should be avoided at these times as it potentially increases plasma concentrations of the antidepressant (Hori et al. 2003; Ueda et al. 2009).

Typical therapy with one of the first-choice antidepressants, **fluoxetine**, has proved effective according to the following procedure: the commencement dose is a single morning dose of 5–10 mg, depending upon age and weight of the child or adolescent. If tolerated, the dosage is increased every 5–7 days by 5–10 mg. For the majority of children, a single morning dose of 20 mg is adequate. Where a satisfactory effect is not seen in adolescents or patients with higher body weight after a reevaluation time of 4–6 weeks, a better effect might be expected from a stepwise dosage increase by (5–)10 mg every 2–3 weeks to a level of 40–60 mg/day (Heiligenstein et al. 2006; see also Table 14.1). Higher dosages are generally required for the treatment of obsessive-compulsive disorders and bulimia as for depressive symptoms (see Bezchlibnyk-Butler and Virani 2007; Geller et al. 2001; Hay and Claudino 2012).

The stepwise dose titration of the other first-choice antidepressant escitalopram is within the range of 2.5–20 mg/day (Owley et al. 2005; see also Table 14.1). Total daily dosages for second-choice antidepressants are presented in Table 14.1.

The **serotonin syndrome** describes a rare but potentially fatal ADR involving CNS serotonergic overactivity. It is life-threatening when disturbance of heart rate, seizures, or coma develops. **Particular caution** in this respect applies to **fluoxetine**, because of its active metabolites and its consequently long elimination half-life.

The serotonin syndrome is **treated** by immediately withdrawing the medication. Where high fever is presented, it is advisable to cool the patient, and adequate fluid intake should be assured. Infusion therapy and intensive care may be necessary in individual cases. Methysergide may be prescribed as pharmacological therapy.

Table 14.1 Daily dosages of selected antidepressants used in children and adolescents for the indication depression, their approval status and/or references for the listed dosages

Agents	Total daily dosages	Approval/references
Citalopram	20–40 mg/day as single morning dose	Off-label use in children and adolescents (Wagner et al. 2004; von Knorring et al. 2006)
Duloxetine	40–60 mg/day in one or two dosages/day Maximum: 120 mg/day	Off-label use in children and adolescents (Prakash et al. 2012)
Escitalopram	10–20 mg/day as single morning dose	US FDA approved ≥12 years
Fluoxetine	10–20 (−40) mg/day as single morning dose	US FDA approved and in Europe approved ≥8 years (Emslie et al. 2008; Gibbons et al. 2012)
Fluvoxamine	50–200 mg/day in two dosages/day (larger dose, if so, in the evening)	US FDA approved ≥8 years
Mianserin	30–120 mg/day in one, two, or three dosages/day Average dose: 1 mg/kg body weight per day Larger dose at bedtime	Off-label use in children and adolescents (Dugas et al. 1985; authors' personal experience)
Mirtazapine	15–45 mg/day in one or two dosages/day Mainly at bedtime	Off-label use in children and adolescents (Haapasalo-Pesu et al. 2004)
Paroxetine	20–40 mg/day as single morning dose	Off-label use in children and adolescents (Keller et al. 2001)
Reboxetine	3–8 mg/day in two dosages/day	Off-label use in children and adolescents (Tehrani-Doost et al. 2008; Arabgol et al. 2009; Cohen-Yavin et al. 2009; Golubchik et al. 2013)
Sertraline	25–200 mg/day as single morning dose	Off-label use in children and adolescents (Wagner et al. 2003; Alderman et al. 2006)
St. John's wort	900 mg/day in three dosages/day	Approved in some European countries for adults and partly for adolescents (Findling et al. 2003; Simeon et al. 2005)
Venlafaxine	37.5–225 mg/day in two or three dosages/day or as extended release formulation	Off-label use in children and adolescents (Emslie et al. 2007a, b; March et al. 2007; Rynn et al. 2007; Brent et al. 2008)

When **switching** to another antidepressant (see Table 14.2) or **terminating therapy**, it is necessary to do so gradually. This applies in particular to SSRIs with short elimination half-lives, such as fluvoxamine. Abrupt withdrawal can lead to vertigo, gait disturbances, gastrointestinal complaints, disturbed perception, and deterioration of mental state.

14.4.2 Other Antidepressants

14.4.2.1 Mianserin and Mirtazapine

α_2-Adrenoceptor antagonists are no agents of first or second choice in the treatment of depressive episodes in children and adolescents. As with all antidepressants, dosage titration of mianserin and mirtazapine should be gradual (Table 14.1). The initial **dosage** of 10–30 mg **mianserin** can be divided into three doses. Depending upon age and weight, according to the authors' experience, children and adolescents receive up to 60–120 mg daily; because of its sedative effect, a higher evening dose can be advantageous.

Mirtazapine should be gradually introduced, commencing with 15 mg. After gradual titration, up to 45 mg can be given daily (Haapasalo-Pesu et al. 2004). A single **dose** is adequate for this antidepressant, two dosages a day are also possible; in cases with sleep disturbances, its sedative effect renders evening administration appropriate. Treatment with mirtazapine has the advantage that it rarely causes sexual dysfunction.

Table 14.2 Change of antidepressant therapy in nonresponders

Ineffective antidepressant	Switch to	Recommended procedure
SSRIs	Other SSRI	Taper off and switch
	Tricyclic antidepressant	Wait for about 5 $t_{1/2}$ of the SSRI before introducing tricyclic antidepressants (caution with fluoxetine, long $t_{1/2}$ of active metabolite)
	Venlafaxine	Wait for ca. 5 $t_{1/2}$ of the SSRI
	Moclobemide	Wait for ca. 5 $t_{1/2}$ of the SSRI
Moclobemide	Tricyclic antidepressants	Wait 2–3 days
	SSRIs	Wait 2–3 days (caution)
	Venlafaxine	Wait 2–3 days (caution)
Venlafaxine	Tricyclic antidepressants	Immediate change possible
	SSRIs	Wait 3 days (caution)
	Moclobemide	Wait 3 days (caution)

Modified from Bezchlibnyk-Butler and Virani (2007)
$t_{1/2}$ elimination half-life, *SSRI* selective serotonin reuptake inhibitor

For the monitoring of the treatment with these drugs, please see the recommendations for the use of SSRIs in Sect. 4.4.1.1.

14.4.2.2 Venlafaxine

Venlafaxine is no antidepressant of first or second choice in the treatment of depression in children and adolescents. It should be gradually titrated. The initial dosage in adults is 37.5 mg; if this is not effective, the daily **dosage** can be increased by 37.5 mg increments. There are no official dosage recommendations for children and adolescents. Our experience is that a standard dosage for adolescents of 75–150 mg is appropriate. In studies on venlafaxine treatment in this age group, total daily dosages up to 225 mg were administered (Brent et al. 2008; Emslie et al. 2007; March et al. 2007; Rynn et al. 2007, see also Table 14.1). The administration of a slow-release formulation reduces the frequency of ADRs that are discussed in Sect. 4.4.1.4. For the monitoring of the treatment with venlafaxine, please see the recommendations for the use of SSRIs in Sect. 14.3.1.

Venlafaxine should not be abruptly withdrawn, as withdrawal phenomena can occur. It is therefore recommended that dosage be gradually reduced over a period of 2–4 weeks.

14.4.2.3 St. John's Wort Extracts

The **source** of commercial St John's wort extract preparations is **clinically important**. The comparison of eight different St John's wort preparations with respect to their hyperforin and hypericin content not only found major variations between various commercial products but also between different samples of the same preparation (Wurglics et al. 2001).

Well-defined St. John's wort products that have been studied include LI-160 (Lichtwer), Ze117 (Zeller), and WS-5570 (Schwabe). Some of these may be purchased online; however, physician prescription is still advised. The common daily dosage of concentrated St. John's Wort is 900 mg (see Table 14.1), often given in divided doses two to three times per day in tablet form, amounting to about 1.0 mcg of hypericin (the active component) and/or 0.5–5 % of hyperforin (depending on whether the extract is standardized to reduce hyperforin). However, more severely depressed adult patients may need up to 1,800 mg/day (Sarris 2013).

Important potential ADRs include elevated photosensitivity, gastrointestinal complaints, and allergic reactions (for further information see Sect. 4.4.4). Women taking oral hormonal contraceptives can experience breakthrough bleeding. Due to

potential drug interactions, additional methods of contraception have to be recommended.

For the monitoring of the treatment with St. John's wort, please see the recommendations in Sect. 4.4.4.

14.4.3 Psychopharmacological Agents as Co-medication

14.4.3.1 Benzodiazepines

Suicidal ideation and acts are an urgent indication for antidepressive medication. Immediate supplementary anxiolysis and sedation with a benzodiazepine might also be advisable, such as acute 1–2.5 mg lorazepam or three doses of 2.5 mg across the day. This supplementary medication, however, should only be short term, given the danger of tolerance.

14.4.3.2 Low-Potency Antipsychotics

Where motor restlessness, agitation, and sleep disturbances are marked, co-medication with a low-potency antipsychotic can be appropriate. For example, single doses of 25–75 mg melperone (depending on age and body weight) are mostly sufficient to treat sleep disturbances in depressive children and adolescents.

14.4.4 Procedures in Cases Where Antidepressive Therapy Is Ineffective

In cases where symptoms have not been improved by treatment with an antidepressant (nonresponse), the **following procedure** has proved **useful**:

- Increase the dosage of the initiated monotherapy, and continue the adequately dosed monotherapy. Patients who are showing minimal or no response after 8 weeks of treatment are likely to need alternative treatments (Brent et al. 2008).
- Reconsideration of the diagnosis and checking of compliance.
- Undertaking TDM, particularly when a tricyclic antidepressant is being used. Table 4.6 provides an overview of recommended effective concentrations of various antidepressants in adults. Corresponding reference values for children and adolescents are, however, not available.
- Switching medication to an antidepressant with a different effects profile. Even the transfer from, for instance, one SSRI to another SSRI can lead to marked clinical improvement. During the changeover phase, TDM of both agents is advisable in order to avoid toxic and overdosage effects. The procedures outlined in Table 14.2 have proved useful in the switch from an ineffective antidepressant therapy to another pharmacological option. Be certain to continue the first SSRI for 2 weeks after reaching the therapeutic level for the second new medication or you will see the patient deteriorate.

If none of these measures leads to success, the following **augmentation strategy** options can also be explored (with close TDM monitoring):

- Combination of antidepressive medication with a second- or third-generation antipsychotic in persistent depressive states that also include delusional content (Birmaher et al. 2007; Schmauss and Messer 2007).
- Combination of two antidepressants with differing effects profiles. There are, however, no empirically secure data for this approach in children and adolescents. A meta-analysis of mostly uncontrolled studies in adults found a small effect for combination therapy with two antidepressants (Lam et al. 2002). An option that would be appropriate (while remaining mindful of ADRs) is the combination of an SSRI with mirtazapine.
- Combination of an antidepressant with an agent that inhibits the catabolism of the antidepressant and thus increases its efficacy such as carbamazepine. Combination of an antidepressant with lithium salts, in particular, but also with thyroid hormones, has shown good antidepressive effects in adults in controlled studies (Carvalho et al. 2007; Schmauss and Messer 2007). There is, however, only little experience with children and adolescents in this regard.

The augmentation procedure always involves the cautious, incremental introduction of an additional medication while retaining the current maintenance dosage of the original medication, monitoring serum levels of each by TDM. If the original preparation responds to augmentation, its dosage may be reduced relative to therapeutic levels, if ADRs render this desirable.

14.4.5 Duration of Therapy

Antidepressive therapy should be continued for 6–12 months (Birmaher et al. 2007; National Institute for Health and Care Excellence 2005) after depressive symptoms have subsided. Throughout this period, the most recent effective dosage of the antidepressant should be retained. Should the patient remain symptom free, the medication can subsequently be slowly tapered off (around 25 % of the dosage each week).

14.4.6 Long-Term Therapy/Phase Prophylaxis

For those children and adolescents at high risk of relapse, including those with recurrent depressive episodes, an extended period of psychotherapy and support to self-monitor symptoms of relapse are recommended (National Institute for Health and Care Excellence 2005). In adults, three clear depressive episodes in the sense of unipolar depression constitute the indication for longer-term relapse prophylaxis. The AACAP practice parameters (Birmaher et al. 2007) recommend maintenance treatment for longer than 1 year in those children and adolescents with at least two episodes of depression or one severe episode or chronic episodes. In adults, antidepressants have proved effective for this purpose, as have **mood stabilizers** (see Chap. 7) such as lithium salts, carbamazepine, valproic acid, oxcarbazepine, and lamotrigine. Of these, lithium salts are the best investigated agents with respect to the age group of children and adolescents, however mostly for the indications of conduct or bipolar disorder (Geller et al. 2012; Lopez-Larson and Frazier 2006; Müller-Oerlinghausen and Lewitzka 2010). Because of its narrow therapeutic range, serum lithium concentrations should lie between 0.6 and 0.8 mmol/L and be regularly monitored by TDM. The lithium dosage is normally divided into morning and evening doses (see Chap. 7).

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Drug- or Substance-Related Disorders

15

Rudolf Stohler, Manfred Gerlach,
and Gerhard A. Wiesbeck

Contents

R. Stohler, MD (✉)
Substance Use Disorders, Treatment and Research, Psychiatric University Hospital, Selnaustr. 9, 8001 Zurich, Switzerland
e-mail: stohler@dgsp.uzh.ch

M. Gerlach, PhD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Laboratory for Clinical Neurobiology and Therapeutic Drug Monitoring, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: manfred.gerlach@uni-wuerzburg.de

G.A. Wiesbeck, MD
University Hospital of Psychiatry, University of Basel, Wilhelm-Klein-Strasse 27, 4012 Basel, Switzerland
e-mail: gerhard.wiesbeck@upkbs.ch

15.1 Definition, Classification, and Target Symptoms

The term "drug" is not employed in the International Classification of Diseases, 10th revision (ICD-10) classification (World Health Organisation 1996), which refers instead to groups of psychotropic substances, the ingestion of which – usually on a regular and medically inappropriate basis – can lead to mental disorders and behavioral abnormalities: alcohol, opioids, cannabinoids, sedatives or hypnotics, cocaine, other psychostimulants (including caffeine), hallucinogens, tobacco, and volatile solvents. Disorders arising from alcohol abuse are not discussed here, but in Chap. 10. It is difficult to accommodate so-called party drugs in these categories, so they will be discussed in a separate section.

Disorders that arise directly from the misuse of these substances are **classified by ICD-10** as follows:

- **Acute intoxication** (ICD-10 F1X.0). This is characterized by disinhibition, lability of mood, and aggression and can be accompanied by attention deficits, impaired judgment, gait and postural instability, and disturbed consciousness.
- **Withdrawal syndrome** (ICD-10 F1X.3, F1X.4). A condition succeeding discontinuation or reduction of drug consumption, characterized by nausea, sweating, restlessness, sleep disturbances, accelerated heart rate, shaking, fever, and a general feeling of malaise. In

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severe cases, hallucinations and seizures may also be possible.

- **Substance-induced psychotic disorder** (ICD-10 F 1X.5). A psychotic state, frequently characterized by hallucinations that develops during or immediately following the use of psychotropic substances, and usually regresses completely within a month, and certainly within 6 months.
- **Harmful use** (ICD-10 F1X.1). The diagnosis "harmful use" (abuse) requires that substance dependence has not (yet) developed, but physical or psychological health has already been impaired.
- The **dependence syndrome** (ICD-10 F1X.2). The characteristic features are a strong desire or compulsion-like need to consume the drug ("craving"), reduced control of the initiation, termination, and level of drug consumption, a physical withdrawal syndrome, evidence of tolerance, progressive neglect of interests in favor of drug use, and persistent consumption despite the damaging physical, psychological, and social consequences.

Harmful use is often, but not always, the first stage on the path to a dependence disorder. While harmful use is characterized by a usage pattern that results in actual, and not just theoretical, injury of health, dependence is distinguished by consumption in which the relevant substance or substance group advances to being the major structural element of daily life. ICD-10 lists eight criteria for dependence, of which at least three must have been satisfied in the year prior to diagnosis.

The criteria for the dependence syndrome are similar in both ICD and the Diagnostic and Statistical Manual of Mental Disorders (DSM) classification systems. The **DSM-5** (American Psychiatric Association 2013) combines substance abuse and dependence into one disorder: **substance use disorders**. The overall category of substance-induced disorders includes intoxication, withdrawal, and other substance/medication-induced mental disorders. ICD 10 coding rules require that all withdrawal codes imply a comorbid co-occurrence substance use disorder for that substance; in DSM-5, the withdrawal syndrome may be coded independently from the substance use disorder of that substance. The substance-related disorders include in DSM-5 – very similar to ICD-10 – (for alcohol use syndrome see Chap. 10) the related disorders of caffeine, cannabis, phencyclidine, inhalants, opioids, sedatives, hypnotics, anxiolytics, psychostimulants, and tobacco.

Other psychotropic agent-related disorders, such as the amnesic syndrome, do not play a major role in child and adolescent psychiatry and are therefore not discussed here. It should also be noted that not all the listed pharmacological agent groups lead to each type of substance-related disorder. For example, caffeine- and opiate-induced psychotic disorders do not occur, nor do clinically relevant intoxication syndromes arise from tobacco consumption.

The **principal aims of pharmacotherapy** are ensuring **survival and prevention of harmful consequences**, such as a psychotic disorder. Furthermore, pharmacological therapy of intoxication and withdrawal aim to avoid or ameliorate the symptoms associated with these states. In cases of dependence or harmful use, ancillary goals can be the reduction of consumption, the transition from dependent to controlled consumption, and the achievement of abstinence. Finally, pharmacotherapy can contribute to preventing a lapse or relapse into uncontrolled drug use.

Harmful use and dependence upon psychotropic substances by adolescents (and naturally also adults) – as with alcohol – can also be **associated with other mental disorders**. Strikingly frequent is the co-presentation of conduct disorders, of antisocial and emotionally unstable personality development, and of aggression, impulsivity (including ADHD), suicidality, affective disorders including anxiety and eating disorders. Furthermore, the use of one psychotropic substance is a predictor of more frequent misuse of other psychotropic drugs (Macleod et al. 2004). Such "co-occurring disorders" also require to some degree specific pharmacotherapy, regarding which the reader is referred to the corresponding chapters of this book. The same applies to somatic diseases associated with drug use.

15.2 Therapeutic Framework

The therapeutic framework of the pharmacotherapy of drug-related disorders is largely **identical with that for alcohol-related disorders**; the discrepancies result from the differing legal status of the abused substances. The frequent threat of legal sanctions necessitates special consideration with respect to the sometimes desirable involvement of the social sphere of the patient.

With respect to the therapeutic framework of children and adolescents, the guiding **principle** is that the treatment setting should be **no more constraining than absolutely necessary** (least restrictive setting possible). The necessity for institutional treatment is more dependent, however, upon the social environment of the patient than it is for adults. It is not the severity of the individual substance disorder or any other associated medical problems that determines the treatment modality, but rather the degree to which a patient is entangled in "dysfunctional" peer groups, or the assessment as to whether the patient's family environment is compatible with therapeutic success or not (see Thomasius et al. 2008 further information).

15.3 Selection of Pharmacotherapy and Treatment Strategies

Pharmacotherapies of substance-related disorders include the following stages of treatment: intoxication, withdrawal or other methods of abstinence initiation, use reductions, and maintenance or relapse prevention. Evidence-based guidelines for the pharmacological management of these treatments in adults are published elsewhere (Lingford-Hughes et al. 2012; Ross and Peselow 2009).

There is limited data on the treatment of substance use disorders in younger people on which recommendations to guide specific pharmacological approaches could be based. However, it is important that pharmacotherapy be considered, particularly in opioid or nicotine dependence, and ideally by a specialist multidisciplinary service (Lingford-Hughes et al. 2012).

Pharmacological treatment should be **based on adult treatment** with appropriate dose adjustments for age-related pharmacokinetic and pharmacodynamic changes; younger people with harmful substance use, abuse, or dependence should have full routine health screens with identification and treatment of mental or physical health problems; there should be a lower threshold for admission for inpatient assessment and treatment, for example, for opioid stabilization in younger people.

15.3.1 Medications for Treatment of Nicotine Dependence

Preferred medications for the treatment of nicotine dependence are the antidepressants bupropion and nortriptyline as well as nicotine replacement preparations. Varenicline, a partial agonist of nicotinic acetylcholine receptors, is not recommended as a first-choice agent for the treatment of children and adolescents.

There are five **nicotine replacement formulations** US FDA-approved for adults: transdermal patch, gum, lozenge, nasal spray, and vapor inhaler. The efficacy of these various nicotine replacement preparations in adults is comparable (Silagy et al. 2004). The transdermal patch is a one long-acting nicotine replacement therapy and provides continuous release of nicotine for 16–24 h, while the inhaler, nasal spray, gum, and lozenge constitute a short-term nicotine replacement therapy.

Nicotine replacement therapies work via the mechanism of agonist substitution, reducing the reinforcing properties of nicotine delivery by tobacco and also reducing the severity of cravings and withdrawal symptoms. A meta-analysis comparing the efficacy of various forms of nicotine replacement therapy demonstrated that all nicotine replacement therapies approximately double the chance of long-term (≥6 months) abstinence from tobacco products and reduce craving with no appreciable differences between the patch and the short-acting nicotine replacement therapy (see Ross and Peselow 2009).

Although the administration of nicotine replacement products has theoretical risks of addiction itself, nicotine replacement therapies

have low addictive potential, especially compared to the inhalation of nicotine from tobacco, and they are not associated with withdrawal symptoms on discontinuation (Ross and Peselow 2009).

There are several reasons to believe **antidepressants might help** to stop smoking (Lingford-Hughes et al. 2012). Nicotine withdrawal may produce depressive symptoms or precipitate a depressive episode; nicotine may have antidepressant effects that maintain smoking; thus, antidepressants may substitute for this effect. Some antidepressants may have a specific effect on neural pathways (e.g., inhibiting monoamine oxidase) or receptors (e.g., blockade of nicotinic cholinergic receptors) underlying nicotine addiction.

The atypical antidepressant **bupropion** has been well studied and was the first non-nicotine agent to get FDA approval in adults for smoking cessation as a first-line agent. Results of a meta-analysis of 49 trials show bupropion to be more effective than placebo in promoting continuous abstinence from smoking (see Lingford-Hughes et al. 2012). This effect appears to be independent of its antidepressant action, and the effect is also independent of the patient's history of depression. As a partial explanation of its efficacy, it is thought that bupropion alters brain reward circuits by modulating dopaminergic and noradrenergic neurotransmission by inhibition of dopamine and noradrenaline transporters as well as by stimulating nicotinic acetylcholine receptors (Cryan et al. 2003). A randomized, double-blind, prospective study supported the efficacy of treatment with bupropion (150 mg p.o. for 90 days, beginning a week prior to the agreed date for quitting smoking) in 16–19-year-old subjects (Niederhofer and Huber 2004). The most significant adverse drug reactions (ADRs) are associated with the increased sympathetic tone elicited by the medication. Bupropion is not suitable for epileptic patients.

Evidence for the efficacy of **nortriptyline**, a tricyclic antidepressant that acts as a noradrenaline and dopamine reuptake inhibitor, is derived from studies in adults. Nortriptyline is a **second-line** agent, because of its ADRs profile including anticholinergic effects (i.e., dry mouth, constipation, sedation, and delirium), potentially fatal cardiac arrhythmogenic properties, and potential for dangerous drug interactions, especially with monoamine oxidase inhibitors (Prochazka et al. 1998). Meta-analysis of the six randomized trials of nortriptyline indicate that, like bupropion, it approximately doubles the rate of smoking cessation (≥6 months) compared with placebo (see Lingford-Hughes et al. 2012; Ross and Peselow 2009). Like bupropion, its anti-addictive effects seem to be independent from its antidepressant properties. The exact mechanism of action is unknown. The fact that SSRIs are ineffective in the treatment of nicotine dependence suggests that dopaminergic and noradrenergic effects are central to its efficacy in curbing nicotine consumption. Its anticholinergic properties make dosage titration necessary. Administration begins 10 days prior to the planned quit date with 25 mg/day per orally. The average maintenance dosage in adults is 75 mg/day, usually for a period of 6 weeks.

In total, the pharmacological strategies described here improve the chances of nicotine abstinence over 1 year (in comparison with non-pharmacological approaches) by 50–100 %, whereby the results for combined treatments (nicotine replacement preparations plus bupropion or nortriptyline) are somewhat (if not impressively) better.

A recent **Cochrane review** of smoking cessation trials in **young people** reported that the majority of trials included some form of motivational enhancement and that complex psychological interventions in particular showed promise (see Lingford-Hughes et al. 2012). Only a small trial of nicotine replacement treatment, one together with bupropion and one with bupropion alone, failed to show efficacy (see Lingford-Hughes et al. 2012).

15.3.2 Medications for Treatment of Opiate-Related Disorders

There are two major pharmacotherapeutic strategies for the treatment of dependence upon heroin and other opiates:

- Abstinence-oriented therapy
- Substitution therapy

"Maintenance to abstinence" treatment represents a compromise, during which the preconditions for the goal of medium-term opiate abstinence are established under the protection of substitution treatment. It can be regarded as an extended form of abstinence treatment (see also Sect. 15.3.2.3). Substitution therapy is regarded as the first choice approach for adults, as abstinence-oriented treatments are associated with high recidivism rates (Magura and Rosenblum 2001; Sees et al. 2000). In **adolescent heroin addicts** – particularly where dependence has not existed for more than 1 year – **opiate abstinence** is instead the **primary goal**, and only when this has failed substitution treatment should be attempted. Where heroin-addicted adolescents can be retained in abstinence-oriented therapies, the results are favorable (Hopfer et al. 2002; see also Sect. 15.3.2.3). However, other authors have reported less favorable longer-term outcomes for abstinence-oriented therapies (Polsky et al. 2010; Strang et al. 2003).

15.3.2.1 Acute Intoxication

There is limited evidence of optimal pharmacotherapy for detoxification, so advice for adults can be followed. For the treatment of acute, sometimes life-threatening intoxication (clouded or lost consciousness, reduced respiration, vomiting, limb pain, pale skin, constricted pupils), the μ-opioid receptor antagonist **naloxone** can be applied intravenously (i.v.) or subcutaneously. The medication, which was approved in German-speaking countries, exhibits a elimination half-life ($t_{1/2}$) in adolescents and adults of about 70 min. If the patient is opiate-dependent, a withdrawal syndrome can be triggered that in turn requires treatment. Because of its shorter $t_{1/2}$, the effects of opiates with longer $t_{1/2}$ (such as heroin, methadone) can appear suddenly again, so that **patients** treated with naloxone **must be monitored**.

If possible, an ampule of naloxone (0.4 mg) should be slowly applied i.v. in order to achieve sufficient alertness without eliciting a withdrawal syndrome; if i.v. application is not possible, it can be applied intramuscularly. The injection can be repeated up to four times if required. The subsequent intramuscular application of a further ampule prolongs the effect, but still monitoring is required. ADRs are rare and consist mostly of nausea and vomiting.

15.3.2.2 Treatment of Withdrawal

The aim of opiate withdrawal treatment is to minimize the symptoms of the withdrawal syndrome and thereby to reduce the risk of relapse during the withdrawal process itself or immediately thereafter.

Two major approaches can be distinguished:

- Immediate termination of access to opiates and symptomatic treatment of the withdrawal syndrome.
- Primary substitution of a pharmaceutically defined opiate for "street heroin" (or other inappropriately employed opiates) and the consecutive slow withdrawal of the substitute (Fishbain et al. 1993).

Symptomatic Treatment

The CNS-active α_2-adrenoceptor agonists **clonidine** and **lofexidine** inhibit noradrenergic neurons in the locus caeruleus, thereby chiefly ameliorating the noradrenaline-mediated symptoms of opiate withdrawal ("noradrenaline storm"), such as tachycardia and hypertonia, but also to a certain degree tremor, restlessness, and anxiety. This counteraction of CNS manifestations of opiate withdrawal as hyper-adrenergic states is a common feature across spectrum withdrawal syndromes, including alcohol and nicotine, and likely represents an activation of brain stress systems (see Ross and Peselow 2009). A Cochrane review demonstrated that withdrawal symptoms and withdrawal completion rates are similar for α_2-adrenoceptor agonists and methadone at tapered doses, but α_2-adrenoceptor agonists appear inferior to buprenorphine in alleviating withdrawal symptoms and in the withdrawal completion (see Lingford-Hughes et al. 2012). Nevertheless, they are effective and may be an appropriate choice for patients who prefer not to have opioid drugs. The danger of pharmaceutical induction of hypotonia by clonidine may limit application, but the risk is lower for lofexidine.

Clonidine should be **administered orally**, beginning with half a tablet (0.075 mg). The maximum dosage should not exceed three tablets

a day. **Blood pressure must be regularly checked**. Vertigo and sleepiness are the most common ADRs. Pregnant women and nursing mothers should not be treated with clonidine.

Apart from a number of further symptomatically acting medications, including baclofen, benzodiazepines, carbamazepine, mianserin, tiapride, and trazodone, none of which offers clear advantages over treatments with α_2-adrenoceptor agonists (at least not in patients with only one dependency), an approach that has attracted particular attention is so-called **ultra-rapid opiate detoxification** (Legarda 1998). Various combinations of medications are employed in this procedure. Common to all this approaches is that opioid receptor antagonists, such as naloxone and naltrexone, are administered under the protection of narcosis or deep sedation and are claimed to compress the withdrawal process to such an extent that the patient awakes "withdrawn." Apart from the (almost obvious) 100 % retention rate during treatment, this express process does not necessarily lead to an improvement of the long-term results, which are more significant for the evaluation of therapy efficacy (Krabbe et al. 2003); furthermore, it is associated with complications, some quite severe (delirium, cardiopathies, nephropathies; Roozen et al. 2002).

"Express withdrawals" should not be the first choice approach in adolescents.

Withdrawal by Means of Pure Opiate Preparations

The principle underlying this approach is the substitution of "street heroin" with pure opiate preparations such as methadone or buprenorphine and their consecutive gradual withdrawal. Both medications are fully or semisynthetic agonists at the μ-opioid receptor. **Buprenorphine** also antagonizes the κ-opioid receptor, while **methadone** is an agonist of all opioid receptors. A Cochrane review of 11 studies of five different psychosocial interventions and two detoxification medications (buprenorphine and methadone) found that adding a psychosocial treatment to any detoxification treatment showed benefit in terms of reduced dropouts, use of opiates during treatment and at follow-up, and clinical absences during the treatment (see Lingford-Hughes et al. 2012).

Methadone is usually employed for this indication. Beginning with a maximum of 30 mg and possibly adding a further 10 mg every 4 h, a dosage is sought at which opiate withdrawal symptoms are either abolished or at least rendered tolerable. Methadone medication can be gradually withdrawn thereafter. Slow withdrawal of methadone is tolerated to varying degrees. In general, doses of more than 70 mg/day can be reduced fairly quickly, whereas doses under 20 mg require much more time.

Despite pharmacological differences, **buprenorphine** does **not** appear to be markedly **superior** to methadone for withdrawal treatment (Ebner et al. 2004). A randomized controlled trial (Marsch et al. 2005) compared buprenorphine with clonidine in detoxification of 36 opioid-dependent adolescents (13–18 years old): Buprenorphine improved retention in treatment for one month compared with clonidine (72 vs. 39 %), provided more opiate-free urines (64 vs. 32 %), and more started naltrexone afterwards (61 vs. 5 %).

15.3.2.3 Substitution Therapy

If withdrawal treatments have failed or are otherwise unsuitable, a substitution therapy with methadone or buprenorphine should be undertaken. The goals of such treatment are the reduction of the use of illegal heroin and the associated elevated mortality as well as a reduction of drug use-associated diseases and delinquent behavior (Farrell et al. 1994).

Methadone was developed in the 1940s as an analgesic medication and introduced by Dole and Nyswander in New York City in the 1960s to combat a heroin epidemic (Ross and Peselow 2009). It is the most **widely used agent** in medically managed opiate maintenance programs. Unlike a short-acting opiate (i.e., heroin, with a $t_{1/2}$ of approximately 1 h, which needs to be dosed several times per day), methadone has a $t_{1/2}$ of

24–36 h (13–50 h) and can be administered once daily.

Methadone is available in oral (liquid and tablet) formulations and as injectable preparation. Tablet formulations are not recommended in recent UK treatment guidelines because of the risk of injecting crushed tablets and the increased risk of diversion (Lingford-Hughes et al. 2012). However, studies of the effectiveness of oral maintenance therapy do not address different formulations, probably because the dangers of misuse and diversion are low in treatment programs in which consumption is supervised.

Methadone maintenance is the only treatment for opiate dependence that has clearly been shown in clinical trials to **diminish illicit opiate use** more than detoxification, placebo, no treatment, or drug-free treatment, and in a Cochrane review comparing methadone maintenance to no opiate replacement therapy, methadone was more effective in terms of treatment retention and decreased illicit opiate use (see Ross and Peselow 2009). The research evidence remains firmly based on programs with supervised consumption, whereas in practice, many treatment programs provide methadone without supervision of consumption.

In accordance with the Drug Abuse Treatment Act of 2000, in October 2002, the FDA approved the use of **buprenorphine** as a schedule III agent to treat opiate dependence in outpatient office-based practices by physicians who received 8 h of specialized training and attained a waiver from the Department of Health and Human Services (see Ross and Peselow 2009). Because buprenorphine is only a partial agonist, unlike pure κ-opioid agonist like methadone or heroin, it is **safer in overdose** because it has a ceiling on respiratory suppression; however, there have been deaths reported when buprenorphine was injected along with benzodiazepines (see Ross and Peselow 2009).

There are currently no criteria for the better choice – methadone or buprenorphine; either medication can be used safely in long-term therapy. The high affinity of buprenorphine for the μ-opioid receptor means that it displaces other opiates from this receptor, and this can result in a withdrawal syndrome when a user of full agonists, such as heroin, takes buprenorphine for the first time. The ADRs (such as respiratory depression, endocrine changes, reduced seizure threshold, obstipation, hyperhidrosis) are familiar from pain therapy. Once steady-state conditions have been reached, ADRs in general subside (Kreek 1996).

Adequate dosage is very **important** for the propitious course of substitution treatment (Faggiano et al. 2003; Mattick et al. 2008). The dosage for adolescents is the same as that for adults. As a rough guide, target daily dosages for **methadone** should be between 60 and 120 mg, for buprenorphine between 8 and 32 mg. More precise dosage information is not possible because of individual differences with regard to tolerance, resorption, metabolic status, opioid receptor expression, and blood–brain barrier state. Dose-dependent prolongation of the QTc interval by methadone is a recognized ADR; dosage reduction or, if this is not possible, a change of preparation must be considered for intervals of greater than 450 ms. **Buprenorphine** can be administered only on alternating days; this can be convenient if the dispensing of "take home doses" is inappropriate, as the process of social integration may be disturbed by the requirement to visit the treatment center on a daily basis.

15.3.3 Medications for the Therapy of Cocaine- and Psychostimulant-Related Disorders

15.3.3.1 Acute Intoxication

As far as psychiatry and neurology are concerned, acute intoxication with cocaine or psychostimulants – particularly after long-term use – can lead to psychotic and deliriant symptoms, anxiety states, panic attacks, agitation states, acute suicidality, epileptic seizures, and neurological lesions (Preuss et al. 2000). **Benzodiazepines** are the preferred medications for acute treatment, should removal to peaceful surroundings and calming conversation not achieve the desired success. For example, 5 mg diazepam can be given orally (p.o.) or i.v., and this dosage can be repeated if necessary. Tonic-clonic epileptic seizures can

be treated with *clonazepam*, 1–2 mg i.v. (Soyka 1998). Psychotic disturbances of longer duration or delayed onset (toxic psychoses) require therapy with *antipsychotics*.

15.3.3.2 Dependence and Harmful Use

Despite intensive research, there is still no available medication for the treatment of cocaine and psychostimulant dependence (De Lima et al. 2002; Lingford-Hughes et al. 2012; Ross and Peselow 2009). **Psychosocial interventions** such as cognitive behavioral therapy and contingency management remain the **mainstay of treatment** (Lingford-Hughes et al. 2012). The pharmacological treatment of comorbid disorders and the consequences of psychostimulant use are symptom-based and discussed in the corresponding chapters of this book.

In their evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction, and comorbidity, Lingford-Huhges et al. (2012) recommended the following:

- **Disulfiram** is not yet an established treatment for cocaine use, but clinicians should be alert to further studies as the current small evidence base is of interest.
- There is no clear evidence to support substitute prescribing of **D-amphetamine** for the treatment of cocaine or amphetamine dependence, but definitive studies are warranted and clinicians should be alert to further studies.

A relatively frequent special case involves the **abuse of cocaine and psychostimulants** by adolescents receiving substitution treatment for heroin dependence. In such patients, an increase in the level of the substituted opiate (usually methadone or buprenorphine) is sometimes enough to reduce cocaine use (Borg et al. 1999).

15.3.4 Medications for the Therapy of Hallucinogen-Related Disorders

The imprecise term "hallucinogens" describes a group of substances that elicit hallucinations if taken at (usually) higher dosages. In this section, disorders associated with hallucinogens in the narrower sense (agonists of the serotonin 5-HT_{2A}-receptor; tryptamine and phenethylamine) are discussed. **Typical examples** of hallucinogens are the naturally occurring **mescaline** and **psilocybin** as well as the semisynthetic **LSD-25**. Drugs sometimes subsumed under the category of hallucinogens, such as MDMA (methylenedioxymethamphetamine, "ecstasy") or cannabis, will be discussed in the sections on "party drugs" and "cannabis."

The hallucinogen salvinorin A (the active constituent of the Mexican "diviner's sage," *Salvia divinorum*), which exerts its effects via the κ-opioid receptor, could be inactivated on the basis of theoretical considerations with κ-opioid receptor antagonists. To our knowledge nothing has been published in this respect.

Harmful use and **dependence have not been described** for hallucinogens. They do not harm human organ systems and are not "reinforcing" (Nichols 2004). Danger and injuries can nevertheless result from the intoxicating experience, where, for example, the user believes that he or she possesses superhuman powers, such as the ability to fly (Reynolds and Jindrich 1985). The pharmacological **treatment of unpleasant intoxications** ("bad trips") caused by hallucinogens involves the administration of **benzodiazepines** (e.g., 5–10 mg diazepam p.o.). There is no conclusive information regarding the pharmaceutical treatment of flashback states.

> Antipsychotics are not indicated in the treatment of unpleasant intoxications, as in these cases they are usually ineffective and can intensify dysphoric states (Abraham et al. 1996).

15.3.5 Medications for the Therapy of Cannabinoid-Related Disorders

There are no secure data regarding the effective pharmacotherapy of these disorders. Intoxication-associated disturbances, such as anxiety and tachycardia, are treated symptomatically (benzodiazepines, β-blockers).

15.3.6 Medications for the Therapy of Party Drug-Related Disorders

There is no evidence for the pharmacotherapy in treating **MDMA** and **cannabis** dependence or withdrawal. **Psychosocial approaches** are recommended (Lingford-Hughes et al. 2012). Acute and longer-term complications associated with MDMA use can be relevant to both neurology and psychiatry. Depending upon dosage and frequency of use (to some degree persisting), psychotic and affective disorders can develop; tonic-clonic seizures have also been described. The therapy is symptomatic.

Chronic MDMA use can be associated with (sub-)clinical sleep disturbances, depression, anxiety, impulsivity, emotional lability, and reduced cognitive performance. These symptoms possibly reflect injury to CNS serotonin pathways. The therapy here is also symptomatic (Liechti 2003).

In recent years, **GHB** (γ-hydroxybutyrate) and its synthetic precursors **GBL** (γ-butyrolactone) and **BDO** (1,4-butanediol) have established a reputation, particularly in the techno scene, as mood enhancers and supposed aphrodisiacs. On the other hand, these substances are also employed as "after-party drugs" and to "come down" after long dancing night. GHB has also acquired a reputation as a "date rape drug."

Intoxications with these substances are potentially **life threatening**. Particularly in combination with alcohol or opiates but also with benzodiazepines, barbiturates, or antihistamines, an intensely dangerous state can develop, characterized by vomiting (danger of suffocation), reduced respiratory rate or even respiratory arrest, muscular convulsions and cramps, clonic-tonic seizures, hypotonia, and coma. The therapy is symptomatic (intensive care, close monitoring, support of vital functions).

If these drugs are used at sufficiently high doses for long enough periods, party drugs can induce a **dependence syndrome** similar to that of alcohol abuse (including delirium; McDonough et al. 2004). Pharmacological treatment is comparable with that for alcohol withdrawal syndrome and may require hospitalization. Successful management of withdrawal has been achieved using high-dose benzodiazepine regimes, either alone or in conjunction with baclofen. This approach is the treatment of first choice at present (Lingford-Hughes et al. 2012).

The **acute withdrawal** of GHB/GBL/BDO is of **particular importance for child and adolescent psychiatrists** (Zepf et al. 2009). It can present with symptoms close to psychotic episodes or acute alcohol withdrawal and is a life-threatening condition that requires immediate intensive care treatment along with continuous monitoring of vital parameters. In some cases, high-dose treatment with benzodiazepines was successful in acute GHB-/GBL-/BDO-withdrawal syndrome (Zepf et al. 2009). Complications were severe dystonia under antipsychotic treatment, and also ADRs of treatment with benzodiazepines. Further problems were vegetative symptoms, electrocardiographic changes, rhabdomyolysis, acute renal failure, and death.

15.3.7 Medications for the Therapy of Sedative-Related Disorders

15.3.7.1 Acute Intoxication

Flumazenil, which must be applied by i.v. injection, is a **benzodiazepine antagonist** and appropriate for this indication. Flumazenil injection is approved in the USA by the FDA in adults for the complete or partial reversal of sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose.

In pediatric patients (aged 1–17 years), flumazenil injection is indicated for the reversal of conscious sedation induced with benzodiazepines. One ampule (0.2 mg) is infused in "titrating"manner over about 15 s; if required, further doses of 0.1 mg can be administered at one-minute intervals, up to a total dose of 1 mg. If the treated patient is an epileptic or is benzodiazepine-dependent, seizures can occur, but this is rarely the case. This also applies to mixed intoxications in which the effects

of seizure threshold-lowering medications may be unmasked by the elimination of benzodiazepine protection. Flumazenil is otherwise well tolerated and can also be administered in emergency situations to pregnant women and nursing mothers.

The comments made regarding the use of opioid receptor antagonists (see Sect. 15.3.2.1) apply analogously to treatment with flumazenil (triggering of a withdrawal syndrome, resurgence of benzodiazepine effect for medications with $t_{1/2}$ greater than 60 min).

15.3.7.2 Withdrawal Therapy

To determine the presence or absence of physiological withdrawal symptoms and the dependence syndrome is important in determining whether pharmacological treatment is appropriate (Lingford-Hughes et al. 2012). **Benzodiazepines** can be acutely **withdrawn with antiepileptic protection** by, for example, carbamazepine (300–500 mg twice daily). An alternative is gradual withdrawal. As with opiates, higher doses can be initially reduced more rapidly, following which medication is more cautiously withdrawn, according to clinical response. Depending upon the dosage employed, withdrawal treatment can last months. The adaptation that can occur in the course of therapeutically justified employment of benzodiazepines must be distinguished from dependence resulting from abuse. The first case does not require treatment (O'Brien 2005).

A randomized, placebo-controlled study showed that **flumazenil** reduced withdrawal symptoms and craving compared with an oxazepam taper over 8 days in benzodiazepine-dependent patients; flumazenil-treated patients also had greater abstinence rates post detoxification (Gerra et al. 2002). A flumazenil infusion has also been shown to be a safe and effective treatment for benzodiazepine withdrawal (Hood et al. 2009).

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Eating Disorders

16

Beate Herpertz-Dahlmann and Christoph Wewetzer

Contents

B. Herpertz-Dahlmann, MD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, RWTH Aachen University, Neuenhofer Weg 21, 52074 Aachen, Germany
e-mail: bherpertz-dahlmann@ukaachen.de

C. Wewetzer, MD
Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Florentine-Eichler-Str. 1, 51067 Köln, Germany
e-mail: wewetzerc@kliniken-koeln.de

16.1 Definition, Classification, and Core Symptoms

16.1.1 Anorexia Nervosa

Anorexia nervosa (AN) is characterized by significant self-induced weight loss or insufficient age-appropriate weight gain, combined in many but not all (mostly female) patients with the deep-rooted conviction that despite their low weight, the sufferer is overweight or fat. The International Classification of Diseases, 10th revision (ICD-10) classification (World Health Organisation 1996) stipulates a body mass index (BMI) threshold of 17.5 kg/m^2 as the **weight criterion**. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5, American Psychiatric Association 2013) is less precise in defining the weight threshold. According to its definition, an adult with a BMI less than 17.0 kg/m^2 is considered to have a significantly low body weight. However, "an adult with a BMI between 17.0 and 18.5 kg/m^2 or even above might be considered to have low body weight" if the clinical history or physiological findings support this estimation.

As the BMI changes with growth and age, a BMI below 17.0 kg/m^2 indicates a genuine underweight status only from late adolescence. To acknowledge the **developmental dependence of the weight criterion**, the German guidelines for eating disorders define the 10th age-adapted percentile as the weight threshold (for calculation, see http://www.mybmi.de) for the definition of

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AN in children and adolescents (Herpertz et al. 2011). In the DSM-5, a BMI in children and adolescents below the 5th percentile is considered a low body weight; however, "also children and adolescents with a BMI above this benchmark may be judged to be significantly underweight."

In eating disorders, self-acceptance and self-esteem are largely tied to the perception of one's own figure and appearance, and the majority of affected persons exhibit a weight phobia or distorted body image. For this reason, anorectic patients avoid high-calorie foods.

The ICD-10 and DSM-5 differentiate between the restricting type of AN, in which weight reduction is achieved exclusively by fasting or excessive physical activity, and the binge eating/purging type, characterized by episodes of binge eating and/or, in addition to fasting and exercise, more invasive weight-reducing measures, such as self-induced vomiting and the employment of laxatives or other weight reduction medication.

Many patients with AN lack the ability to recognize their disease. Further, AN is associated with symptoms of starvation, such as amenorrhea, bradycardia, reduced body temperature, hypotension, acrocyanosis, lanugo hair, and osteopenia or osteoporosis. In situations in which only some of the criteria for AN are met, the ICD-10 and DSM-5 allow the diagnosis of atypical AN.

Target symptoms in the **treatment** of AN are as follows:

- Abnormal eating behavior
- Starvation (markedly reduced body weight)
- Dysfunctional thoughts regarding figure and weight
- Distorted body image
- Weight phobia
- Low self-esteem
- Comorbid depressive, anxiety, or obsessive-compulsive disorders

16.1.2 Bulimia Nervosa

Characteristic symptoms of bulimia nervosa (BN) include recurring episodes of binge eating accompanied by a loss of control. Large quantities of food, usually of high caloric content, are consumed, followed by behaviors aimed at the prevention of weight gain, including self-induced vomiting, fasting, and inappropriate use of laxatives, diuretics, and other weight reduction medications (including appetite suppressants). BN, similar to AN, is marked by a pathological fear of becoming fat. Distorted body image is also evident in many, but not all, cases.

In cases in which only some of the criteria for BN are met, the ICD-10 allows the diagnosis of atypical BN. The DSM-5 allows a diagnosis of BN with a lower frequency of binge eating (at least once a week) and/or more limited duration (less than 3 months).

Target symptoms in the **treatment** of BN are as follows:

- Binge eating with loss of control
- The bulimic "vicious circle" of binge eating, weight reduction behavior, especially vomiting or purging, and renewed binge eating
- Dysfunctional thoughts regarding figure and weight
- Distorted body image and weight phobia
- Insufficient self-esteem
- Comorbid depressive, anxiety, or compulsive disorders, addictions, attention deficit/hyperactivity disorder (ADHD), and impulse control disorders
- In some cases, personality disorders, particularly borderline disorders

16.2 Therapeutic Framework

For the **diagnosis** of eating disorders, a full medical and psychiatric assessment is necessary. Other somatic explanations of starvation must be excluded. Laboratory diagnostics are employed to detect accompanying somatic abnormalities, particularly electrolyte changes, pancreatitis, and alterations of kidney function. A cardiological examination is advisable in cases of severe starvation (bradycardia, prolonged QT interval, pericardial effusion). It is also important to determine whether there are potentially **comorbid mental disorders**, such as depression, obsessive-compulsive disorder, and anxiety disorders.

The essentially **multimodal therapeutic approach** encompasses measures for weight normalization, the specific modification of eating behavior, individual, and group psychotherapeutic activities involving the family and the social environment of the patient. In some patients with BN, pharmacological treatment might be helpful (American Psychiatric Association 2006).

In the short term, a combination treatment of BN involving cognitive behavioral psychotherapy and antidepressive medication is superior to exclusively pharmacological treatment with an antidepressant; however, in the long term, there is no significant difference (National Institute for Clinical Excellence "NICE" 2004; Mitchell et al. 2001).

In many patients with eating disorders, **somatic stabilization** is necessary. The treatment of starvation, in addition to weight rehabilitation, also involves the treatment of its medical consequences, requiring, for example, supplementation with vitamins (vitamin D), trace elements, or electrolytes. The need for pharmacological therapy may be related to the prominent physical hyperactivity and the sometimes "delusional" body perception disturbances of patients with AN, as well as the core symptoms of bulimia (breaking the "vicious circle" of binge eating and vomiting). However, in AN, the effectiveness of pharmaceutical treatment has yet to be assessed. In some cases, pharmacological therapy of comorbid psychopathological abnormalities may be needed, when weight restoration has achieved.

16.3 Choice of Pharmacotherapy

To date, no medication for AN has been approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA). Fluoxetine may be prescribed for the treatment of BN from the age of 18 years.

For information regarding indications, age- and indication-specific aspects of approval status, recommended dosages, adverse drug reactions (ADRs), medication interactions, and contraindications of the medications discussed in this chapter, please refer to the corresponding chapters of this book (Chaps. 4, 5, 6, and 7). Most of these preparations are employed outside the areas of application and age groups for which they are approved ("off-label use": see Sect. 2.1.2), whereby there are a number of issues to consider (see Sect. 2.1.4).

16.3.1 Anorexia Nervosa

Patients with AN were treated with **antipsychotics** as early as the 1960s and 1970s, at which time a possible nosological relationship between AN and schizophrenic psychosis was discussed. Further, clinicians hoped for positive therapeutic benefits derived from the sedative, anxiolytic, and weight-promoting effects of antipsychotics. The positive reports of open-label therapeutic trials, however, were not confirmed by early controlled studies (Vandereycken 1984; Vandereycken and Pierloot 1982).

In exceptional cases, the treatment of AN with second-generation antipsychotics can have a positive effect on the physical hyperactivity experienced by some patients as a compulsive need for movement. In clinical practice, low-potency antipsychotics, such as **pipamperone** and **melperone**, have sometimes proven **useful** in the treatment of excessive motor activity and internal tension. **Thioridazine should not be used** in patients with eating disorders because of the danger of QT interval prolongation; there is a particular risk for those with disorders of potassium balance (Alvarez and Pahissa 2010).

Some, rather small, open-label studies pointed to a positive effect of second-generation antipsychotics, such as olanzapine, risperidone, and quetiapine (Mehler et al. 2001; Powers et al. 2002). At a dosage of 2.5–15 mg olanzapine (or more in some particularly severe cases), weight gain, improvements with respect to weight phobia and disease insight, and reduced hyperactivity were observed (Hillebrand et al. 2005). The reduction of depressive and anxious symptoms in AN was similarly reported (Barbarich et al. 2004).

A controlled study involving only a small number ($N=30$) of outpatient adult AN patients

found that **olanzapine** was superior to placebo with regard to weight increase only in the bulimic subtype. There was also a significant improvement (compared to placebo) on few psychopathologic dimensions of eating disorder inventories, such as feelings of ineffectiveness, maturity fear, and persistence (Brambilla et al. 2007). In a further controlled study ($N=34$) of adult patients with AN, olanzapine or placebo was administered for 10 weeks in the context of day patient treatment. This study found a significantly greater weight increase, an earlier achievement of target weight, and more marked improvement of compulsive symptoms in the olanzapine-treated patients (Bissada et al. 2008). Consequently, olanzapine was **considered to be helpful** during the last years.

However, in some recent randomized controlled studies and a meta-analysis, adjunctive treatment with second-generation antipsychotics in adult and adolescent AN patients did not prove to be effective (Lebow et al. 2013). In a placebo-controlled pilot study of 20 adolescent females, the percent change in median body weight did not differ between the two treatment arms. However, a trend of increasing fasting glucose and insulin levels was found in the patient group treated with olanzapine (Kafantaris et al. 2011). In another double-blind, placebo-controlled study on **risperidone**, 40 adolescent patients were randomized to receive either risperidone or placebo in addition to the usual eating disorder program. After 9 weeks, there were **no** significant **differences** between the treatment arms or in the majority of eating disorder symptoms (Hagman et al. 2011).

In a very recent systematic review and meta-analysis of the effect of olanzapine, risperidone, and amisulpride in both adult and adolescent patients, no significant increase in BMI or decrease of the drive for thinness and body dissatisfaction (based on eating disorder questionnaires) was found. Whereas medication with second-generation antipsychotics led to an increase in eating disorder symptoms and anxiety, patients reported a significant reduction in depression (Lebow et al. 2013).

As is generally necessary for therapy with second-generation antipsychotics, one must be alert to the development of metabolic disorders, especially diabetes mellitus and hyperlipidemia (see Chap. 5). Extrapyramidal motor ADRs can also occur, whereby it is not clear whether very underweight anorectic patients are at particular risk. Given these adverse effects, the recently observed increase in the use of second-generation antipsychotics in AN in the USA may be concerning (Fazeli et al. 2012).

The former assumption of a nosologic relationship between affective and eating disorders motivated the use of **tricyclic antidepressants** in the hope that not only their thymoleptic effect but also certain secondary effects might be therapeutically useful. Amitriptyline and clomipramine were the most commonly employed members of this group. In various rather small open-label studies in adults, they exhibited not only a positive thymoleptic effect, but their improved appetite and initial sedative effects were also valuable (Corwin et al. 1995; Halmi et al. 1986). In controlled investigations, however, a significant effect on the degree of **weight increase** or the reduction of depressive or anorexia-specific symptoms could **not** be **demonstrated**. Considerable ADRs were observed in some cases (Biedermann et al. 1985; Halmi et al. 1986).

More recent investigations have examined **SSRIs**, chiefly fluoxetine, during the weight rehabilitation period and the "weight maintenance period" of therapy. The treatment of underweight anorectic patients with SSRIs proved to be **ineffective** (Attia et al. 1998; Ferguson et al. 1999). This lack of effect is most likely attributable to reduced CNS serotonin concentrations in these patients, which are in turn explicable by a restrictive diet with inadequate tryptophan intake (metabolic precursor of serotonin: see Sect. 1.3.2.3). A similar effect is found in depressive patients receiving SSRI medication who maintain a low-calorie diet (Delgado et al. 1999). In a controlled, 12-month investigation of relapse prevention in young adults, it was found that fluoxetine was associated with a lower relapse rate than placebo, improved weight stabilization, and reduced depressive symptoms (Kaye et al. 2001). This study, however, was limited by a very small sample number and a high dropout rate; more than half of the prospective participants declined

to participate even before the study had commenced. In a controlled, multicenter study, 93 weight-restored patients were treated with both fluoxetine and cognitive behavioral psychotherapy. **As an adjunctive medication**, **fluoxetine** was no **more effective** than placebo, even with regard to depressive and anxiety symptoms (Walsh et al. 2006). The results of this study provided no conclusive evidence for the efficacy of fluoxetine in relapse prevention.

In a retrospective study of adolescent females who had been treated with a variety of SSRIs for 6 months after having reached the 10th age-adapted BMI percentile during inpatient treatment, no effect of pharmaceutical therapy upon eating disorder symptoms, depression, and compulsive symptoms (compared with patients not receiving medication) could be detected (Holtkamp et al. 2005). However, other observations indicate that the treatment of depression, anxiety, or compulsive symptoms in weight-restored patients with AN – always in combination with psychotherapy – maybe beneficial (Powers and Bruty 2009). It has been discussed whether SSRI treatment of these symptoms in AN patients might have a counterproductive effect upon feelings of satiety, an effect that could ultimately result in weight loss. This hypothesis, however, has not been sustained by studies or in clinical practice.

The majority of comorbid mental disturbances in AN is aggravated by undernourishment, or is actually sometimes induced by starvation, a phenomenon that was impressively demonstrated in healthy persons by the so-called Minnesota Experiment of Keys and colleagues (1950). For this reason, one should **wait for the "antidepressive" and "anti-obsessive" effects** of weight rehabilitation to present **before initiating pharmacotherapy**. For cases in which significant depressive symptoms persist despite weight stabilization, or depressive symptomatology was manifest prior to the development of AN, the administration of SSRIs may be helpful, although there are also no controlled studies regarding this question.

Anxiolytics of the benzodiazepine group were formerly employed to reduce anticipatory anxiety of anorectic patients prior to meals, but there have been no major controlled investigations of the use of **benzodiazepines** for this indication. These medications are sometimes indicated in severely ill patients with crisis-like escalation of anxiety and extreme physical agitation. The dependence potential of benzodiazepines has rendered their longer-term employment obsolete (see Chap. 6).

Lithium salts, of which the mood-stabilizing effects in bipolar disorder are well established (see Chap. 7), have similarly been used in patients with AN, with particular emphasis upon its mood-stabilizing and weight-promoting effects. A controlled study found that a group treated with lithium carbonate exhibited significant weight gain by the end of treatment (Gross et al. 1981). The results, however, are not entirely secure, as the placebo and lithium treatment groups were inadequately parallelized. A positive influence upon anorexia-typical symptoms could not be found.

On the basis of findings regarding the importance of noradrenergic mechanisms for the regulation of hunger and satiety, **clonidine** has been tried, but without positive effects with regard to weight increase or its influence upon behavioral abnormalities typical for AN (Casper et al. 1987).

16.3.2 Bulimia Nervosa

Similar to the pharmacological treatment of AN, there have been very few controlled investigations of BN in adolescent patients. Most of the studies described below involved young adults.

There have been a number of controlled investigations of the efficacy of **antidepressants** in the treatment of BN (Bacaltchuk et al. 2000; Mitchell et al. 1993; Walsh and Develin 1992). Both tricyclic antidepressants (such as amitriptyline, desipramine, and imipramine) and *SSRIs* (including fluoxetine and fluvoxamine) have been employed. These antidepressants achieved **significant improvements** (compared with placebo) in the course of treatment, reducing both the frequency of binge eating with a loss of control and of self-induced vomiting. There were no significant differences in efficacy between the individual antidepressants.

Significantly **higher antidepressant dosages are required** for the treatment of bulimic eating disorders than for the treatment of depressive disorders, as found, for instance, for **fluoxetine** in a multicenter study (Fluoxetine Bulimia Nervosa Collaborative Study Group 1992). In this investigation, a dosage of 60 mg was significantly superior to 20 mg with regard to reducing binge eating and self-induced vomiting. The corresponding dosage for **fluvoxamine** is 100–150 mg. A positive effect was manifested quite early in many cases, sometimes after only a week (Fluoxetine Bulimia Nervosa Collaborative Study Group 1992). An open label, non-controlled study involving 10 adolescent patients with BN similarly found a significant reduction of binge eating and vomiting during treatment with 60 mg fluoxetine/day. The patients received 4 weeks of supportive psychotherapy prior to the introduction of fluoxetine as preparation for the pharmacotherapy (Kotler et al. 2002).

Although a few studies support a relapse-preventing effect of SSRIs (Fichter et al. 1996; Romano et al. 2002), others indicate that relapses are not unusual even if medication is continued (Walsh et al. 1997). A few studies have examined the treatment of BN with carbamazepine or lithium salts, but without demonstrating the superiority of either over placebo (Chen and Silverstone 1990).

16.3.3 Improvement of Physical Health as a Prerequisite for Weight Rehabilitation

If starvation is severe, cautious weight rehabilitation with a gradual increase in dietary intake is advisable, commencing with 600–1,000 kcal. Excessive dietary fat should be avoided, as this can lead to a rise in both amylase and lipase activity. The so-called "**refeeding syndrome**" is **dangerous** and can cause hypophosphatemia and cardiac, renal, and neurological complications.

Continuous weight rehabilitation is necessary in cases of pronounced starvation resulting from AN. Weekly weight increases of between 500 and 1,000 g are recommended (National Institute for Clinical Excellence "NICE" 2004, for a review see Herpertz-Dahlmann and Salbach-Andrae 2009). In rare cases in which the patient is not capable of feeding herself, tube feeding may be indicated.

The following **procedure for weight rehabilitation** has proved useful:

- Begin with an amount of 500–800 kcal/day (distributed over six regular meals or tube feeding, if absolutely necessary, depending on prior food intake). If the patient has limited not only his or her solid diet but also his or her fluid intake to a significant degree, fluid intake and elimination must be balanced. Excessively high or rapid fluid substitution can lead to cardiac complications (chiefly pericardial effusion) but also to reversible cerebral edema, with the danger of epileptic seizures. In most cases, 2–2½l across the day (including any amount taken in via tube feeding) is sufficient.
- In the following days, gradually increase to a daily food intake of between 2,200 and 2,500 kcal/day. As basal metabolism is changing, the required quantity must often be repeatedly adjusted.
- The phosphate content must be regularly checked, particularly when employing meal replacement products ("tube feeding diet") (see above), and cautious phosphate substitution should be undertaken in cases of hypophosphatemia.
- Daily weighing of the patient is appropriate at the beginning of the increase in dietary levels, but should later be reduced to once or twice a week.
- Many patients with AN complain about marked bloating after meals. Motility-promoting medications, such as metoclopramide and domperidone, can be employed for hunger-related gastroparesis. Extrapyramidal ADRs are possible, particularly in severely underweight patients. Note that both drugs may be associated with potentially life-threatening long QT syndrome and torsade de pointes, especially in the presence of electrolyte changes.
- Self-induced vomiting, dehydration, and laxative abuse ("purging") necessitate the regular assessment of electrolyte levels. Hypokalemia is a frequently observed consequence of vomiting and laxative abuse and can lead to cardiac abnormalities that are life-threatening in the worst cases, as well as to nephropathies and myopathies.

In cases of **zinc deficit**, the trace element can be supplemented (as effervescent tablets). A number of placebo-controlled investigations, however, indicate that zinc substitution does not elicit a consistently significant improvement of the overall clinical symptoms (Birmingham et al. 1993; Lask et al. 1993).

To **prevent osteopenia** and **osteoporosis**, physical inactivity (for instance, all day bed rest) should essentially be avoided. A physiotherapeutic program from the beginning of treatment or an exercise program supervised by the nursing staff is helpful. Adequate calcium intake (at least 1,200 mg daily) should be ensured, as should vitamin D (400 IU) supplementation (Heer et al. 2004).

In a recent study, the effect of physiologic **estrogen replacement** was investigated (Misra et al. 2011). The sample was divided in mature girls with a bone age ±15 years and immature girls with a bone age <15 years. The first group was randomized to receive either 100 μg of 17 β-estradiol (complemented by cyclic progesterone) or placebo transdermally for 18 months. The younger group received an increasing low dose of oral ethinyl estradiol to mimic pubertal estrogen changes or the placebo for the same period of time. Spine and hip **bone density** were **increased** in the verum group compared to placebo, thus indicating that physiologic estradiol replacement might prevent or reduce osteopenia or osteoporosis in AN.

16.4 Treatment Strategies

16.4.1 Anorexia Nervosa

In some severely starved patients with AN, low-potency antipsychotics or even benzodiazepines can be appropriate for acute treatment in cases in which pronounced hyperactivity, severe weight phobia, and "inner" restlessness are presented. Administration of **pipamperone** or **melperone** (dosage recommendations: see Prescribing Information) or **lorazepam**, both at low dosage (dosage recommendations: see Prescribing Information), for example, may be useful. Dosage should be divided across the day. The medication is principally required at the beginning of treatment. It can usually be reduced as weight rehabilitation progresses and then gradually withdrawn. Note, however, that these drugs might induce long QT syndrome, especially in combination with laxative- or re-alimentation-induced hypokalemia. **Olanzapine** sometimes proves valuable at the beginning of treatment, often even at low dosage, for the management of pronounced tension states and weight phobia. In chronic starvation, the possibility of leukopenia must be considered. Regular ECG monitoring is necessary.

NB: In cases of marked starvation, orthostatic problems frequently develop at the beginning of treatment. Patients should therefore initially be accompanied after rising.

The administration of an **SSRI** can be recommended in cases in which marked **depressive or obsessive-compulsive symptoms** persist after weight rehabilitation (see Chaps. 15 and 21). As there is a danger of increased appetite loss or agitation, the latter being more frequent in children and adolescents than in adults, it is advisable to begin with a low dosage that can then be slowly increased. An effect is often evident only after 3–4 weeks. The duration of treatment and the discontinuation procedure are governed by the criteria of the relevant comorbid disorder.

16.4.2 Bulimia Nervosa

Medication with an SSRI can be appropriate for the acute and long-term treatment (relapse prevention) of BN. As psychotherapy is often the more effective treatment form, a **primary attempt** with **cognitive behavioral therapy** should be made. If the patient experiences no improvement after six treatment sessions, the

addition of an **SSRI** may be indicated. Most clinical experience concerns fluoxetine and fluvoxamine, but it is possible that other SSRIs are similarly effective. The longer elimination half-life of fluoxetine therapy is in some cases a valuable advantage, as the medication might be vomited with the ingested meal. An initial dosage of 10 mg is appropriate, and this dose can be increased within a few days to a week to 20 mg fluoxetine. The dose can then be further elevated every 1–2 weeks by a further 20 mg to a maximum dosage of 60 mg/day. It is often advisable to continue medication for 6–12 months as relapse prevention, but relapses can occur even during therapy with SSRIs.

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Elective (Selective) Mutism

17

Karin Egberts and Jürgen Seifert

Contents

17.1 Definition, Classification, and Target Symptoms

Elective or selective mutism (Latin *mūtus*, "speechless," "silent") is categorized by the International Classification of Diseases, 10th revision (ICD-10; World Health Organisation 1996), as one of the "disorders of social functioning with onset specific to childhood and adolescence" (F94). Biological constitution ("inhibited temperament"), model learning, cultural change, and difficulties of language acquisition are regarded as risk factors. A familial disposition is postulated, as selectively mute children and adolescents, in comparison with healthy controls, are significantly more likely to have noticeably introverted relatives who are more insecure, themselves sufferers of selective mutism, or are pathologically anxious (Alyanak et al. 2013; Melfsen and Warnke 2007; Sharkey and Mc Nicholas 2008). The families are generally characterized by higher levels of psychopathological abnormalities (Remschmidt 2001). A controlled study found that the proportion of parents who had at some point in their life suffered a social phobia was higher for children with selective mutism than for a control group, supporting the supposition of a **familial association of mutism and social anxiety** (Chavira et al. 2007). Interacting with this predisposition are factors that reinforce the disease, such as increased attention, being the focus of the family, and avoidance of unpleasant situations. Long-term studies interpret elective mutism as a potential precursor

K. Egberts, MD (✉) • J. Seifert, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy,
University of Würzburg,
Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: egberts@kjp.uni-wuerzburg.de; seifert@kjp.uni-wuerzburg.de

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of the development of social phobia in adulthood (Sharkey and Mc Nicholas 2008).

The **ICD-10 distinguishes** elective (selective) mutism (F 94.0) from total mutism. **Elective mutism** is characterized by selective speaking with certain persons or in defined situations. The articulation and receptive and expressive speech of the affected person are typically within the normal range; at worst, they are – relative to the development level of the child – mildly impaired. However, literature suggests that many children with selective mutism have premorbid speech and language problems (38 %; Steinhausen and Juzi 1996). Mutistic behavior usually develops in a slow, continuous manner and is most common in socially anxious, sensitive, shy children lacking self-confidence but can also be presented by "unruly" children, who typically talk in environments where they feel comfortable, but not in childcare, in school, or in unfamiliar situations (Alyanak et al. 2013; Krysanski 2003). Diagnosis according to ICD-10 requires a certain consistency of presentation and symptomatic persistence, as well as a minimum duration of the symptoms of 1 month. In **total mutism**, the child does not speak at all, although the capacity for speech is fundamentally intact.

In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (**DSM-5**), "selective mutism" (312.23) is classified as a **subtype** of an **anxiety disorder** (American Psychiatric Association 2013). There is no distinction between selective and total mutism. The duration of the mutism should be at least 1 month and should interfere with educational or occupational achievement or with social communication.

In the differential diagnosis, elective mutism must be distinguished from developmental disorders of language and speech acquisition, inadequate speech comprehension (e.g., migration background), speech loss syndromes related to organic brain disorders (head trauma, aphasia), audimutitas and schizophrenic psychoses, as well as deafness or restricted hearing capacity.

Target symptoms of pharmacological therapy are the anxiety and emotional disorders that may accompany mutism (overview of therapy: Melfsen and Warnke 2007; Wong 2010).

17.2 Therapeutic Framework

As the disorder tends to chronification, **early treatment** is **essential**. An **individualized, multidimensional intervention** is generally recommended for elective mutism, including cognitive-behavioral therapeutic, family therapeutic, psychosocial, and psychopharmacological elements (Cohan et al. 2006; Sharkey and Mc Nicholas 2008). A detailed explanation of the disorder and counseling of the parents and carers or teachers of the child or adolescent are important preconditions for effective implementation of treatment measures.

The **goal** of therapy is to lead the children to **verbal communication**, not just in the therapeutic situation, but also in everyday situations that cause the child anxiety (Melfsen and Warnke 2007). The principle underlying **behavioral therapy** is the facilitation of conversation with adults and therapists in order to gradually construct a generalization (contingence management). This can commence with encouragement of nonverbal communication behavior; in the next stage, linguistic behavior is systematically promoted and rewarded, while mimic-gestural compensations are broken down. Model learning and exposure therapy techniques are also employed to actively increase the opportunities for speech. Cognitive-behavioral therapeutic elements contribute to relieving the child of their anxiety regarding speaking and to supporting positive reinforcement of all spoken communication. A combination of individual and group therapy (to promote social competences and different communicative capabilities, including nonverbal) is advisable, as is family counseling.

The **family therapy approach** serves the conditions and factors identified that may have triggered or maintained the disorder but also specifically exploits the skills of the family for co-therapy. In psychosocial interventions, the relevant social group (such as the preschool or school) as well as leisure activities are incor-

porated into the overall treatment plan (e.g., Oerbeck et al. 2012). The patient is encouraged through creative individual and group activities (such as sport) to develop normal communicative behavior (Melfsen and Warnke 2007).

17.3 Choice of Pharmacotherapy

In addition to the non-medication-based treatment approaches, pharmacological therapy with **antidepressants** (fluoxetine or imipramine in particular) or **antianxiety medications** as "off-label use" is indicated, if psychotherapeutic interventions alone have not been sufficiently successful, especially in anxious-depressive forms of mutism (Kaakeh and Stumpf 2008; Wong 2010). Studies with small case numbers and short observation periods as well as individual case reports indicate that some patients with elective mutism respond to therapy with other selective serotonin reuptake inhibitors (**SSRIs**), including fluvoxamine and sertraline (Carlson et al. 1999). In a double-blind placebo-controlled study in which 16 subjects with elective mutism were enrolled, significant improvements over time on ratings of elective mutism, anxiety, and social anxiety, rated by clinician, parents, and teachers were demonstrated in both fluoxetine- and placebo-treated subjects (Black and Uhde 1994). Subjects treated with fluoxetine were significantly more improved than placebo-treated subjects on parent's ratings of mutism change and global change. However, clinician and teacher ratings did not reveal significant differences between treatment groups. Although improved, most subjects in both treatment groups remained very symptomatic at the end of the study period. The average maximum daily dosage in this study was 0.6 mg/kg fluoxetine and in an open-label study 28 mg/day (Dummit et al. 1996).

Second-line treatment may involve monoamine oxidase (MAO) inhibitors, type A (Kumpulainen 2002; Wong 2010). Golwyn and Sevlie (1999) showed that phenelzine, an irreversible nonselective MAO inhibitor (see Sect. 1.4.1), was helpful in four prepubertal children and also in one case after fluoxetine had shown only minimal improvement after 10 months. However, because of the possibility of serious food and drug interactions, selective MAO-A inhibitors such a moclobemide should be reserved for cases only that do not respond to behavior therapy and fluoxetine or other SSRIs.

Information regarding fluoxetine and imipramine (recommended dosages, adverse drug reactions, medication interactions, contraindications, and special precautions) is found in Chap. 4. Experience with other antidepressants is limited and cannot be generalized. Short-term application of benzodiazepines to reduce anxiety can be useful in clinical practice in individual cases.

17.4 Treatment Strategies

To date, studies about the long-term outcomes for the different treatments of selective mutism are lacking. One small nonrandomized pilot study showed improvement under medication treatment with SSRIs in 6–8 months, which was limited to the severely mute population and was not attained by patients who were not medicated (e.g., only received non-medication-based therapies or who received no therapy at all; Manassis and Tannock 2008). The practical conclusion is that treatment should consist primarily of cognitive-behavioral therapeutic interventions.

Pharmacotherapy of mutism remains difficult, is **reserved for chronic forms**, and is especially indicated in patients with **comorbid depression** and any other **anxiety disorder** (most commonly social anxiety disorder, separation anxiety, and specific phobias). The same guidelines apply to the employment of fluoxetine and imipramine as for their use in the treatment of anxiety (Chap. 11) and depressive disorders (Chap. 14). The long-term results of clinical response are mostly good, but symptomatic improvement is frequently associated with a symptomatic transformation (social phobia, anxiety disorders, conduct disorders).

It must be remarked with respect to all the above-described therapeutic strategies as qualification that the scientific evaluation of their effectiveness is still largely based upon reports and opinions of expert panels, consensus conferences, and clinical experience (level of evidence V).

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Encopresis

18

Alexander von Gontard

Contents

A. von Gontard, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Saarland University Medical Center and Saarland University Faculty of Medicine, 66421 Homburg, Germany
e-mail: alexander.gontard@uniklinikum-saarland.de

18.1 Definition, Classification, and Target Symptoms

Encopresis is described by the International Classification of Diseases, 10th revision (ICD-10; F98.1), as the "repeated, voluntary or involuntary passage of feces, usually of normal or near-normal consistency, in places not appropriate for that purpose in the individual's own sociocultural setting" (World Health Organisation 1996). The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) classification (American Psychiatric Association 2013), is comparable except for the criterion of a shorter duration of 3 months (instead of 6 months). Also, it differentiates more precisely between the two subtypes with and without constipation (American Psychiatric Association 2013)

The international **Rome III classification** of pediatric gastroenterology suggests using the neutral term of fecal incontinence instead of encopresis (Rasquin et al. 2006). It also offers an exact listing of symptoms, frequency, and duration needed for diagnosis (see von Gontard 2011, 2013). Rome III distinguishes between the following:

- Functional constipation (with or without soiling)
- Non-retentive fecal incontinence

In other words, constipation is defined as a superordinate diagnosis that can, but must not, be associated with fecal incontinence. There is also a second group of children who soil without any signs of constipation (i.e., non-retentive fecal incontinence). Constipation cannot be diagnosed

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on the basis of low stool frequency alone, as many children retain feces despite daily defecation. Other symptoms, such as abdominal pain, pain during defecation, altered stool consistency, reduced appetite, and sonographic evidence of enlarged rectum, are typical (von Gontard and Neveus 2006; von Gontard 2012).

The distinction between primary (never clean) and secondary encopresis (relapse after at least 6 months) is of no relevance for therapy. The comorbidity rate of mental disturbances in children with encopresis is high (ca. 30–50 %), particularly where soiling frequency is high (Joinson et al. 2006; von Gontard et al. 2011). These disturbances are heterogeneous and include separation and generalized anxiety disorders, social and specific phobias, depression, attention deficit/hyperactivity disorder (ADHD), and conduct disorder with oppositional behavior (Joinson et al. 2006).

18.2 Therapeutic Framework

Diagnosis according to ICD-10 requires a developmental age of at least 4 years, a soiling frequency of at least once per month for at least 6 months (3 months in DSM-5), and the exclusion of an organic etiology (physical-neurological examination and sonography; any other diagnostic procedures only if indicated). For the differential diagnosis of organic causes (c. 5 % for encopresis with constipation, <1 % without constipation), the reader is referred to von Gontard (2012), von Gontard and Neveus (2006), Koletzko and Grosse (2007), and Burgers et al. (2013).

Behavioral therapeutic measures are the **primary treatment** approaches for both forms of encopresis (Brazzelli et al. 2011; Burgers et al. 2013; Cox et al. 1998; Felt et al. 1999; Nurko et al. 2008; von Gontard 2012). In structured toilet training, children are asked to sit on the toilet, relaxed and with their feet on the floor, for 10 min after meals, three times a day. The aim is regulation of the postprandial gastrocolic evacuation reflexes. The atmosphere of the toilet sessions should be positive and can be supplemented by positive reinforcement. Parents are actively involved. The course is documented in a chart. Detailed training includes intensive psychoeducation, reinforcement schedules, demonstration of the defecation process, and toilet sessions with contraction and relaxation exercises (Cox et al. 1998). Biofeedback procedures, in contrast, are ineffective in both forms of encopresis and therefore not indicated (Cox et al. 1998).

Pharmacotherapy with laxatives is not appropriate for (non-retentive) encopresis without constipation and can lead to symptom exacerbation. For **encopresis with constipation**, an initial evacuation of stool masses (disimpaction) is necessary. This should be followed by a maintenance phase of at least 6 months (maximum 24 months) with **oral laxatives** because of the unfavorable long-term prognosis, together with the toilet training described above (Felt et al. 1999; van Ginkel et al. 2003).

Further indications for pharmacotherapy arise from any **comorbid behavioral disturbances**, such as ADHD. Because of the high comorbidity rates, screening with validated, broadband behavioral questionnaires is recommended in all settings (von Gontard et al. 2011). A full child psychological or psychiatric assessment and treatment is indicated when relevant symptoms are present (von Gontard et al. 2011). Comorbid emotional and behavioral disorders need to be treated in addition to encopresis and constipation. If nocturnal enuresis or daytime urinary incontinence is present, encopresis should always be treated first, as the wetting problem can stop as a result of the treatment of encopresis/constipation alone. For further information regarding the therapy of encopresis, the reader is referred to recent review articles (Burgers et al. 2013; von Gontard 2012).

18.3 Choice of Pharmacotherapy

Pharmacotherapy is indicated only for encopresis with constipation. Stool masses in the rectum and colon must be evacuated at the beginning of treatment (disimpaction). During the maintenance phase, re-accumulation of stool should be avoided and normalization of defecation achieved.

18.3.1 Agents for Disimpaction

Disimpaction is usually achieved either orally with **polyethylene glycol** (PEG, Macrogol) or rectally

with enemas – both are effective (Bekkali et al. 2009). Oral disimpaction with PEG is successful in most children; use of PEG for this indication is not recommended in children below the age of 12 years by the US Food and Drug Administration (FDA). In Germany, it is approved for this indication from the age of 5 years and above. The recommended initial dosage is 26 g PEG (four sachets) per day and can be increased daily by 13 g (two sachets) per day to a maximum of 78 g (12 sachets) per day until the bowels are emptied. The "Guidelines for pediatric gastroenterology" recommends a different procedure: 1.5 g PEG/kg body weight per day for 3–4 days and then reduction of the dose (Koletzko and Grosse 2007).

Rectal disimpaction is achieved by applying **phosphate-containing enemas**. This has to be repeated in some children and can be monitored by ultrasound. Enemas are supplied in single use tubes of 120 ml and contain 16 g sodium dihydrogen phosphate and 6 g disodium phosphate per 100 ml. The dosage is 30 ml/10 kg body weight, that is, about half a pouch for preschool children and three quarters to a whole pouch for school-aged children. Phosphate intoxication has been described in infants and toddlers. For children younger than 2 years or those with kidney problems, sorbitol-containing enemas are preferable as a safer alternative (Keller 2002). The NICE guidelines recommend rectal disimpaction only if all oral disimpaction trials have failed with a preference of sodium citrate enemas (NICE 2010). In severe cases, colonic irrigation or even surgical removal of stool masses may be necessary (von Gontard and Neveus 2006).

18.3.2 Agents for Maintenance Therapy

Following disimpaction, long-term oral laxative treatment, combined with toilet training, is indicated. Osmotic laxatives are preferable in children. In recent years, **PEG** has become the clear **first-choice laxative** because of its effectiveness and lack of significant side effects (Candy and Belsey 2009). It is correspondingly recommended by the "Guidelines for pediatric gastroenterology and nutrition" and is approved for use from the age of 2 years in Germany (Koletzko and Grosse 2007; von Gontard and Neveus 2006). In the USA, PEG is available over the counter without prescription. PEG is dosed according to the clinical effect. The dose can be increased if stools are hard and should be reduced if diarrhea develops. The typical starting dose is 0.4 mg/kg body weight per day in two doses (Nurko et al. 2008) - with a wide therapeutic range from 0.27–1.47 mg/kg body weight per day in one study (Pashankar and Bishop 2001).

The **second-choice** agent is **lactulose**, a disaccharide that is not resorbed and binds fluid in the colon, although it is less effective than PEG according to a recent Cochrane Review (Lee-Robichaud et al. 2010). It can be administered as a powder or in solution. In each case, the daily fluid dosage is 1–3 ml/kg body weight as one to three doses or a total of 20–30 ml in preschool children and 30–90 ml in school children (one to three doses per day; Keller 2002). Dosage should be guided by the clinical symptoms. Although lactulose is well tolerated over longer periods, bloating, abdominal pain, and diarrhea are possible. Some children also regard the sweet taste as unpleasant.

Further options include lubricants, such as paraffinum subliquidum at a daily dosage of 1–2 ml/kg body weight (NB, aspiration), and CO_2-releasing suppositories (Koletzko and Grosse 2007).

Other interventions: for patients with unbalanced diets, fiber-rich food may be appropriate, although there is little scientific evidence for the therapeutic benefit of increased dietary fiber (Keller 2002). In cases of constipation, disimpaction should be undertaken prior to increasing fiber intake. Increased fluid intake can also be appropriate in some children (NICE 2010).

18.3.3 Psychopharmacological Agents in the Treatment of Accompanying Mental Problems

Depending upon the accompanying symptoms, different psychopharmacological agents may be indicated, the most important of which are:

- Psychostimulants (for ADHD, see Chap. 8)
- Antidepressants (for emotional symptoms involving dysthymia, anxiety, or compulsive

tendencies, see Chap. 4). **NB**: tricyclic antidepressants exacerbate constipation, so that SSRIs are preferable.
- Anxiolytics (above all in crisis interventions in anxiety disorders; see Chap. 6)
- Psychopharmacological agents useful in relieving tension in conduct disorders with aggressive symptoms and impulse control disorders (particularly antipsychotics, see Chap. 6). **NB**: anticholinergic ADRs of many psychopharmacological agents (especially antipsychotics) aggravate constipation!

18.4 Treatment Strategy

Outpatient treatment is adequate for most cases of encopresis. Because of the unfavorable long-term prognosis, this must be continued for as long as required and with regular follow-up monitoring (Felt et al. 1999; van Ginkel et al. 2003). Treatment in hospital is only necessary for chronic cases or where severe comorbid mental disorders, lack of social support, or the necessity for intensive behavioral therapeutic programs that could be more effectively undertaken in a hospital setting are factors (von Gontard 2012).

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Enuresis and Functional Urinary Incontinence

19

Alexander von Gontard

Contents

A. von Gontard, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Saarland University Medical Center and Saarland University Faculty of Medicine, 66421 Homburg, Germany
e-mail: alexander.gontard@uniklinikum-saarland.de

19.1 Definition, Classification, and Target Symptoms

The International Classification of Diseases, 10th revision (ICD-10; World Health Organisation 1996), clinical criteria define enuresis (F98.0) as "involuntary voiding of urine in a child 5 years of age or older after ruling out organic causes" (World Health Organization 1996). The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), classification (American Psychiatric Association 2013) is comparable but less clear regarding defining frequency of wetting required for diagnosis (twice a week or significant stress or impairment). Specific subgroups are delineated neither in ICD-10 nor in DSM-5. As outlined in detail, both ICD-10 and DSM-5 classification systems do reflect the current research status on incontinence and are therefore not up to date (von Gontard 2011, 2013).

The **classification** of the **International Children's Continence Society** (ICCS) differentiates between **nocturnal enuresis** (NE) and **daytime urinary incontinence** (DUI). DUI is rarely due to organic causes (neurogenic, structural, or other medical causes). Most cases are functional. The term diurnal enuresis is obsolete and should be avoided. If a child wets during sleep and while awake, two diagnoses are given. The following subgroups of intermittent incontinence are distinguished (Austin et al. 2014; Neveus et al. 2006):

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NE (incontinence during sleep)
  - Monosymptomatic NE (without signs of bladder dysfunction)
  - Non-monosymptomatic NE (with symptoms of bladder dysfunction, such as urgency, hesitancy, or dis-coordination)
- DUI (incontinence while awake)
  - Urge incontinence ("overactive bladder," with excessive urgency, frequency, small voided volumes, and holding maneuvers)
  - Dysfunctional voiding (straining to initiate micturition, intermittent urine steam, incomplete bladder voiding)
  - Voiding postponement (habitual delay of micturition with holding maneuvers until incontinence occurs)

Each form of NE can occur both as primary (never dry) and secondary enuresis (reoccurrence after a dry interval of at least 6 months); that is, a total of four forms of enuresis nocturna can be distinguished.

For information on less common forms of DUI, such as stress incontinence, giggle incontinence, and "underactive bladder" (formerly "lazy bladder syndrome"), the reader is referred to von Gontard and Neveus (2006), von Gontard (2012), and the ICCS document (Austin et al. 2014; Neveus et al. 2006).

19.2 Therapeutic Framework

A **diagnosis** of NE or DUI according to ICD-10 requires a minimum duration of 3 months and two incontinence events per month for patients under 7 years of age or once a month in older children. The DSM-5 requires either a frequency of two times per week or significant distress or impairment. Organic etiologies are to be excluded by a pediatric and neurological examination, sonography (kidneys, ureters, bladder), 48-h micturition diary, and urine analysis (only if a urinary tract infection is suspected, urine bacteriology). Further diagnostic procedures (such as uroflowmetry pelvic-floor EMG, micturition cysto-urography or cystoscopy) are only required when specifically indicated.

In 20–40 % of affected children there are **comorbid psychological disturbances**, particularly in children with DUI (Joinson et al. 2006) and in children with secondary NE (von Gontard and Neveus 2006). Screening for behavioral and emotional symptoms is recommended in all settings. Full child psychological or psychiatric assessment and therapy are indicated if clinically relevant psychopathology is present (von Gontard et al. 2011b).

All ineffective measures should be discontinued. Concurrent encopresis and/or constipation (see Chap. 18) must always be **treated** before therapy of NE or DUI. Also, treatment of DUI precedes that of NE. In non-monosymptomatic NE, the daytime bladder dysfunction is treated before nighttime bed-wetting (Franco et al. 2013).

Symptom-oriented, non-pharmacological interventions are preferable in all forms of NE and DUI because they are more effective (Houts et al. 1994; Lister-Sharp et al. 1997). **Pharmacotherapy** is only indicated for NE, urge incontinence (or if urgency is presented in the context of non-monosymptomatic NE), and in the rare cases of giggle incontinence. For information regarding antibiotic pharmacotherapy and prophylaxis of urinary tract infections, see von Gontard and Neveus (2006).

19.2.1 Nocturnal Enuresis

As the first step, **documentation** ("baseline") **of incontinence episodes** in a diary is recommended for 2–4 weeks (Cochrane Review: Glazener and Evans 2004; American and German pediatric psychiatric guidelines: AACAP Official Action 2004; von Gontard 2007). This simple measure will lead to dryness in about 15 % of children.

The **first-choice treatment** approach is alarm treatment with either body-worn or bedside alarms (Cochrane Review: Glazener et al. 2005; American, United Kingdom, and German pediatric psychiatric guidelines: AACAP Official Action 2004; NICE clinical guideline 111 2010; von Gontard 2007). Meta-analyses show that about 70 % of children achieve dryness with alarms, with excellent long-term success: c. 50 % remain

dry (Glazener et al. 2005; Houts et al. 1994). If required, the effect of alarm-based behavioral therapy can be augmented by supplementary behavioral modules or programs such as the arousal training (Glazener et al. 2004; van Londen et al. 1995; von Gontard 2007).

The **second-choice** treatment is **pharmacotherapy** with desmopressin. Parents should be advised that behavioral therapeutic approaches achieve the greatest long-term benefits. Pharmacotherapy of NE is appropriate if:

- Other therapeutic methods have failed.
- A combination of behavioral therapeutic measures and pharmacotherapy is planned.
- The motivation for alarm therapy or other behavioral therapeutic approaches, which require participation, is initially lacking.
- Family factors which render alarms and other behavioral therapies problematic (sleep deprivation, care for infants, work issues of parents, etc.).
- Short-term relief from NE is required (school excursions, sleepovers, vacations, etc.).

The following medication or medication groups can be considered:

- Desmopressin
- Tricyclic antidepressants
- Anticholinergics (only for non-mono-symptomatic NE with signs of urgency)

Other medications such as indomethacin or diclofenac are not effective and not indicated (Glazener et al. 2007b).

19.2.2 Functional Daytime Urinary Incontinence

In all forms of functional DUI, **specific non-pharmacological interventions** (change of drinking and voiding habits, toilet training, cognitive-behavioral therapeutic programs) are the **first-choice** approaches (see von Gontard 2007).

Pharmacotherapy is appropriate:

- For urge incontinence ("overactive bladder") after behavioral therapy has been unsuccessful.
- For giggle incontinence (uncommon)

The following medication or medication groups can be considered:

- Anticholinergics
- Methylphenidate

19.3 Choice of Pharmacotherapy

19.3.1 Pharmacotherapy of Nocturnal Enuresis

19.3.1.1 Desmopressin

Desmopressin is, after alarm-based behavioral therapy, the second-choice therapy of NE (Neveus et al. 2010). Around 40–70 % of treated children experienced a significant reduction in the number of wet nights under medication (van Kerrebroeck 2002; Glazener and Evans 2006; Glazener et al. 2007a). Special indications (such as need for short-term dryness) were mentioned above. Desmopressin acetate tablets are approved for the management of primary NE in pediatric patients 6 years and older by the US Food and Drug Administration (FDA) and in European countries.

Desmopressin is an analogue of the naturally occurring antidiuretic hormone, vasopressin, and its main effect is to reduce nocturnal urine production. It is assumed that there are also additional CNS mechanisms. It is administered as a tablet. Application as a nasal spray is no longer available for the indication of NE because of the higher rate of adverse drug reactions (ADRs). The clinical relevance of melt tablet formula of desmopressin is not yet clear despite first positive reports (Juul et al. 2013).

The **standard dosage** is 200 µg (1 tablet) before going to sleep in the evening, continued for 2 weeks. The dose can be increased in unsuccessful cases to 400 µg (2 tablets) in the third and fourth weeks. Should no major improvement be achieved after 4 weeks, the medication should be withdrawn ("nonresponder"). If the patient is dry, the medication is continued at the lowest effective dose for a further 8 weeks. After 12 weeks in total, a withdrawal is recommended. In case of relapse, the medication can be continued, with further treatment breaks after a maximum of 12 weeks to assess if the child has become dry.

Desmopressin is generally well tolerated, and its efficacy has been verified by numerous studies (Houts et al. 1994; Lister-Sharp et al. 1997; van Kerrebroeck 2002). The following ADRs have been described: headache (rare), nausea, and abdominal pains; scattered cases of allergic reactions in the form of itching and exanthema and fever, bronchospasm, and anaphylaxis have also been reported. In cases of excessive fluid intake, water retention is very occasionally reported, with weight gain, hyponatremia, cerebral seizures, cerebral edema, and loss of consciousness; these cases may require intensive care.

NB:

- **Hyponatremia** and/or **water intoxication**, with a danger of cerebral seizures, can be a problem during desmopressin therapy in rare instances involving excessive fluid intake or overdosage (because of fear of relapse, for instance). The first indications are weight gain, headache, and nausea (Ferring 1998). Parents and children should therefore be urgently advised of this danger. Balanced water intake and excretion must be assured. Because of this rare, but severe ADR, it is recommended that fluids should not be drunk after taking the evening dose.
- Most children experience a **relapse** after discontinuing desmopressin. In contrast to alarm treatment, the long-term benefit is less pronounced. According to Houts et al. (1994), 22 % of children remain dry long term after discontinuing medication; according to van Kerrebroeck (2002), 18–38 % are still dry after 6 months.
- **Contraindications** are allergies to any of the components of the medication as well as habitual or psychogenic polydipsia.

The ICCS guidelines for NE recommend desmopressin when alarm-based behavioral therapy has failed and also vice versa (Neveus et al. 2010). A switchover from one to the other (alarm/desmopressin) has proven successful (Kwak et al. 2010). Only after both have proved ineffective tricyclic antidepressants can be recommended as treatment of third choice.

19.3.1.2 Imipramine

There are many studies and widespread clinical experience regarding medication with imipramine (Houts et al. 1994; Lister-Sharp et al. 1997). Treatment with imipramine (as **third-choice** agent) is indicated in instances of resistance to alarm and other behavioral measures as well as to desmopressin. Its main indications, therefore, are unsuccessful cases despite standard therapy, where they have shown to be effective (Gepertz and Neveus 2004; Neveus and Tullus 2008).

Imipramine belongs to the tricyclic antidepressants (see Chap. 4). Even at lower doses (0.3–1 mg/kg body weight) it has an anti-enuretic effect; at higher doses (3 mg/kg body weight) it is also antidepressive and analgesic. Imipramine is approved for use in children older than 6 years for NE by the US FDA and in European countries.

Imipramine is employed in the form of sugar-coated pills at 10 mg (mite) and 25 mg. **Therapy begins** with a **low evening dosage** of 10–25 mg (0.3–1 mg/kg body weight); in the majority of cases an evening dose of 25 mg is sufficient, while in older children 50 mg is effective. The tablets are taken un-chewed with fluid, and the onset of effect can be expected after about 5 days.

The relapse rate after the end of imipramine therapy is also high (up to 50 %; AACAP Official Action 2004). Houts et al. (1994) reported that 14 % of treated children remain dry long term after discontinuation of the medication.

NB:
Imipramine, particularly in children, has a **cardiotoxic potential** as well as high **acute toxicity in cases of overdosage**. For this reason the following recommendations should be heeded:

- Prior to commencement of therapy, a detailed family history should be taken, and a physical examination of the patient with regard to cardiac disorders should be performed.
- An ECG of at least two minutes' duration prior to treatment, after reaching plasma level steady state, and with daily dosages exceeding 3 mg/kg body weight.
- No employment of imipramine or other tricyclic antidepressants in patients with prolonged QTc interval.
- Slower cardiac conduction (PR interval >0.20 ms, QRS interval >0.12 ms) can indicate dosage reduction is necessary (seek cardiological advice!).
- A dose of 2.5 mg/kg per day should not be exceeded; ECG changes of unknown significance have been reported in pediatric patients with doses twice this amount (Prescribing Information).

Between 1986 and 1992 at least four sudden deaths during medication of children with desipramine (not with imipramine!) were reported. A 1995 review concluded, however, that even for desipramine there was no strong association between the use of the medication and sudden death in children between 5 and 14 years old (Biederman et al. 1995; Schatzberg et al. 2003). Imipramine can be combined with desmopressin, if necessary (Neveus et al. 2010). For contraindications, interactions, further ADRs, and the corresponding countermeasures, see Sect. 4.4.1.1. If imipramine must be discontinued, it should be withdrawn slowly to avoid withdrawal reactions, such as restlessness, nausea, vomiting, and sleep disturbances.

19.3.1.3 Other Medications

For non-monosymptomatic NE with daytime urgency symptoms (frequency, urgency, small voided volumes), a combination treatment with **oxybutynin** (or propiverine) and alarm-based behavioral therapy is appropriate, as compliance and effectiveness can be increased. An evening dose of 5 mg oxybutynin (or propiverine) is often adequate. If higher doses are required, recommendations described below for the treatment of urge incontinence ("overactive bladder") should be applied. Anticholinergics such as tolterodine are not effective for NE alone (Neveus and Tullus 2008).

Tricyclic antidepressants other than imipramine also exhibit an anti-enuretic effect, including **clomipramine**. However, clomipramine has been US FDA approved only for obsessive-compulsive disorders from the age of 10 years and older. The dosage is 10–25 mg in the evening.

Reboxetine, a selective noradrenalin-reuptake inhibitor, has an indication in therapy-resistant NE and can be combined with desmopressin (Lundmark and Neveus 2009). A placebo-controlled study found that atomoxetine leads to a significant reduction of incontinence episodes (Sumner et al. 2006), but this initial study allows no general recommendations.

19.3.2 Pharmacotherapy of Functional Urinary Incontinence

19.3.2.1 Oxybutynin

Oxybutynin, an anticholinergic and a spasmolytic, is only indicated for urge incontinence ("overactive bladder") and should only be used when behavioral therapy has been rigorously undertaken for at least 4 weeks without reasonable improvement being achieved (von Gontard and Neveus 2006; von Gontard 2007). It is important that cognitive-behavioral therapeutic training be continued even during medication.

Urge incontinence involves defective central inhibition of peripheral contractions of the detrusor muscle (Franco 2007). Oxybutynin acts locally to increase bladder capacity and to reduce uncontrolled detrusor contractions. It is **US FDA approved** for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage,

urge incontinence, dysuria) from 5 years of age. In **Europe** it is also approved in children over 5 years of age for NE associated with detrusor overactivity, in conjunction with nondrug therapy, when other treatment has failed.

The usual formulation is tablets at 5 mg, with **dosage** as follows:

- Start with 1.25 mg = ¼ tablet in the morning (<8 years) or 2.5 mg = ½ tablet in the morning (>8 years).
- Increase dosage by ¼ or ½ tablet every 2–3 days, divided into 2–3 doses/day.
- The average target daily dosage is 0.3 mg/kg body weight and should be maintained for at least 4 weeks. Where the effect is insufficient, the dosage can be raised to a daily maximum of 0.6 mg/kg body weight (total maximum 15 mg/day).

Charts (such as those in von Gontard and Neveus 2006) should be filled out to document the response and to determine the lowest required dosage.

NB:

- To avoid ADRs, a maximum dosage of 15 mg/day should not be exceeded.
- The frequency of ADRs is reduced by slow increases in dosage.
- ADRs have recently been described by von Gontard and Neveus (2006) – impaired concentration and other central ADRs (anxiety, apathy, aggression) – that can harm school performance.
- Urinary retention can cause accumulation of residual urine, which in turn facilitates urinary tract infections. **Close ultrasound monitoring** is therefore recommended, particularly if residual urine is present at the commencement of therapy.
- **Constipation** can also be increased, which can further aggravate the urgency problem (Franco 2007).
- Disturbed ocular accommodation (sleepiness, squinting, photosensitivity, dilated pupils), particularly at the beginning of treatment, during dosage increases, and changes of medication, can impair **driving ability** (also bike-riding, skating etc.). It is therefore essential that ADRs be discussed with the patient and their parents and that this be documented.
- Reduced sweat gland secretion can occasionally lead to hyperthermia, particularly during hot weather (Prescribing Information).

The ADRs are dose-dependent, reversible, and related to the anticholinergic effects of the medication: dry mouth (frequent), occasional reduced sweat secretion, erythema, impaired ocular accommodation, tiredness, and tachycardia, amongst others. If ADRs do not develop early in therapy, however, oxybutynin is also well tolerated in the long term. Oxybutynin and other anticholinergic medications are mutually reinforcing in their effects. This also applies to tricyclic antidepressants, such as imipramine.

Typical symptoms of **intoxication** are mydriasis; fever; red, hot skin; and dry mucous membranes. Agitation, nervousness, reduced blood pressure, and tachycardia are also possible, as are even hallucinations and coma.

Therapy of intoxication: Emergency treatment is urgently required! The highest priority must be to ensure adequate respiration! Further measures include immediate gastric lavage. Slowly administered physostigmine (in children 30 µg/kg body weight i.v.) assists these measures. Nervous agitation can be addressed with diazepam (10 mg slowly i.v.). For tachycardia, i.v. propranolol is appropriate. Bladder catheterization is necessary in cases of urinary retention.

19.3.2.2 Propiverine

The effect of propiverine is comparable with that of oxybutynin. A randomized, controlled study found a significant reduction of micturition and incontinence frequency as well as an increase in urinary volume (Marschall-Kehrel et al. 2008). The ADR rate of 22 % is somewhat lower than for oxybutynin and included abdominal pain, dry mouth, obstipation, disturbed accommodation, and headache. Further ADRs correspond to those of oxybutynin and are dose-dependent and reversible.

Propiverine is **approved** for use in children aged 5 years and older for urge incontinence (overactive bladder) in some **European countries** and **Japan**, so far. Specifically, it is indicated for the symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency in patients with overactive bladder syndrome or neurogenic detrusor overactivity (detrusor hyperreflexia) from spinal cord injury. In the latter organic causes of incontinence, it may be used even in young children from the age of 1 year onwards. Where oxybutynin fails to achieve improvement, propiverine can be employed instead and vice versa. Particularly where ADRs are complicating oxybutynin therapy, a rapid switch to propiverine is advisable, as its side effect rate appears to be lower.

Dosage: in children oxybutynin should be gradually titrated to a maximum of 0.8 mg/kg body weight per day, divided into two to three doses. For propiverine a maximum daily dosage of 15 mg should not be exceeded (in children with a body weight of over 35 kg, the maximum dose is two times 15 mg per day).

19.3.2.3 Tolterodine

Tolterodine, like oxybutynin, is an antagonist of muscarinic acetylcholine receptors (see Sect. 1.3.1), and its effect is similar to increase bladder capacity and to reduce uncontrolled detrusor contractions, but its selectivity for the bladder is greater. For this reason, ADRs are significantly less common as for other anticholinergics (Kilic et al. 2006; Nijman et al. 2007). Tolterodine is currently only approved in Europe and by the US FDA for use in adults; the lack of proof of efficacy from large randomized, controlled studies prevents its registration for use in children (Nijman et al. 2005).

Tolterodine is administered in the form of film tablets at 1 and 2 mg. **Dosage** for children is 1 mg morning and night; this dosage can be started immediately (Hjälmas et al. 2001). At higher dosages (2 mg twice daily) the rate of ADRs (mostly headache) increases markedly, while the ADR profile otherwise corresponds to that of other anticholinergic agents.

19.3.2.4 Trospium Chloride

Trospium chloride is a further alternative if the standard preparations oxybutynin and propiverine do not show an adequate effect. Its efficacy in children (5–13 years) could be demonstrated in a randomized, controlled study, with an ADR rate of only 10 % (Lopez Pereira et al. 2003). Interestingly, it is reported in the Summary of Product Characteristics that trospium chloride use in children under 12 years of age is contraindicated, since no data are available. The dosage is c. 15 mg/day, divided into three doses (adult dosage 45 mg/day in three doses).

19.3.2.5 Other Medications

Other anticholinergics, such as darifenacin, fesoterodine, and solifenacin, are used successfully in adults, and pediatric trials are under way. Antidepressants such as duloxetine are similarly used in adults for the treatment of stress incontinence. The lack of relevant pediatric studies also means that they cannot currently be recommended for children.

19.3.2.6 Methylphenidate

In giggle incontinence, sudden and complete bladder emptying occurs as a reflex action triggered selectively by giggling or laughter (von Gontard and Neveus 2006). It can be accompanied by cataplexy. Behavioral therapeutic measures have been employed with success. The overlap between giggle incontinence and the cataplexy/narcolepsy suggests the use of pharmacotherapy with methylphenidate. The necessary dosage was higher than that employed for the treatment of ADHD: 0.3–0.5 mg/kg body weight methylphenidate every 4–5 h; an additional

5–20 mg was given before social activities where laughing might occur (Sher and Reinberg 1996). A new retrospective analysis reported positive treatment results even with low-dose methylphenidate (Chang et al. 2011).

19.4 Treatment Strategies for Comorbid Disorders

Comorbid behavioral and emotional disorders are more common than in continent children and affect 20–40 % of all children with NE or DUI (von Gontard et al. 2011a). They are, however, more frequent in DUI than in NE and also more common in secondary than in primary forms of NE.

ADHD is the most frequent comorbid disorder in NE (Baeyens et al. 2005; von Gontard et al. 2011b). The spectrum of disorders associated with DUI, but externalizing disorders such as conduct disorders and ADHD predominate (Joinson et al. 2006; von Gontard et al. 2011a, b). The success rates in the treatment of NE/DUI are reduced by inadequate compliance when the child is affected by a comorbid disorder. In these cases, it is therefore necessary to undertake both symptom-oriented treatment of NE/DUI and child psychiatric treatment of the comorbid disorder. Because of the relevance of comorbid disorders, it is essential that all children be screened with validated, broadband behavioral questionnaires – with referral for child psychological and psychiatric assessment and treatment when necessary (von Gontard et al. 2011a). A multiaxial child psychiatric or psychological assessment should be initiated when clinically relevant psychopathology is present in order to enable recognition and treatment of comorbid disorders.

Frequent comorbid disorders are:

- Encopresis and constipation. These should be treated before the enuresis (see Chap. 18).
- Emotional, introversive disorders, such as anxiety or depression. The approach to their treatment can include non-pharmacological measures as well as antidepressants (see Chap. 4) or anxiolytics (see Chap. 6). **NB**: anticholinergic interactions!
- Oppositional Defiant Disorders. Behavioral therapeutic measures are the primary approaches for these disorders. Only rarely are medications necessary to reduce aggression (see Chap. 9). **NB**: anticholinergic interactions!
- ADHD. Medication with psychostimulants is necessary (see Chap. 8).

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Manic Episode and Bipolar Affective Disorder

20

Silke Rothenhöfer, Andreas Warnke, and Christoph Wewetzer

Contents

S. Rothenhöfer, MD (✉) • C. Wewetzer, MD
Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Florentine-Eichler-Str. 1, 51067 Köln, Germany
e-mail: rothenhoefers@kliniken-koeln.de; wewetzerc@kliniken-koeln.de

A. Warnke, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: warnke@kjp.uni-wuerzburg.de

20.1 Definition, Classification, and Target Symptoms

The clinical criteria of the International Classification of Diseases, 10th revision (**ICD-10**), define **manic episodes** (F30) as involving elevated or irritable mood and a marked increase in physical and mental activity (World Health Organization 1996). The following **subtypes** are distinguished:

- Hypomania (F30.0)
- Mania (F30.1)
- Mania with mood-congruent (F30.20) or mood-incongruent (F30.21) psychotic symptoms (F30.2)

Further common symptoms are an increased sense of self-esteem and self-overestimation, pressure of speech, flight of ideas, loss of normal social inhibitions, increased distractibility, reduced need for sleep, increased libido, perceptual changes, and extravagant delusions. These defined disorder characteristics are also the **target symptoms** of pharmacological treatment. Pharmacotherapy aims to stabilize mood and drive, to achieve behavioral control and normalization of sleep, and to abolish any psychotic symptoms present.

Bipolar affective disorder (F31), according to ICD-10, is characterized by repeated episodes of an affective disorder, where at least one episode must include manic features. In bipolar disorder with rapid change of phase, at least four episodes occur within a year. A mixed episode is characterized by a combination or rapid exchange of manic and depressive symptoms.

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In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (**DSM-5**), the "**bipolar I disorder**" (296.x) involves the "manic episode" and "hypomanic episode" (American Psychiatric Association 2013). The "**bipolar II disorder**" (296.89; F31.81) includes the "hypomanic episode." The bipolar II disorder requires the lifetime experience of at least one episode of major depression and at least one hypomanic episode. In bipolar I disorder there should have been at least one manic episode, and the occurrence of the manic and of major depressive episode(s) is not better explained by another psychiatric disorder (e.g., schizophrenia).

The quality and degree of the affective **symptoms** in children often **differ markedly from** those in **adult** cases (Findling 2005): irritability, hyperactivity, logorrhea, sleep disorders, and weakness of concentration often have priority. According to DSM-5, the "depressed mood" in children and adolescents may be "irritable mood," and instead of weight loss, failure to make expected weight gain should also be considered.

20.2 Therapeutic Framework

Three **areas of treatment** of manic and bipolar disorders must be **distinguished**:

- Acute treatment of a manic episode
- Acute treatment of a depressive episode (see Chap. 14)
- Long-term treatment with
  - Maintenance therapy
  - Phase prophylaxis

The **diagnosis** must be clinically secured prior to the initiation of treatment. The indication for pharmacological treatment of the acute symptoms is provided by the diagnosis. Phase prophylaxis is indicated by a high probability of relapse, which is to be assumed in cases of genetic predisposition, and by the occurrence of a second episode.

Pharmacologic therapy has **priority**, and treatment of acute symptoms should be undertaken only on an inpatient basis. Psychotherapeutic procedures subserve stress reduction, the encouragement of social competences, and the learning of problem solution strategies (Miklowitz 2006; West and Pavuluri 2012). Explanation of the nature of the disease and the type of therapy, as well as family counseling, is essential. Everyday burdens and cognitive demands should be incrementally increased, with the goal of gradual reintegration into school or the workplace. Further reintegrative measures beyond clinical treatment are often required, for which reason close cooperation with youth welfare services may be necessary (see Kowatch et al. 2005; Vitiello et al. 2012 for further information).

20.3 Choice of Pharmacotherapy

According to the practice parameter for the assessment and treatment of children and adolescents with bipolar disorder, the choice of medication(s) is usually based on the evidence of efficacy, safety profile, phase of illness, presence of psychosis or rapid cycling mood swings, patient's and family's preferences, and history of medication response (McClellan et al. 2007). For further information regarding the psychopharmacological agents discussed below (including age- and indication-specific aspects of approval status, clinical efficacy studies, recommended dosages, adverse drug reactions [ADRs], medication interactions, contraindications, and special precautions), please refer to the corresponding special Chaps. 4, 5, 6, and 7.

20.3.1 Lithium Salts

Lithium salts are a benchmark treatment for adult patients with bipolar disorder (Cousins and Young 2007; Fountoulakis et al. 2012; Geddes et al. 2004). Lithium salts were used over 40 years ago to treat "manic-depressive illness" in children and are **approved** by the US Food and Drug Administration (FDA) for the "treatment of manic episodes and maintenance treatment of bipolar disorder" in patients aged 12 years and older. These agents are the only licensed agents for this indication in Europe.

In the treatment of children and adolescents, monotherapy with second- and third-generation antipsychotics or the traditional mood stabilizers,

lithium salts, is the currently recommended **first-line treatment** (Goldstein et al. 2012; McClellan et al. 2007), although it has been shown in a recent systematic review that second- and third-generation antipsychotics are superior to mood stabilizers in the treatment of pediatric mania (Correll et al. 2010). Unfortunately, definitive randomized controlled trials of lithium salts have not been performed in pediatric populations suffering from mania or mixed states in bipolar disorder (see Sect. 7.4.1). This doubt is justified in clinical practice by its narrow therapeutic range, requiring reliable taking of the medication and regular serum level monitoring, as well as by ADRs that undermine compliance (Bowden 2000).

Geller et al. (1998) reported positive effects with reference to antimanic efficacy in adolescents ($N=25$) with bipolar and substance abuse disorders in a 6-week placebo-controlled, double-blinded study. As presented by Liu et al. (2011), there have been open-label clinical trials involving lithium carbonate in the treatment of mania in children and adolescents with bipolar disorder. The **response rate** for manic symptoms in these studies ranged from **23 to 55** %, with an average response of 40 %. In one of these trials, the acute response rate of lithium carbonate (0.88 ± 0.35 mmol/L lithium) as monotherapy in children and adolescents (aged 8–18 years) was 38 % (Kowatch et al. 2000). Recently, Findling et al. (2013) found in an open-label study with children and adolescents that lithium therapy if there was an initial positive effect can also be safe and effective as longer-term treatment.

20.3.2 Mood-Stabilizing Antiepileptics

As an **alternative** to lithium salts, mood-stabilizing antiepileptic medications (see Chap. 7), such as carbamazepine, lamotrigine, topiramate, and valproate products, may be considered for the treatment of acute mania and for phase prophylaxis, either as monotherapy or in combination with second- or third-generation antipsychotics, or lithium salts. Extended-release **carbamazepine** is US FDA **approved** for use in adults with acute manic or mixed episodes associated with bipolar disorder I. In addition, it is approved in Canada, Japan, and Australia and several European countries for these indications in adults. **Lamotrigine** is licensed for the prevention of depressive episodes in the context of bipolar disorder in adults. **Valproate** products (valproic acid, sodium valproate, divalproex sodium) are approved by the US FDA and in Europe for the treatment of manic syndromes as well as (in slow-release form) for phase prophylaxis in adults.

As discussed in detail in Chap. 7, in children and adolescents, the **evidence** of the efficacy of mood-stabilizing anticonvulsants in the acute treatment of mania and bipolar disorder comes predominantly **from open-label trials**. The three published double-blind placebo-controlled studies of mood-stabilizing anticonvulsants (one each for extended-release valproate, oxcarbazepine, and topiramate) for children and adolescents who have acute mania showed no superiority of active treatment over placebo as differences in response rates (Hazell and Jairam 2012): Response rates to active treatment ranged from 24 to 42 %, whereas response to placebo ranged from 22 to 26 %.

A recent review and meta-analysis of pharmacologic treatment for pediatric disorder reported 14 open-label studies of lithium salts, carbamazepine, and divalproex sodium in the treatment of pediatric bipolar disorder encompassing 915 subjects (Liu et al. 2011). The overall response rate was very similar between the open-label acute monotherapy (41 %) and the double-blind studies (40 %) for divalproex sodium. Double-blind response rates for lithium salts and carbamazepine monotherapy are lacking at this time. Overall, these results suggest some antimanic efficacy for mood stabilizers, but these results should be viewed cautiously because efficacy has not been documented in double-blind studies.

There have been three open-label and two double-blind studies of other anticonvulsants such as lamotrigine, oxcarbazepine, and topiramate, encompassing 244 subjects (Liu et al. 2011). Very similar response rates were observed in the open-label (43 %) and double-blind (39 %) studies. Again, these response rates should be viewed cautiously because of the lack of evidence for efficacy from double-blind studies.

Topiramate is unique because of its ability to cause weight loss at doses of 50–200 mg daily in

adults. In an open-label trial, Tramontina et al. (2007) found topiramate is effective during the maintenance phase in 10 adolescents with bipolar disorder; a positive feature of the 11 weeks study was the loss of body weight gained during previous treatment with other medications. Thus, topiramate could be **useful to treat weight gain**, which is a common problem in bipolar patients.

20.3.3 Antipsychotics

Antipsychotics are traditionally used clinically in the treatment of acute manias in adults (Fountoulakis et al. 2012). High-potency antipsychotics were long preferred for treatment of manias with psychotic features, low-potency, sedative antipsychotics for hyperactivity. The rapid onset of action of antipsychotics is advantageous for these applications. Treatment with second- and third-generation antipsychotics has in the meantime become increasingly prominent, because data from **double-blind placebo-controlled studies** demonstrate that all antipsychotics (aripiprazole, 10 or 30 mg; olanzapine, 2.5–20 mg; quetiapine, 400 or 600 mg; risperidone, 0.5–2.5 or 3–6 mg; and ziprasidone, 20–160 mg) evaluated are more likely than placebo to induce a clinically significant **reduction** in **core symptoms** of mania in children and adolescents (Berk and Dodd 2005; Hazell and Jairam 2012; Liu et al. 2011). In children and adolescents with bipolar I disorder mania, numbers needed to treat of the pooled dose arms for "response" (defined as at least a 50 % reduction in the Young Mania Rating Scale [YMRS] total score) compared to placebo ranged from three to four, corresponding to large to moderate effect sizes (Correll et al. 2011).

Head-to-head studies (Correll et al. 2010) between **antipsychotics** and **conventional mood stabilizers** in children and adolescent showed that quetiapine (mean dose: 450 mg) added to valproate products was superior in adolescents with bipolar I mania to valproic acid monotherapy. In addition, in one active-controlled trial, quetiapine and divalproex were equally effective regarding the change in the YMRS, but quetiapine was superior regarding a 50 % reduction in the YMRS score, and speed of response was faster with quetiapine (DelBello et al. 2006). Finally, in a study comparing risperidone with valproic acid, risperidone was also superior to the mood stabilizer. This superiority of second-generation antipsychotics compared to mood stabilizers for pediatric mania was also confirmed in a systematic review and indirect comparison of placebo-controlled trials with either antipsychotics or lithium salts/mood-stabilizing antiepileptics (reviewed in Correll et al. 2010).

Aripiprazole is FDA **approved** for "acute treatment of manic or mixed episodes associated with bipolar disorder I as monotherapy and as adjunct to lithium or valproate" for children and adolescents aged 10–17 years. **Olanzapine** is labeled for the "treatment of manic or mixed episodes associated with bipolar disorder I and maintenance treatment" in adolescents 13–17 years old. **Quetiapine** and **risperidone** are FDA approved for the "acute treatment of manic or mixed episodes associated with bipolar disorder I as monotherapy" in children and adolescents (aged 10–17 years).

As discussed in Sect. 5.4.4, antipsychotics' safety profile is crucial for the treatment strategy in children and adolescents with bipolar disorder, because of the long-term course of pharmacological therapy. Second- and third-generation antipsychotics are considered safer than the first-generation agents, but they are frequently associated with ADRs, including weight gain and metabolic complications, elevation in prolactin levels, extrapyramidal motor ADRs, sedation, and cardiac effects that require careful monitoring (Amor 2012; Fraguas et al. 2011; Masi and Liboni 2011).

In contrast to treatment standards in Europe, the lower age of patients in some US studies, including those discussed above, is striking; diagnosis of bipolar disorder in some cases, for instance, was made in preschool-aged children (Pavuluri et al. 2006). The typically high comorbidity with a hyperkinetic disorder should similarly be critically regarded as also the frequent co-medication of study participants.

20.3.4 Benzodiazepines as Adjuvant Medications

Benzodiazepines (e.g., lorazepam) cannot be employed alone but are frequently useful as co-medications during treatment in hospital (McClellan et al. 2007).

20.3.5 Other Pharmaceutical Alternatives

In adults, a variety of agents have been shown to be useful in the treatment of bipolar disorder including allopurinol, dopaminergic agonists, ketamine, modafinil, and *N*-acetylcysteine (Fountoulakis et al. 2012). The data basis for these therapeutic approaches is limited so that they cannot be recommended for use in child and adolescent psychiatry. A prospective study of the use of omega-3 fatty acids in 20 children and adolescents with bipolar disorder found good tolerability but only a minor improvement of manic symptoms (Wozniak et al. 2007). In summary, the employment of omega-3 fatty acids for therapy of bipolar disorder cannot currently be recommended (Kowatch et al. 2005). The same holds true with flax oil, tested in a randomized, double-blinded controlled clinical trial that demonstrated no significant differences in primary outcome measures when compared by treatment assignment (Gracious et al. 2010).

20.4 Treatments Strategy

20.4.1 Acute Mania Therapy

As discussed above, there is a substantial rigorous evidence base regarding treatment of mania in children and adolescents. Depending upon the symptoms and the cooperation of the patient, acute mania is treated with lithium salts and/or antipsychotics as described in Table 20.1. Overall, the data currently available suggest that second- and third-generation antipsychotics have better efficacy for treatment of acute mania in bipolar disorder than the classical mood stabilizers (Goldstein et al. 2012; Hazell and Jairam 2012). As **emergency treatment** in the case of pronounced agitation, aggression, and

Table 20.1 Recommended acute therapy of mania

Symptoms	Psychopharmacological agents	Special features/interactions
Mild mania without psychotic symptoms		
Cooperative patient	Lithium salts, aripiprazole, olanzapine, quetiapine, risperidone	
Sedation necessary, cooperative patient	Lithium salts + low- to medium-potency antipsychotics/ benzodiazepine	
Mild to severe mania with psychotic symptoms		
Cooperative patient	Lithium salts + preferably second- and third-generation antipsychotics	Increased risk of neuroleptic malignant syndrome and neurotoxic symptoms (especially for **first-generation antipsychotics**)
Sedation necessary, cooperative patient	Lithium salts + preferably second- and third-generation antipsychotics/benzodiazepine	
Uncooperative patient, lithium medication not possible	Preferably second- and third-generation antipsychotic	
Sedation necessary, uncooperative patient; lithium medication not possible	Preferably second- and-third generation antipsychotics	
Lithium medication not possible or inadequate	Valproate products or carbamazepine	Carbamazepine enhances via enzyme induction its own catabolism and that of other psychopharmacological agents (such as antipsychotics, tricyclic antidepressants) SSRIs in particular elevate plasma carbamazepine levels Carbamazepine + antipsychotics. Caution: hematological changes

SSRIs selective serotonin reuptake inhibitors

the absence of compliance, **haloperidol** still is clinically indicated.

The narrow therapeutic range of lithium therapy means that a high degree of dependability on the part of the patient and their carers is crucial. The initial delay in the onset of effect generally makes **co-medication** with antipsychotics or benzodiazepines during the first weeks or months of treatment **essential** (Gerlach and Warnke 2010; Kafantaris et al. 2001; Pavuluri et al. 2004).

Monotherapy with lithium salts is usually only feasible for mild mania without psychotic features or as relapse prophylaxis.

Table 20.2 summarizes recommendations for dosages of lithium salts. In the treatment of children and adolescents resistant to monotherapy, combinations of lithium salts/mood-stabilizing antiepileptics and antipsychotics are common clinical scenarios, but there is limited evidence to guide this treatment. In addition, the elevated risk of ADRs should be noted.

In the therapy of acute mania with agitation or insomnia, benzodiazepines (such as lorazepam) can be effective as adjunct medication and as anxiolytics.

Table 20.2 Recommended dosages for lithium

Acute therapy	Plasma levels 1.0–1.5 mmol/L Assessment of plasma levels twice a week, determined 12 h after most recent dose; steady state after about 1 week Onset of action after 5–21 days
Phase prophylaxis	Plasma levels 0.6–1.2 mmol/L Assessment of plasma levels twice a month Slow release medication preferable (initial dosage, e.g., 200–400 mg/day lithium carbonate; dosage increased by 200–400 mg at intervals of 3–5 days based upon plasma levels and psychopathology)

From Findling et al. (2011), Gerlach and Warnke (2010)

Benzodiazepines should generally be employed on only a short-term basis because of the risk of dependence.

After the acute symptoms have subsided, it is recommended that **maintenance therapy** (symptom-suppressive therapy) be continued for 6–12 months and that supplementary medication be gradually reduced while maintaining mood-stabilizing medication.

20.4.2 Phase Prophylaxis

The indication for phase prophylaxis is the high probability of relapse (genetic predisposition) and a clear risk of social integration being compromised as well as the occurrence of a second episode. As discussed above and in detail in Chap. 7, in comparison with data regarding acute manic/mixed episodes, few studies have examined continuation and/or maintenance treatment of bipolar disorder in children and adolescents. In contrast to the robust evidence for second- and third-generation antipsychotics in acute pediatric bipolar manic/mixed episodes, there are **limited maintenance data** from which to draw conclusions (Goldstein et al. 2012). Preliminary open data with lithium salts, divalproex sodium, and extended-release carbamazepine suggest that maintenance therapy with these mood stabilizers seems well tolerated and may be associated with further symptomatic improvement (see Chap. 7).

The recommended staged procedure for phase prophylaxis is outlined in Table 20.3.The duration of prophylaxis must be at least 18 months after complete abatement of the acute phase, and medication should be continued indefinitely if indicated, even though again in this part the data basis is not satisfactory. A phase prophylaxis **monotherapy** with **lithium salts** would be advisable. In the case of insufficient effect, first compliance, dosage and serum level should be checked and probably increased. In the case of persistent therapy resistance, combinations of mood stabilizers and second- or third-generation antipsychotics or

Table 20.3 Recommendations for phase prophylaxis therapy

Indication	Medication	Special features/interactions
Indication for phase prophylaxis	Lithium salts	Full mood-stabilizing effect sometimes manifested only after several months Anti-suicidal effect
Treatment with lithium salts not possible or inadequate	Slow release valproate, carbamazepine, aripiprazole, olanzapine, quetiapine or risperidone	Valproate products are better tolerated than carbamazepine
Insufficient efficacy of monotherapy	Lithium salts, valproate products or carbamazepine + aripiprazole, olanzapine, quetiapine, or risperidone	Serum levels of each must be monitored **Carbamazepine enhances** via enzyme induction its own **catabolism** and that of other psychopharmacological agents (e.g., antipsychotics) Carbamazepine + antipsychotics. **Caution**: hematological changes
	Lithium salts + valproate products or carbamazepine	Serum levels of each must be monitored. Even at normal serum levels, the combination of lithium salts and carbamazepine is associated with a higher risk for ADRs

combinations of two mood stabilizers can be given, even though the data basis is deficient.

20.4.2.1 Mood Stabilizers

Because of the narrow therapeutic range of lithium salts (see Sect. 7.4.1. for lithium intoxication), the dosage must be adjusted according to the serum levels of lithium and the clinical picture of the patient (clinical effect, ADRs, disease course). Table 20.2 summarizes dosage recommendations for lithium salts.

The **titration** of lithium dosage should only be undertaken **on an inpatient basis**. For adolescents, it is recommended that therapy commence gradually, with 8 mmol/L per day (e.g., 300 mg/day lithium carbonate) as initial dosage, increased every 3–4 days by 8 mmol/L per day (=300 mg lithium carbonate).

For children who weigh less than 25 kg, the initial dosage should lie between 4 and 8 mmol/L per day (=150–300 mg/day lithium carbonate). The final daily dosage can be c. 0.8 mmol/L per kg body weight (= c. 30 mg/kg body weight lithium carbonate); serum levels are decisive and must be especially tightly monitored during the titration phase (see Chap. 7). The dosage should be administered as two doses (one third in the morning, two third in the evening).

For the **combination** of lithium salts and antipsychotics, it is recommended that a comparatively low antipsychotic dosage be employed and that the serum lithium level be maintained below 1 mmol/L. Although serum levels provide the key dosage point of reference, the clinical symptoms are ultimately decisive in this regard (see Sect. 7.4.1).

Following discontinuation of lithium medication, its efficacy may be reduced in any renewed therapy, increasing the risk of relapse. If medication with lithium salts is to be terminated, the dosage should be reduced in stages over a period of months.

The dosage of the mood-stabilizing antiepileptic medications carbamazepine and valproate should be guided by serum levels. Recommended dosages are summarized in Table 20.4.

20.4.2.2 Antipsychotics

The recommended dosages for antipsychotics are analogous to those for the treatment of schizophrenia (see Chap. 25). For the combination of lithium salts and antipsychotics, the dosage of the antipsychotic should be relatively low and the lithium serum level maintained below 1 mmol/L.

20.4.3 Recommendations for Switching Medication

Therapy resistance in long-term therapy can be assumed if at least five episodes have occurred,

Table 20.4 Recommended dosages for the mood-stabilizing antiepileptics carbamazepine and valproate

Carbamazepine	Serum level 4–12 µg/mL Initial dosage for children 50–100 mg/day, for adolescents 100–200 mg/day, dosage increased by 100–200 mg at intervals of about 2 days to a level of 600–1,200 mg/day (15–30 mg/kg body weight), divided into three individual doses Onset of action after 7–14 days Slow-release preparations are preferable
Valproate	Serum level 50–100 µg/mL Initial daily dosage 10 mg/kg body weight, dosage increased every 3 days to a level of 600–1,500 mg/day (c. 20 mg/kg body weight) Onset of action after 3–10 days

From Bowers (1998)

including two in the past 3 years. Switching from lithium salts to carbamazepine or valproate products should be undertaken gradually over several months, with overlapping administration of lithium and of its replacement. For the switch from carbamazepine to valproate, a more rapid transition is recommended, depending upon valproate serum concentrations.

20.4.4 Special Situations

20.4.4.1 Recommendations for Rapid Cycling Bipolar Disorder

Antidepressants should **not be employed**, given their mania-inducing effects (tricyclic antidepressants > SSRIs). Treatment with valproate products or olanzapine is to be preferred, possibly in combination (Fountoulakis et al. 2012). Where treatment of depressive episodes is the priority, lamotrigine as a mood stabilizer should be considered (Chang et al. 2006).

20.4.4.2 Recommendations for Relapsing Manic Episode

Phase prophylaxis should be undertaken as for bipolar affective disorders, whereby clinical experience is limited in this regard. Olanzapine can be recommended for relapsing manic episodes if it has proved effective in the treatment of the manic symptoms.

20.4.4.3 Recommendations for Bipolar Depression

On the basis of the current state of knowledge, we recommend that **adjunct treatment with** an **antidepressant** should **not** be undertaken in cases with mild depression, in order to avoid the risk of induction of a manic episode or of a rapid phase change. If there already is a phase prophylaxis therapy, the dosage and serum level should be optimized. If there is no phase prophylaxis therapy, it should be considered if one is indicated and probably should be started already in the depressive phase. Lamotrigine proved in an open-label, prospective study to be effective in the treatment of 20 adolescents with bipolar depression (Chang et al. 2006). In the treatment of children and adolescents, also quetiapine as monotherapeutic agent is advisable. Severe depressive symptoms should be treated with an adjunct antidepressant (preferably an SSRI).

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Obsessive–Compulsive Disorders 21

Christoph Wewetzer and Susanne Walitza

Contents

C. Wewetzer, MD (✉)
Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Florentine-Eichler-Str. 1, 51067 Köln, Germany
e-mail: wewetzerc@kliniken-koeln.de

S. Walitza, MD
Department of Child and Adolescent Psychiatry, University of Zurich, Neumuensterallee 9, PO Box 1482, 8032 Zurich, Switzerland
e-mail: susanne.walitza@kjpdzh.ch

21.1 Definition, Classification, and Target Symptoms

Obsessive–compulsive disorders (OCD) are recurrent and persistent thoughts, behavioral patterns, ideas, and impulses/urges that impose themselves against internal resistance and are experienced by the patient as senseless (for specification of insight in the disorder, please see below), excessive, or distressing. According to the International Classification of Diseases, 10th revision (**ICD-10**), OCD can be **divided** into (World Health Organization 1996):

- Predominantly obsessional thoughts
- Predominantly compulsive acts
- Or both

Obsessive thoughts are ideas, images, or impulses that impose themselves upon patients against their will, with which they are repeatedly occupied. It usually involves obsessive fears that can be focused on contamination, bacteria, infections, symmetry, precision, or the collection of objects. Alternatively, it may involve images and ideas of an aggressive, sexual, or religious nature that force their way into consciousness. In contrast to psychotic symptomatology, obsessive thoughts are experienced as being the individual's own thoughts and not imposed from outside or delivered by other persons or other beings.

Compulsive acts are frequently repeated, stereotyped acts, the performance of which is generally very difficult to suppress by the affected person, although the acts are subject to voluntary control.

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If a compulsive act cannot be realized, the person experiences an increase in tension and anxiety.

In children and adolescents, obsessional thoughts and compulsive acts occur together in the majority of cases. These symptoms are the **targets of pharmacotherapy**.

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (**DSM-5**), patients with OCD may be independent of age – good, poor, or no insight in the senselessness of their obsessions and compulsions; though their lives may be consumed by them, patients find themselves unable to stop or resist them (American Psychiatric Association 2013). Young children may be not able to articulate the aims of the obsession or compulsion.

Three major **changes are introduced** in the DSM-5 regarding OCD (300.3): The first change is that OCD will be classified in the diagnostic category "obsessive–compulsive and related disorders" including "obsessive–compulsive disorder" and, as related disorders, "body dysmorphic disorder" (300.7; F 45.22), "hoarding disorder" (300.3; F42), "hair-pulling disorder" (trichotillomania 312.39; F 63.2), excoriation ("skin-picking disorder" 698.4; L98.1), "substance/medication-induced obsessive–compulsive and related disorder" (F14,F15, F19), "obsessive–compulsive and related disorder due to another medical condition" (294.8; F06.8), "other specified obsessive–compulsive and related disorder", (300.3; F42.8), and "unspecified obsessive–compulsive and related disorder" (300.3; F 432.9). The second important change is that clinicians have to specify the degree of insight into the symptomatology (good/fair, poor, or absent insight). The third change is that clinicians have to specify whether the individual has a current or past history of tic disorders, this will be classified as a tic-related obsessive–compulsive disorder (American Psychiatric Association 2013; Thomsen 2013).

21.2 Therapeutic Framework

The treatment of OCD in children and adolescents is based on a thorough **assessment** of the **severity of OCD** and the presence of **comorbid disorders**. Multimodal treatment programs have proved useful in clinical practice in the treatment of OCD in children and adolescents. The evidence-based treatment of OCD in children and adolescents includes psychoeducation and reduction of psychosocial stress, cognitive behavioral psychotherapy (CBT), and medication (AACAP Official Action 2012; Thomsen 2013).

According to the practice parameters for the assessment and treatment of OCD (AACAP Official Action 2012), the **first choice** of treatment in children and adolescents with mild or moderate cases of OCD is to start with **cognitive behavioral therapy** (CBT). The most important behavioral therapeutic method within the CBT is exposure and response prevention. The findings of meta-analyses of randomized controlled and open trials of CBT (O'Kearney et al. 2006; Freeman et al. 2014) indicate that this type of treatment is highly effective. **Combination** of psychotherapy, particularly CBT and pharmacological treatment strategies with selective serotonin reuptake inhibitors (**SSRIs**) were especially effective in the first controlled investigations (Pediatric OCD Treatment Study [POTS] Team 2004). Conversely among children and adolescents with OCD and partial response to SSRI use, the addition of CBT to medication management compared with medication management alone resulted in a significantly **greater response rate** (Franklin et al. 2011). Improvement after CBT seems to be stable in the long term. Patients examined 3 years after treatment were even found to have a further, mild improvement of their symptoms (Shalev et al. 2009).

For **moderate and severe OCD**, if the motivation for behavioral therapeutic treatment is not yet developed or **CBT** is **not available** (that is the case in a considerable proportion of patients, AACAP Official Action 2012), **medication** is **indicated** in addition to CBT. Furthermore, pharmacological treatment is often required to render the behavioral therapeutic approach feasible. At least comorbid disorders influence the effects of medication. Children with OCD and tic disorders responded insufficiently to CBT or sertraline alone, but on combination or need more frequent augmentation with antipsychotics (March et al. 2007; McDougle et al. 2000). Finally, a proportion of adolescent

patients suffers from chronic symptomatology and requires medicinal support in order to continue school education or occupational training (Stewart et al. 2012; Walitza et al. 2011).

21.3 Choice of Pharmacotherapy

SSRIs and **clomipramine** were found to be significantly **superior to placebo** in different meta-analyses including randomized and controlled pharmacological therapy studies in children, adolescents, and adults (Abramowitz et al. 2005; Geller et al. 2003; Gentile 2011; Watson and Rees 2008). A cochrane analysis (Soomro et al. 2008) including data form 17 studies and 3,097 adults with OCD found that SSRIs as a group are more effective than placebo in reducing the symptoms of OCD between 6 and 13 weeks posttreatment, which was measured according to the Yale–Brown Obsessive Compulsive Scale (Y–BOCS). However, there are differences between the adverse drug reactions (ADRs) of individual SSRI drugs.

Although clomipramine is more potent as a medication than **SSRIs**, the latter are regarded as the first-choice medications in OCD because of their **more favorable ADR profiles** (AACAP Official Action 2012; Blier et al. 2006; Stewart et al. 2012). For further information regarding SSRIs and clomipramine (including age- and indication-specific aspects of approval status, efficacy studies, recommended dosages, ADRs, medication interactions, contraindications, and special precautions), please refer to Chap. 4.

Fluoxetine and **fluvoxamine** are **approved** by the US Food and Drug Administration (FDA) for the treatment of children and adolescents with OCD (≥7 years). **Sertraline** is labeled for this indication from 6 years up. From the tricyclic antidepressants, only **clomipramine** has been FDA-approved for OCD from the age of 10 years and older.

21.3.1 SSRIs as First-Line Agents

The pharmacological treatment of children and adolescents with SSRIs is well established. There have been numerous placebo-controlled studies that confirmed the efficacy and safety of fluoxetine, fluvoxamine, paroxetine, and sertraline in the therapy of OCD in children and adolescents (see Geller et al. 2003; Gentile 2011 for review). In most studies, treatment success was measured with the Children's Y–BOCS (CY–BOCS, Scahill et al. 1997) and was defined by a 25 or 35 % reduction of the CY–BOCS score. A recent 6-week randomized, double-blind, fixed-doses (20 mg) trial of fluoxetine versus citalopram in 29 children and adolescents with OCD showed that citalopram is as safe and effective as fluoxetine (Alaghband-Rad and Hakimshooshtary 2009).

In an analysis of controlled studies of the employment of SSRIs for OCD in children and adolescents (Geller et al. 2003; Watson and Rees 2008), the following ADRs were most frequently reported: gastrointestinal problems, restlessness, agitation, insomnia, headache, and vertigo.

SSRI medication has been described as associated with **suicidal thinking** or behavior among youths (Bridge et al. 2007). The pooled absolute risk difference between youths with OCD receiving SSRIs or placebo was 0.5 %. But up to now no suicides were observed in any pediatric randomized controlled trial regarding SSRIs. Patients and parents should be informed about the possibility of an increase of suicidal behaviors, self-harm, and hostility in the first weeks of treatment with SSRIS (National Institute for Health and Clinical Excellence 2005). Comparing studies on SSRIs in anxiety disorders and OCD with studies on depressive patients, suicidal behaviors are much rarer, but regarding the comorbidity of OCD and depression, we recommend to consider the FDA recommendation regarding antidepressive treatment strategies anyway.

21.3.2 Clomipramine as Second-Line Medication

The efficacy and safety of clomipramine in the therapy of OCD in children and adolescents have been demonstrated in randomized controlled studies (Gentile 2011). Clomipramine is superior (according to its effect size) in children and adolescents compared to the SSRI's fluoxetine, fluvoxamine, and paroxetine (Geller et al.

2003). Nevertheless, due to ADRs, clomipramine is never a first-line medication in children or adolescents with OCD.

Prior to the use of clomipramine, a family cardiac and non-febrile seizure history should be obtained in addition to lipid profile, liver and kidney enzymes, and examination with auscultation of the heart, pulse, and blood pressure. In addition, a baseline electrocardiogram should be requested (AACAP Official Action 2012).

The most frequent ADRs associated with clomipramine (see also Chap. 4) in children and adolescents with OCD were dry mouth, sleepiness, vertigo, exhaustion, tremor, headache, and constipation (DeVeaugh-Geiss et al. 1992).

21.4 Treatment Strategies Using Medication

21.4.1 Monotherapy

The SSRI choice should include profiles of ADRs, potential interaction with other medications, comorbidity, and a family history of positive response to specific SSRIs. As the onset of action of SSRIs and clomipramine can be expected only after 4–10 weeks, dependent upon adequate dosage, **therapeutic success** can be evaluated only **after about 10–12 weeks** of treatment using the highest tolerated dose within the dosage guidelines (Table 21.1). Only when an effect is not evident after this period, or if ADRs occur, the change to another SSRI is indicated. After second nonresponse or ADRs, a change on clomipramine or SSRI augmentation should be considered.

Procedure for dosage titration of SSRIs (sertraline as example). At the beginning of the therapy, children receive a morning dose of 12.5 mg; adolescents can begin with 25 or 50 mg. The dosage is then elevated in weekly steps of 25 mg until improvement of OCD symptomatology can be seen. Ongoing monitoring of ADRs is required. The maximum daily dosage for children lies between 50 and 100 mg, and for adolescents between 75 and 200 mg.

Clomipramine dosage (Table 21.1), like that of the SSRIs, should be slowly increased from a low initial dosage (children 6.25–10 mg; adolescents 25 mg, **NB**: hasty dosage increases can trigger seizures). The dosage can then be increased, according to the clinical effect, every 4–5 days to about 200 mg, depending upon age and tolerability; up to 3 mg/kg body weight is recommended as a guide (Blier et al. 2006). According to our own experiences, however, considerable improvement in OCD symptomatology can frequently be achieved even in adolescents at much lower dosages (for example, 75 mg). Because of its longer elimination half-life, a single morning or evening dose is sufficient once steady state levels are reached. The transition to slow release preparations has also proved effective.

21.4.2 Augmentation Strategy

According to the Practice Parameter for the Assessment and Treatment of Children and Adolescents with Obsessive-Compulsive Disorders (AACAP Official Action 2012), medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy. Failure of adequate trials of at least two SSRIs or one SSRI and a clomipramine trial, and a failure of adequately delivered CBT would constitute treatment resistance.

Adding clomipramine to an **SSRI** may be helpful. The rationale is to combine the serotonergic effects of each while minimizing ADRs across different drug classes. There are only scattered positive reports for this combination therapy in children and adolescents. However, in adults a double-blind, placebo-controlled trial comparing the efficacy of adding clomipramine to a treatment regimen consisting of fluoxetine demonstrated that the clomipramine–fluoxetine combination is a safe and effective treatment for fluoxetine nonresponders, especially those who cannot tolerate high doses of fluoxetine (Diniz et al. 2011).

It should **be noted** that the SSRIs differ with respect to their **pharmacokinetics**, in some cases markedly, so that an intensification of ADRs is also

Table 21.1 Dosage recommendations for the pharmacotherapy of obsessive–compulsive disorder with antidepressants (AACAP Official Action 2012; see also Table 4.5)

Antidepressant	Initial daily dosage (mg)		Typical mean dose range (mg)
	Preadolescents	Adolescents	
Citalopram	2.5–10	10–20	10–60
Clomipramine	6.25–25	25	50–200
Fluoxetine	2.5–10	10–20	10–80
Fluvoxamine	12.5–25	25–50	75–150
Paroxetine	2.5–10	10	10–60
Sertraline	12.5–25	25–50	50–200

possible (see Chap. 4). In addition, SSRIs affects the metabolism of clomipramine by inhibition of the cytochrome P_{450} (CYP) system. Clomipramine can be added to a small dose of fluvoxamine (a CYP1A2 inhibitor) in treatment-resistant patients (25–75 mg/day; AACAP Official Action 2012).

Cave! Due to inhibition of CYP2D6, combination of clomipramine and fluoxetine or paroxetine can lead to toxic serum dosage levels of clomipramine. Advice regarding the procedure for changing medication is found in Chap. 4.

If the combination of clomipramine and an SSRI does not lead to an improvement of symptomatology, treatment with **augmentation therapy using antipsychotics** may be helpful. High-quality randomized controlled trials using antipsychotics have been performed in adults with OCD and are summarized in comprehensive meta-analyses (Bloch et al. 2006; Dold et al. 2013), but no controlled data exists for children. There are only some case reports and open-label trials. However, expert consensus has suggested that some children with treatment-resistant OCD may benefit from judicious antipsychotic augmentation, particularly children with tic disorders, poor insight, pervasive developmental disorder symptoms, and mood instability (AACAP Official Action 2012). In adults, significant efficacy was identifiable only for risperidone but not for quetiapine and olanzapine; the results regarding aripiprazole and haloperidol were inconsistent (Dold et al. 2013).

Based on the favorable risk/benefit ratio, **risperidone** at dosages of less than 3 mg/day can be considered as the agent of first choice and should be preferred to quetiapine and olanzapine. However, currently the number of studies is not enough; aripiprazole seems to be preferable to quetiapine and olanzapine (Manusco et al. 2010). Monitoring should include at a minimum regular weight controls, ADRs, lipid profiles, and serum glucose.

21.4.3 Duration of Pharmacotherapy

The duration of pharmacotherapy can be expected to be long. A trial withdrawal – even if therapy has been very successful – should generally not be considered before 6–12 months. Most patients require 12–18 months of pharmacological treatment (AACAP Official Action 2012; Cook et al. 2001; Leonard et al. 1989). Withdrawal of medication should be very gradual (e.g., for sertraline at 150 mg/day, the dosage should be reduced every 2 weeks by 25 mg).

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Personality Disorders

22

Marcel Romanos, Christoph Wewetzer,
and Klaus Schmeck

Contents

M. Romanos, MD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: romanos@kjp.uni-wuerzburg.de

C. Wewetzer, MD
Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Florentine-Eichler-Str. 1, 51067 Köln, Germany
e-mail: wewetzerc@kliniken-koeln.de

K. Schmeck, MD
Child and Adolescent Psychiatry Hospital, University of Basel, Schaffhauserrheinweg 55, 4058 Basel, Switzerland
e-mail: klaus.schmeck@upkbs.ch

22.1 Definition, Classification, and Target Symptoms

Personality disorders (PDs) are defined as an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture (American Psychiatric Association 2013). This disorder is expressed as the impairment of several aspects of personality, including identity, affect, cognition, and social and personal relationships. PDs develop during childhood and adolescence and can have a lifelong course. They are manifested in typical form in early adulthood.

Longitudinal studies reveal that diagnoses of PDs are less stable than expected (Hopwood et al. 2009). In comparison to adult populations, the stability of PDs in adolescence is on a similar level (overview in Schmeck and Schlüter-Müller 2012). Both major classification systems enable a diagnosis prior to the age of 18 years. While the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) required a minimum age of 16 years (exception: antisocial PD from 18 years), there is **no age limit** defined in **DSM-5** (American Psychiatric Association

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2013). Instead according to DSM-5's general criteria of PDs, it is defined that "… the individual's personality trait expression are not better understood as normal for an individual's developmental stage …" (criterion G; American Psychiatric Association 2013).

Diagnosis according to the International Classification of Diseases, 10th revision (**ICD-10**; World Health Organisation 1996) is possible when the diagnostic criteria are fulfilled prior to the 18th birthday and the symptomatology is already recognizably persistent, continuous, and not situation-dependent (Salbach-Andrae et al. 2008; Schmeck and Schlüter-Müller 2009). In the German Guidelines on PDs (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften 2011), it is stated that PDs cannot be reliably diagnosed before the age of 14. The Australian Guidelines (National Health Medical Research Council 2012) recommend that, after appropriate assessment, adolescents aged 12–18 years who meet the diagnostic criteria of a borderline PD should get the diagnosis.

ICD-10 provides catalogues of features for the individual PDs, with defined inclusion and exclusion criteria that categorize each type in an exemplary manner. The DSM-IV cluster classification (the DSM-IV-TR classification system of PDs has been kept in **DSM-5** without changes) is more practical for pharmacotherapeutic purposes, even if secure data relevant to children and adolescents is not available for all PDs. This classification **distinguishes**:

- **Paranoid-schizoid PD** (cluster A; ICD-10, F 60.0; DSM-5, paranoid PD 301.0; schizoid PD, F 60.1;301.20; schizotypal PD, F 21; 301.22). This includes the paranoid, schizoid, and schizotypal PDs. **Target symptoms are** lack of affect and emotional coldness, bizarre and excentric behavior, and mistrust against other persons, often combined with paranoid or magical ideas. Affective lability in the sense of emotional outbursts, anger, rage, and violence and a chronic social interaction disorder are also typical. The demarcation from the borderline type of emotionally unstable PD can sometimes be difficult.
- **Antisocial, emotionally unstable, histrionic, and narcissistic personality PDs** (cluster B; antisocial PD, F 60.2; 301.7; borderline PD, F60.3; 301.83; histrionic PD, F 60.4; 301.50; narcissistic PD, F 60.81; 301.81). **Target symptoms are** affective impulsivity with uncontrolled outbursts of anger and rage and pronounced mood swings. Self-injury, suicide attempts, and threatening behavior are typical. Self-esteem is often marked by feelings of anger, shame, and inferiority. Problems of distance and proximity in social interactions are constant.
- **Anxious-avoidant, dependent, and compulsive** (anankastic) **PDs** (cluster C; avoidant PD, F 60.6; 301.82; dependent PD, F 60.7; 301.6; obsessive-compulsive PD, F 60.5; 301.4). There are very few data regarding cluster C PDs with regard to adolescence. **Target symptoms are** the constant tension and anxiety as well as the persistent feeling of helplessness and dependence with frequent separation anxiety. The target symptoms of compulsive PDs are the excessive assiduity and deficient flexibility as well as "passive aggression." A further target symptom is the sensitivity to criticism and rejection.

22.2 Therapeutic Framework

Diagnostic precondition is a **multiaxial diagnostic procedure**. The criteria for a particular PD must be fulfilled independent of age and situation. Dissocial/antisocial PDs of adulthood are frequently preceded by a conduct disorder in childhood or adolescence; the high comorbidity of social phobia in the anxious-avoidant PD should also be noted. Presentation of other mental disorders is common in all PDs.

A basic principle in the therapy of PDs is that a multimodal procedure be adopted (Herpertz and Wenning 2003). Due to the lack of studies in adolescents, guidelines for the treatment of PDs are based predominantly upon data from studies in adults (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften 2011; Herpertz et al. 2007; National Institute for Health and Clinical Excellence 2009; National Health Medical Research Council 2013). There is a consensus in all guidelines that

treatment with **drugs** should **not** be **first line** as there is no evidence that the core symptoms of PDs can be influenced by pharmacological agents. It is recommended that patients with PDs should be provided with structured psychological therapies that are specifically designed for this kind of disorder.

Structured therapeutic manuals are superior to "open" therapeutic approaches (Bateman and Fonagy 2000; Stoffers et al. 2012). Behavioral modification and educational procedures are the foremost components of therapy for the majority of patients, while pharmacological treatment is frequently to be regarded as an ancillary and temporary measure (Perry et al. 1999).

A number of reviews on the pharmacotherapy of PDs have been published in the last years (Bellino et al. 2011; Ingenhoven et al. 2010; Lieb et al. 2010; Paris 2011; Quante et al. 2008; Ripoll et al. 2011; Triebwasser and Siever 2007) that mostly focus on borderline PD. All psychopharmacological agents discussed in this chapter are employed in children and adolescents outside the age groups and symptoms for which they are approved (off-label use: see Sect. 2.1.2) so that the special conditions discussed in Sect. 2.1.4 must be observed.

The **indication** for **pharmacological therapy** cannot categorically be excluded in any PD. It is particularly indicated in:

- Paranoid-schizoid PD (cluster A), if perception and capacity for emotional experience are significantly impaired or pronounced aggression is evident.
- Antisocial, emotionally unstable, narcissistic, and histrionic personality PDs (cluster B), if marked problems in impulse and aggression control are evident. This is, for instance, the case where there is a major threat of harm to others or to the patient themselves (suicidality), severe self-harming behaviors, and psychiatric comorbidity (such as depression).
- Anxious, dependent, and compulsive PDs, if pronounced permanent tension and persistent, usually diffuse, anxiety are prominent symptoms.
- Compulsive PDs, in case of excessive conscientiousness, extreme inflexibility, and aggression.

22.3 Choice of Pharmacotherapy

The available empirical data regarding therapy with psychopharmacological agents in PDs during adolescence is meager. The efficacy of the therapeutic procedures discussed in this chapter has almost exclusively been investigated in adults. In this respect the following discussion should be understood as a rough guide, and the specifics of pharmacological treatment should be based primarily upon the predominant symptomatology, in accordance with the advice offered in Sect. 22.4.

22.3.1 Paranoid, Schizoid, and Schizotypal Personality Disorders (Cluster A)

22.3.1.1 Antipsychotics

For the schizotypal PD, antipsychotics are chiefly prescribed. Smaller open-label studies but also placebo-controlled investigations have investigated the second-generation antipsychotics olanzapine and risperidone and indicated efficacy at low dosages; in contrast, there have only been open-label studies of the first-generation antipsychotics (Herpertz et al. 2007; Keshavan et al. 2004; Kirrane and Siever 2000; Koenigsberg et al. 2003; Schultz et al. 1999). There is some evidence that pharmacotherapy with mood stabilizers like carbamazepine, lamotrigine, lithium salts, topiramate, or valproate products is associated with greater improvement in global functioning compared with antipsychotic treatment (Ingenhoven et al. 2010).

Antipsychotics would seem the most suitable agents for the paranoid and schizoid PDs in light of their psychosis-like symptomatology. First-generation antipsychotics, such as haloperidol, thioridazine, and pimozide are possibly effective (Coccaro 1993; Goldberg et al. 1986), but second- and third-generation antipsychotics are the first-choice agents because of their more favorable adverse drug reaction (ADR) profile (evidence level C, based on nonrandomized studies).

22.3.1.2 Antidepressants

In a double-blind, placebo-controlled study of patients with various PDs, the selective serotonin reuptake inhibitor (SSRI) fluoxetine exerted a

positive effect upon impulsivity and aggression (Coccaro and Kavoussi 1997). In a further open-label study, in which only four patients with "pure" schizotypal PD participated, fluoxetine exercised a positive effect upon anxiety, depression, and other symptoms. There is no evidence for efficacy of tricyclic antidepressants in paranoid and schizoid PD (Herpertz et al. 2007).

In summary, antidepressants should only be considered in cases presenting comorbid depressive symptoms, whereby SSRIs are to be preferred. Overall, the available evidence does not justify recommendation of antidepressants for cluster A-PDs.

22.3.2 Antisocial, Emotionally Unstable, Narcissistic, and Histrionic Personality Disorders (Cluster B)

The majority of studies concerning the pharmacological treatment of cluster B-PDs are focused on borderline PD. In cases of antisocial PD, one should be alert to the possibility of comorbid attention deficit/hyperactivity disorder (ADHD), which should always be treated first where presented (see Chap. 12).

22.3.2.1 Antipsychotics

Older data regarding low-potency antipsychotics is available from empirical investigations during many years of clinical experience. Double-blind placebo-controlled studies of first-generation (including haloperidol) as well as second- and third-generation antipsychotics (olanzapine, quetiapine, aripiprazole) in borderline PD have been published. Four double-blind controlled randomized studies provided in sum no evidence for convincing efficacy of first-generation antipsychotics in borderline PD (e.g., Soloff et al. 1993; review Herpertz et al. 2007). Five studies of second- and third-generation antipsychotics (four with olanzapine, one with aripiprazole), however, found that they were consistently **effective** with regard to various **aspects of psychopathology** (Bogenschutz and Nurnberg 2004; Herpertz et al. 2007; Nickel et al. 2006; Soler et al. 2005; Zanarini and Frankenburg 2001; Zanarini et al. 2004). In contrast to olanzapine, aripiprazole appears to not lead to notable weight gain (Herpertz et al. 2007; Nickel et al. 2006). In further open-label studies, positive effects were also found for other second-generation antipsychotics (clozapine, quetiapine, risperidone) in borderline patients (Benedetti et al. 1998; review Quante et al. 2008).

The **efficacy** of second- and third-generation antipsychotics is evident even **at low** to moderate **daily dosages** (aripiprazole 15 mg, clozapine 40–250 mg, olanzapine 3–10 mg, quetiapine 175–400 mg, risperidone 3.3 mg), whereby the efficacy in long-term therapy is difficult to evaluate because of the lack of data (Herpertz et al. 2007; Quante et al. 2008). **Ziprasidone** (40–200 mg) was **not superior to placebo** in a randomized, double-blind, placebo-controlled study ($N=60$; Pascual et al. 2008). The administration of antipsychotics reduces affective tension and aggression, while anxious and depressive behaviors are also favorably influenced (evidence level B, requiring the publication of at least one controlled, randomized study).

22.3.2.2 Antidepressants

SSRIs have been increasingly employed in recent years with success, particularly as the mood-stabilizing effects of these agents are accompanied by an influence upon impulse control disorders, on aggression directed against self and others and also on comorbid eating disorders. The efficacy of **fluoxetine** and **fluvoxamine** was demonstrated in several controlled studies, if only with small case numbers (evidence level C; e.g., Coccaro and Kavoussi 1997; Salzman et al. 1995; meta-analysis: Nosé et al. 2006). **Paroxetine** significantly reduced the risk of suicidal behavior during a twelve-month period (Verkes et al. 1998). Fluvoxamine led to a significant reduction of mood swings (Simpson et al. 2004). In a randomized, but not placebo-controlled study, the effect of the combination of fluoxetine and olanzapine was superior to that of fluoxetine only and

equivalent to the effect of olanzapine alone (Zanarini et al. 2004). The issue of whether SSRIs can induce suicidal thoughts or suicidality is discussed in Sect. 4.4.1.2. In subjects with a concomitant affective disorder, SSRIs are effective in decreasing severity of depressed mood, anxiety, and anger (Bellino et al. 2011). However, effects on impulsive behaviors are uncertain.

Positive findings were also reported in an open-label study of venlafaxine, a selective serotonin and noradrenaline reuptake inhibitor (Markovitz and Wagner 1995). Despite evidence for the efficacy of phenelzine, severe ADRs have rendered the use of irreversible, nonselective monoamine oxidase (MAO) inhibitors in children and adolescents obsolete (Herpertz et al. 2007).

Tricyclic antidepressants are similarly **not recommended** for children and adolescents, particularly as their poor ADR profile is not matched by proof of their efficacy. Tricyclic antidepressants can even contribute in some cases to marked exacerbation of symptoms (Soloff et al. 1986). The risk of accidental or intentional overdosage and intoxication means that this class of antidepressant is contraindicated in impulsive-suicidal patients. Other antidepressants (mirtazapine, reboxetine) also appear to worsen the symptomatology (Quante et al. 2008).

22.3.2.3 Mood Stabilizer

Mood stabilizers (see Chap. 7) are chiefly employed in the treatment of impulse control disorder and impulsive aggression and also for severe mood swings. The anti-aggressive effects of lithium salts in children with conduct disorders, for example, have been confirmed by a randomized, double-blind, controlled study (evidence level B; Malone et al. 2000; review Gerlach and Warnke 2010). An open-label study did not support the efficacy of lithium salts in borderline PD (Links et al. 1990). Further, the ADRs associated with the narrow therapeutic range of lithium salts have consequences for compliance in this difficult patient group. The available **evidence** is **insufficient** to justify recommendation of **lithium salts** for these PDs.

A few clinical studies have confirmed the efficacy of mood stabilizers in the treatment of aggression in personality disorders. The evidence regarding carbamazepine is inconsistent (Cowdry and Gardner 1988; De la Fuente and Lotstra 1994), while an open study found that oxcarbazepine (1,200–1,500 mg/day) was effective (Bellino et al. 2005). Valproic acid has repeatedly and consistently proved to be effective, as has topiramate (evidence level C; e.g., Hollander et al. 2003). Crossover design and placebo-controlled studies have shown that lithium salts, phenytoin, and oxcarbazepine are effective in the reduction of aggressive behaviors in prison inmates with a high rate of antisocial personality disorders (review Gerlach and Warnke 2010; Triebwasser and Siever 2007).

Results for other **mood-stabilizing anticonvulsants** from randomized, placebo-controlled studies also suggest their **efficacy in impulse control disorders**, whereby the findings for carbamazepine and lamotrigine are inconsistent, while the data for valproate at a dosage of 500–2,250 mg/day (evidence level C) and topiramate at a dosage of 250 mg (evidence level C) appear more convincing (see for reviews Cardish 2007; Herpertz et al. 2007; Quante et al. 2008; Triebwasser and Siever 2007). The data regarding long-term therapy is inadequate. In emotionally unstable personality disorders, the target symptomatology can be quite diverse. With regard to the pharmacological therapy of aggressive-impulsive syndromes, please refer to Chap. 9.

As one of the results of their systematic review of pharmacological interventions in cluster B-PDs, Bellino et al. (2011) describe the convincing evidence of mood stabilizers like topiramate, valproate, or lamotrigine to treat symptoms like affective dysregulation or impairment of impulse control.

22.3.2.4 Miscellaneous

Theoretical considerations regarding the efficacy of opioid receptor antagonists have thus far not been convincingly confirmed (Triebwasser and Siever 2007).

In clinical practice, **benzodiazepines** are employed for acute affective outbursts, suicidality, and prominent manifestations of anxiety. As borderline PD is associated with suicide in 10 % of cases, suicidality is a frequent indication for pharmacological intervention (Paris 2002).

Diazepam and lorazepam are typically administered in such cases. Benzodiazepines have anxiolytic, sleep-promoting, and aggression-reducing properties (see Sect. 6.4.1). It should be noted, however, that benzodiazepines not infrequently also trigger paradoxical responses, expressed as affective outbursts and aggressive impulses.

> Because of the risk of dependence, **benzodiazepines** should only be employed as short-term "**emergency medication**" (see Sect. 6.4.1). Frequently occurring affective crises with self-harming behavior in borderline PDs should not be treated as a matter of course or permanently with benzodiazepines, especially as the risk of addiction is elevated in this patient group. In cases of acute tension states or aggressive outbursts, low- and medium-potency antipsychotics should be preferred or even long-term medication with, for instance, second- or third-generation antipsychotics (see Chap. 9).

There is evidence from two double-blind randomized controlled trials (Zanarini and Frankenburg 2003; Hallahan et al. 2007) that supplementary omega-3 fatty acids can be useful to treat affective symptoms and impulsive-behavioral dyscontrol in borderline PD patients. Both studies showed a significant reduction of depressive symptoms in borderline PD patients, and there was also a significant reduction of suicidality in the 49 borderline PD patients of the Hallahan et al. (2007) study.

22.3.2.5 Summary of Pharmacological Treatment of Cluster B-Personality Disorders

While there is only rare empirical evidence for the pharmacological treatment of antisocial, narcissistic, or histrionic PDs, evidence for the treatment of cluster B-PDs is on a much higher level and is integrated in the current guidelines. A Cochrane review (Lieb et al. 2010) and a systematic review of the literature (Bellino et al. 2011) come to the conclusion that symptoms of affect dysregulation and deficient impulse control of cluster B-PDs can successfully be treated with the following pharmacological agents:

- Second- and third-generation antipsychotics: aripiprazole and olanzapine
- Mood-stabilizing anticonvulsants: lamotrigine, topiramate, and valproate

There is additional evidence for the beneficial effects of omega-3 fatty acids on the reduction of affective symptoms and impulsive-behavioral dyscontrol, and of SSRIs on the reduction of depressed mood, anxiety, and anger in borderline PD patients with comorbid affective disorders (Bellino et al. 2011). Evidence of pharmacotherapy in the treatment of cluster B-PDs' symptoms is summarized in Table 22.1.

22.3.3 Anxious, Dependent, and Obsessive-Compulsive (Anankastic) Personality Disorders (Cluster C)

The high comorbidity of cluster C-PDs with depressive disorders means that a primary **antidepressive therapy** with SSRIs is advisable. These agents also reduce chronic tension, inquietude or uneasiness, and feelings of helplessness and dependence. There have been **no controlled studies** of the therapy of cluster C-PDs. Although the data is inadequate with respect to the indication of PDs, findings from a number of randomized, placebo-controlled studies indicate a high efficacy for SSRIs in the treatment of anxiety in social phobia and other anxiety disorders (evidence level A: efficacy confirmed by randomized double-blind placebo-controlled studies with sufficiently high case numbers and appropriate design; review Herpertz et al. 2007). Citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline have been investigated. The same applies to venlafaxine. **Fluoxetine** is the **best-investigated** SSRI in children and adolescents, with only a small probability of suicidal ideation and actions developing (see Sect. 4.4.1.2).

Although the selective, reversible MAO-A inhibitor brofaromine has proved efficacious (Fahlen et al. 1995), it is rarely employed in children and adolescents. The same applies to tricyclic antidepressants.

Table 22.1 Evidence of pharmacotherapy in the treatment of cluster B-personality disorders' (BPD) symptoms

Effect on	Overall	Aripiprazole	Carbamazepine	Valproate	Fluvoxamine	Haloperidol	Lamotrigine	Olanzapine	Phenelzine	Topiramate	Ziprasidone
BPD symptoms	NS	–	–	–	✓[1]	NS	NS[1]	✓	NS	–	NS[1]
General psychopathology	✓	✓[1]	NS[1]	–	–	NS	–	✓	NS	✓[1]	NS[1]
Anger	✓	✓[1]	–	NS	NS[1]	–	✓[1]	NS	–	NS	NS[1]
Hostility	✓	✓[1]	NS[1]	NS[1]	–	NS	–	✓[1]	✓	✓[1]	NS[1]
Irritability	✓	–	–	✓[1]	–	–	–	✓	–	–	–
Depression	✓	✓[1]	NS[1]	✓	–	×	–	NS	NS	NS[1]	NS[1]
Anxiety	✓	✓[1]	NS[1]	–	–	NS[1]	–	NS[1]	NS[1]	✓	NS[1]
Suicidality and self-harm	NS	–	–	NS[1]	–	–	–	NS	–	–	NS[1]
General functioning	✓	–	NS[1]	–	–	✓	–	✓	NS	–	–
Interpersonal and social functioning	✓	✓[1]	NS[1]	✓[1]	–	–	–	NS	–	✓[1]	–
Weight gain	NS	–	–	NS[1]	–	NS[1]	NS[1]	NS	NS[1]	✓*	–

According to the Australian Guidelines (National Health Medical Research Council 2012) summarizing the evidence that is listed in the British NICE Guidelines (National Institute for Health and Clinical Excellence 2009)
✓ Statistically significant favouring treatment with more than one trial included in the analysis
✓[1] Statistically significant favouring treatment based on a single trial only
NS Non-significant with more than one trial included in the analysis
NS[1] Non-significant based on a single trial only
× Adverse outcome (statistically significant favouring control group with more than one trial included in the analysis)
– Outcome not reported in trials/not included in meta-analysis
✓* Greater weight gain in the control group

22.4 Treatment Strategies According to Target Symptoms

As the internal diagnostic consistency and discriminatory validity of the different categories of PDs are lower in adolescents than in adults (Becker et al. 1999), it is appropriate to direct pharmacological therapy against particular target symptoms. In contrast to specific behavioral therapeutic treatment, PDs are not pharmacologically treated as such, **therapy** being instead **focused upon the symptomatic treatment of** certain **defined problem areas** (for instance, a high degree of impulsivity) that are in turn components of different PDs, such as the emotionally unstable PDs or asocial PDs. One consequence is that very few empirically controlled studies have investigated "pure" patient groups. As symptomatology can be quite diverse, a pharmacological combination treatment is indicated in individual cases. The indication must nevertheless be carefully considered, particularly as symptoms in these complex, overlapping clinical pictures can easily be misinterpreted (for instance, feelings of emptiness and boredom in borderline patients can be misconstrued as therapy-resistant depression; Herpertz et al. 2007). Therapy recommendations for five groups can be distilled according to the target symptoms (see Table 22.2).

Table 22.2 Recommended oral therapy of personality disorders in children and adolescents according to type of target symptoms

Target symptoms	Agent or agent class	Dosage range
Impulsivity, autoaggression, aggression against others	**Second- or third-generation antipsychotics** (e.g., aripiprazole, olanzapine, quetiapine, risperidone)	Aripiprazole 2–10 mg/day Olanzapine 2–5 mg/day Quetiapine 50–200 mg/day Risperidone 1–3 mg/day
Long-term medication	Mood-stabilizing antiepileptics (topiramate, valproic acid, lamotrigine)	According to clinical response and serum concentrations (for details see Sects. 7.4.4, 7.4.6, and 7.4.7)
Acute affective outbreaks, restlessness, and agitation states	**Low-potency antipsychotics** (e.g., levomepromazine, melperone, thioridazine)	Levomepromazine 25–200 mg/day Melperone 25-100 mg/day Thioridazine 0.5 mg/kg daily
Crisis intervention	**First- or second-generation antipsychotics** (e.g., levomepromazine, haloperidol, olanzapine) **Benzodiazepines** (e.g., lorazepam)	Melperone 25–100 mg/day Levomepromazine 25–200 mg/day Haloperidol 2–20 mg/day Olanzapine 5–10 mg/day Lorazepam 1–7.5 mg/day If i.v. medication is necessary: haloperidol 10 mg and lorazepam 2.5 combined
Psychotic symptoms, derealization	**First-, second- or third-generation antipsychotics**	Aripiprazole 2–5 mg/day Risperidone 0.5–1.5 mg/day Olanzapine 2–5 mg Haloperidol 1–5 mg
Anxiety, social anxiety, depression	**SSRIs** (e.g., fluoxetine, sertraline, paroxetine) **Benzodiazepines** (e.g., lorazepam)	Fluoxetine 20–60 mg/day Lorazepam 1–7.5 mg/day
Dysphoria, affective lability	**SSRIs** (e.g., fluoxetine, sertraline, paroxetine) **Second- or third-generation antipsychotics** (e.g., aripiprazole) **Mood-stabilizing antiepileptics** (topiramate, valproic acid, lamotrigine)	Fluoxetine 20–60 mg/day Aripiprazole 2–5 mg/day According to clinical response and serum concentrations (for details see Sects. 7.4.4, 7.4.6, and 7.4.7)

Bold: first-choice medications or medication classes
i.v. intraveneous
SSRIs selective serotonin reuptake inhibitors

22.4.1 Autoaggression, Outwardly Directed Aggression, and Impulsivity

These target symptoms are usually treated on a long-term basis with SSRIs and antipsychotics, depending upon the quality of the aggression. The pharmacotherapy of aggression is discussed in detail in Chap. 9. Antipsychotics are preferred for impulsive-aggressive acts and autoaggression, **SSRIs** for affectively colored aggression (anxious tension, depressive irritability). Procedures for medication with SSRIs are discussed in Sect. 4.4.1.2 and Chap. 14. It should be noted that the anti-aggressive effect of SSRI therapy is only manifested after 2–3 months so that an overlapping therapy with antipsychotics can be indicated.

The efficacy of **antipsychotics** with regard to their inhibition of impulsivity and (auto)aggression has been verified in clinical studies (see Chap. 9). Second- and third-generation antipsychotics are preferred because of their more favorable ADR profile, although tardive dyskinesias are also not a major problem at lower dosages of first-generation antipsychotics (see Sect. 5.4.4). As antipsychotics can be adequate even in small amounts, a low dosage should initially be employed.

Risperidone is the **best-explored agent** in children and adolescents that is US Food and Drug Administration (FDA)-approved for the treatment of irritability associated with autistic disorder including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods in children and adolescents (ages 10–17 years). At levels of up to 3 mg/day, risperidone is associated with only a narrow range of ADRs, although even at these low dosages prolactin levels are almost always elevated (generally without clinical consequences, however, and within about 12 months they return to normal levels), and weight gain can occur in some cases. At higher dosages, extrapyramidal motor symptoms and orthostatic problems develop quite rapidly. A dosage of up to 1.5 mg/day is usually sufficient.

Aripiprazole, olanzapine, quetiapine, and ziprasidone also appear to be effective in the treatment of aggression (see Chap. 9). Special conditions apply to the prescription of clozapine (see Sect. 5.4.6) so that it is rarely used for this indication. Of ADRs associated with second- and third-generation antipsychotics, **weight gain** is of particular importance in adolescents, causing additional stress to emotionally labile patients in particular. This is mostly marked with clozapine and olanzapine, less so for aripiprazole, quetiapine, and risperidone, and hardly noticeable with ziprasidone.

22.4.2 Acute Affective Outbursts, Restlessness and Agitation States, and Suicidality

Low- to medium-potency antipsychotics but also benzodiazepines are the first-choice medications for the treatment of these acute states (see Chaps. 5, 6, and 9). **Benzodiazepines** should only be considered for short-term management of acute agitation (such as suicidal crises). Their potential for abuse has rendered them obsolete for longer-term medication. Oral lorazepam, with its more rapid influx and shorter elimination half-life, is more easily controlled in the acute situation than diazepam. Suitable **antipsychotics** include levomepromazine and melperone. The administration of haloperidol together with lorazepam i.v. (slowly injected!) can be necessary in states of severe agitation.

22.4.3 Psychotic Symptoms, Derealization, and Cognitive Disturbances

These target symptoms are particularly associated with cluster A-PDs. They must be distinguished from apparently psychotic symptoms in the sense of dissociative symptomatology in cluster B-PDs, which primarily require behavioral therapeutic treatment.

Second- and third-generation antipsychotics are preferred for the long-term pharmacological treatment of psychosis-like symptoms in adolescents, as their better tolerability in comparison with first-generation antipsychotics is valuable in terms of securing compliance.

First-generation high-potency antipsychotics have been associated with unacceptably high dropout rates in clinical studies. Of ADRs associated with second- and third-generation antipsychotics, weight gain is of particular importance in adolescents, particularly with clozapine and olanzapine. Dosage should be adjusted according to clinical symptomatology (see Chap. 25).

SSRIs are **not appropriate** for the treatment of productive psychotic symptoms and can even exacerbate them. They can, on the other hand, be useful in the therapy of cognitive impairment or of a generally depressive-distrustful mood.

22.4.4 Anxiety, Depression, and Social Anxiety

These target symptoms are better treated with SSRIs than with tricyclic antidepressants, especially as the latter can lead to paradoxical and negative effects in personality disorders (see above).

SSRIs are to be particularly preferred than tricyclic antidepressants in cases involving chronic suicidality because of their lower toxicity if accidental or intentional overdosage occurs.

Fluoxetine is currently **recommended** as the most **appropriate** medication for use in children and adolescents (see Chaps. 4 and 14). Further positive findings from double-blind, placebo-controlled studies in adults have been reported for the SSRIs citalopram, fluvoxamine, paroxetine, and sertraline as well as for venlafaxine, a selective serotonin and noradrenaline reuptake inhibitor (evidence level C).

Second- or third-generation antipsychotics can also be used in this patient group. Benzodiazepines, on the basis of their rapid onset of action and good anxiolytic properties, are suitable as short-term crisis intervention medications.

22.4.5 Affective Lability and Dysphoria

These target symptoms should similarly be treated with SSRIs, for which a mood-stabilizing effect has been demonstrated. There are also positive results from open-label studies for the serotonin and noradrenaline reuptake inhibitor venlafaxine. Finally, positive reports regarding lithium salts and mood-stabilizing antiepileptic medications have been published. Studies of PDs, however, have generally been concerned with other target symptoms, including aggression or overall clinical scores.

Slow titration is required when employing carbamazepine in order to avoid allergic skin reactions; this also applies to lamotrigine. A special feature of lithium salts and the antiepileptic medications mentioned above is that they stabilize mood even during longer-term administration. The narrow therapeutic range for lithium salts dictates that compliance be carefully monitored. The high toxicity associated with overdosages also means that they should be employed only with great caution where chronic suicidality is evident.

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Psychiatric Disorders in Children and Adolescents with Intellectual Disability

23

Andreas Warnke and Laurence Greenhill

Contents

A. Warnke, MD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: warnke@kjp.uni-wuerzburg.de

L. Greenhill, MD
NYS Psychiatric Institute, New York Presbyterian Hospital, Riverside Drive 1051, New York, NY 10032, USA
e-mail: llg2@columbia.edu

23.1 Definition, Classification, and Target Symptoms

In the International Classification of Diseases, 10th revision (**ICD-10**), the term correspondent to intellectual disability still is "mental retardation," and it is specified according to current severity on the basis of IQ scores: F70 mild, F71 moderate, F72 severe, and F73 profound mental retardation (World Health Organization 1996). According to DSM-5 commentary in ICD-11, the diagnostic term will be "intellectual developmental disorders".

In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (**DSM-5**), the diagnostic term is "intellectual disability" (code 319: assigned regardless of the severity specifier), and the various levels of severity (mild, moderate, severe, profound) are defined on the basis of adaptive functioning (based on the categories "conceptional domain," "social domain," "practical domain") and not on the basis of IQ scores (American Psychiatric Association 2013). The diagnostic criteria include deficits in intellectual functioning and in adaptive functioning both with onset during the developmental period.

The approach of the World Health Organization's International Classification of Functioning, Disability and Health (ICF, World Health Organization 2001) is the attempt to integrate medical and psychosocial features of disability and ability in activities in specific environmental and personal context.

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Intellectual disability is not per se a psychiatric disorder. But the probability of developing a psychiatric disorder is significantly high in patients with intellectual disability (Arron et al 2011; Bouras 2013; Bouras and Holt 2007; Buckles et al. 2013; de Ruiter et al. 2007; Emerson et al. 2010; Forster et al. 2011; Myrbakk and von Tetzchner 2008). Individuals with intellectual disability and co-occurring psychiatric disorders are at **high risk of problems in social adjustment** and at risk of **suicidal behavior**.

Prophylactic pharmacological measures exist only for some disorders that cause intellectual deficits, such as immunization against infections that can damage the brain. This category also includes dietetic measures, such as the phenylalanine-free diet for those suffering phenylketonuria, and hormonal substitution by timely administration of L-thyroxine during the first 4 weeks of life in congenital hypothyroidism. If the intellectual disability is already manifest, however, psychopharmacological therapy is not directed at these static losses but rather at the psychopathological symptoms or psychiatric disorders of the patients with intellectual deficiency. The **indications** for **pharmacological therapy** are therefore essentially the same as for people without mental handicaps. Medication is, as always, only one part of a care program that includes educational, psychotherapeutic, and socio-integrative measures (for review Sturmey 2012).

The prevalence of psychopharmacological treatment is very high in institutions for the handicapped (Robertson et al. 2000). There are several reasons for this, including:

- Psychotherapy for people with intellectual deficiency is still only very inadequately developed, and the necessary framework and therapeutic qualifications are often lacking.
- Diagnostic difficulties. The severity of psychiatric disturbances and uncertain responses to treatment in this vulnerable population may lead to a greater use of psychopharmacological interventions than in youths without intellectual disability.

Cave! Diagnosis is extremely complex (e.g., see Attiah and Antonacci 2008). As the severity of intellectual disability increases, it becomes increasingly difficult to determine if the symptoms are part of a psychiatric disorder (e.g., mutism in depression) or part of the basic limitations of the intellectual development, e.g., the basic limitations in the use of language that prevent the patient from describing his/her psychiatric symptoms.

23.2 Therapeutic Framework

Therapy with psychopharmacological agents is limited to psychiatric disorders included in the ICD-10 and in the DSM-5, and severe psychopathological symptoms that endanger the patient or others (e.g., self-harm, suicidal tendencies, severe aggressive impulse control disorders), but can also be undertaken in order to allow access to pedagogic and psychotherapeutic measures.

A number of **specific concerns** arise during pharmacotherapy of children and adolescents with intellectual disability.

- The **assessment** of the **benefits** and adverse drug reactions (ADRs) of a medication is, for the same reason, **complicated**.
- The **cause** of the intellectual disability is often **unknown** so that an etiology-based treatment is not possible.
- Pharmacological treatment must be undertaken according to the observable behavioral symptoms and the context in which they are presented (i.e., on the basis of behavioral analysis). The more impeded the capacity of patient with an intellectual deficiency to communicate, the greater the necessity to observe such guidelines.
- Psychiatric and other organic comorbidity (e.g., epilepsy, metabolic disease, cerebral

paralysis, blindness, deafness) are more frequently encountered as the severity of mental handicap increases (Einfeld et al 2011), so that the patient may be subjected to multiple treatments, appreciably increasing the difficulty of monitoring the medication's therapeutic drug benefits, its ADRs, and the interactions between different medications being used to treat the patient.

- In patients with organic brain injuries the expected responses to pharmacological agents might not occur; **unusual** and even paradoxical **effects** may result from the unusual cerebral vulnerability in these patients (Barron and Sandman 1985; Handen et al. 1991, 1992, 1994; Kalachnik et al. 2002; King 2007; Matson and Mahan 2010).
- **Compliance** is more **difficult to achieve**, as with increasing severity of the intellectual deficiency, the ability to communicate and autonomous behavioral monitoring are both reduced; assessment of compliance and drug effects must be undertaken by caregivers.
- The decision to initiate pharmacotherapy should be examined with particular circumspection if it is primarily justified as providing relief for overburdened caregivers. Pharmacological therapy should not be employed to compensate deficiencies in institutions for the occupants with intellectual disability.

23.3 Choice of Pharmacotherapy

There have been very few clinical studies concerning the treatment of psychiatric disorders in youths with intellectual disability. As a result, recommendations are consensus-based and have essentially been derived from the empirical data of a number of therapeutic trials (Bramble 2007; Calles 2008; Häßler and Reis 2010; Handen and Gilchrist 2006; King 2007; Matson and Neal 2009; Matson and Hess 2011; Matson et al. 2000; Reis and Aman 1998; Robertson et al. 2000; Shapiro and Accardo 2010; Sturmey 2012).

23.4 Treatment Strategies

23.4.1 General Aspects of Treatment

Therapy with psychopharmacological agents in children and adolescents with intellectual deficiency, on the basis of these considerations alone, must be managed with particular caution. The complexity of the decision to initiate such therapy is often exacerbated by the fact that the patient is often intellectually incapable of granting legal consent. The following **treatment guidelines** have universal validity but should be particularly heeded in patients with intellectual developmental disorder and the comorbidity of psychiatric disorder:

- Before initiating any treatment, the **diagnosis** and the **assessment of the success** of previously employed therapeutic approaches must be considered. The consensus-based treatment recommendations given by Schur et al. (2003), Jensen et al. (2004), and Pappadopulos et al. (2003) are a useful general guideline for the use of antipsychotics but also for any kind of psychopharmacological treatment (see also Fig. 9.1).
- Do not be misled by the impression evoked by a crisis into a hasty decision to initiate a pharmacological intervention.
- Keep the legal framework for your action in mind.
- Have regard for the wishes of your patient, and inform she or her as far as possible about the measures you adopt.
- Have regard of the opinion and decisions of the "legal adult responsible" person who can provide protections for the intellectually deficient patient. This "**guardian**" may sign consent for psychopharmacological treatment and be called upon to give his agreement to each new change in therapy. Having a specifically assigned family member is better than just picking out any family member transporting the patient to the clinic. This person might change with every clinic visit and not be well informed. People with intellectual disability

often react in a vulnerable fashion to centrally active pharmaceuticals.
- Therapy with psychopharmacological agents alone is rarely effective.
- Therapy with psychopharmacological agents must be integrated into an individual multidimensional therapeutic concept.
- Describe the goals of the treatment or the target symptom as precisely as possible.
- The effect with regard to the defined treatment goals must be systematically documented.
- Prolonged prescription of psychopharmacological agents must be subject to critical review.
- Do not withdraw too rapidly a medication that has been employed for longer periods. Reduction of the dosage of anticholinergic pharmaceuticals is often initially associated with a cholinergic imbalance and thus possibly with agitation and irritability.
- Keep in mind the psychiatric ADRs that can occur. Symptomatic deterioration during adjustment of dosage is typical for such ADRs.
- The general principles of therapy with psychopharmacological agents should be applied (compliance, pharmacodynamics, pharmacokinetics, etc.).
- Pharmacological therapy in children and adolescents with intellectual deficiency additionally requires that the caregivers assume responsibility for reliable dosage, administration, and monitoring of effects.

23.4.2 Therapy in Crisis and Emergency Situations

The ideal of pharmacological therapy is based upon diagnosis, behavioral analysis, a psychoeducative framework (explanation of the diagnosis, of therapeutic alternatives, of the nature and use of the medication, etc.), and obtaining consent from the patient and/or the caregiver to employ a drug, preferably indicated for the intended purpose.

In an emergency situation the baseline conditions are quite different. The patient is often acutely agitated, helpless, and extremely vulnerable; the risk of harm to the patient or to others is significant; personnel are exhausted; the patient lacks insight into his disorder; and the relatives expect relief as quickly as possible. There is insufficient time and opportunity for a complete diagnostic evaluation, and obtaining consent may be impractical.

> **Cave**! In such **emergency situations** there is not only a strong temptation to fast-track the initiation of pharmacological therapy, but it is often also necessary to do so. Documentation of such cases must therefore specifically stipulate that it involves acute pharmacological treatment requiring short-term review, initially on a continuous basis, with regard to indication, effect, and ADRs, and can provisionally be regarded only as a transitional therapy.

Table 24.1 provides an overview of the acute pharmacological treatment of psychiatric emergencies (see Chap. 24). Medications that are frequently employed in emergency situations include:
- Anxiolytics, such as lorazepam (calming)
- Sedatives, such as diazepam (sedative)
- Antipsychotics, such as risperidone, olanzapine, pipamperone, melperone, and haloperidol (calm and sedate psychomotor activity)

23.4.3 Most Common Adverse Drug Reactions

The restricted ability of patients with intellectual deficiencies to communicate, their treatment with several different pharmaceuticals, and, in some cases, their altered cerebral responsiveness necessitate that increased vigilance for ADRs be used when treating children and adolescents with intellectual disabilities. The implementation of therapeutic drug monitoring (TDM) is strongly recommended (see Sect. 2.3). Among the **most frequently** encountered ADRs are the following:
- **The anticholinergic syndrome** associated with the use of low-potency antipsychotics and tricyclic antidepressants is a concern. CNS symptoms include agitation, motor restlessness, dysarthria, disorientation, hallucinations,

and cerebral seizures; peripheral symptoms include obstipation, urine retention, fever, mydriasis, and tachycardia.

- **Constipation**. If overlooked in patients with severe mental handicaps, complaints can lead to uncharacteristic behavioral patterns, such as headache, agitation, depression, and sleep disturbances. Obstipation occurs mostly in association with low-potency antipsychotics, tricyclic antidepressants, benzodiazepines, and carbamazepine.
- **Extrapyramidal-motor disturbances**. Akathisia, stereotypic gaze behavior, and parkinsonian psychomotor symptoms may be mistakenly interpreted as expressions of severe mental disability.
- **Hyperactivity, restlessness, and aggressive agitation** are particularly associated with antiepileptic agents, benzodiazepines, and SSRIs.

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Psychiatric Emergency Therapy in Children and Adolescents

24

Andreas Warnke and Marcel Romanos

Contents

24.1 Definition, Classification, and Target Symptoms

Psychiatric emergencies that have to be pharmacologically treated are:

- Suicidality
- Agitation/severe aggression and self-harming behavior
- Disturbances of consciousness
- Hallucinations and delusions that are the most frequent symptoms of paranoid-hallucinatory schizophrenia

Suicidality must always be treated in the emergency situation, even where the meaning of a suicidal act is regarded more as an attempt to attract attention than to actually kill the patient. Suicidality also always justifies consideration of psychopharmacological intervention (rapid reduction of acute danger). The spectrum of causes and triggers of suicidality extends from critical life events in the absence of underlying child or adolescent psychiatric disease to suicidality in the context of severe psychiatric disorders, such as depression or schizophrenic psychosis.

Agitation is characterized by a loss of inhibitions, increased drive, and loss of control, whereby the latter often leads to aggression against others and/or self-harming behavior. In children and adolescents, agitation is frequently a component of a hyperkinetic conduct disorder as well as of attention-deficit/hyperactivity disorder (ADHD), conduct disorders, impulse control disorders,

A. Warnke, MD (✉) • M. Romanos, MD
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: warnke@kjp.uni-wuerzburg.de; romanos@kjp.uni-wuerzburg.de

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organic brain syndromes caused by the consumption of alcohol or other drugs, and also of acute psychotic episodes.

States of **disturbed consciousness** may be life threatening and can be manifested as confusion, somnolence, stupor, or coma. After emergency treatment the diagnostic process – by the specialist most relevant to the provoking cause or general condition – is paramount, and further psychopharmacological therapeutic measures are only secondary. Qualitatively altered consciousness is also encountered in children and adolescents, although less frequently, for example, as a clouding of consciousness in the context of epilepsy or catatonic schizophrenia.

For further information regarding the clinical management of emergency psychiatry, the reader is referred to books published on this topic (Allen 2002; Riba and Ravindranath 2010).

24.2 Therapeutic Framework

The agitation and helplessness of the patient and their relatives may be combined with the urgent hope, or even demand, that the physician should provide relief through the administration of a medication. The converse can also be problematic. If previous psychotherapeutic and psychopharmacological measures have not proved beneficial, or were associated with unpleasant adverse drug reactions (ADRs), the patient and their caregivers may harbor a negative attitude to any form of therapy, particularly pharmacotherapy, or they may, on the contrary, expect that effective pharmacological assistance might finally be provided. If there is no willingness to cooperate or insight regarding the disorder or its therapy, there can be no insight regarding the necessity or even the rationality of medication.

Time for the patient, a relaxed and open discussion, and attentive listening in a peaceful room are essentially the best preconditions for any further intervention.

As a rule, **careful diagnosis** is **obligatory** before the initiation of therapy and should be based upon a comprehensive psychiatric, pediatric, internal medical, and neurological physical examination. This includes the establishment of a psychopathological indication and the patient's medical history. Such a diagnostic process is, however, in an acute emergency, particularly in extreme cases of aggression against others or acute psychotic symptoms, **not always practical**. In this situation, the initial treatment cannot be diagnosis based but only symptomatic. For all these reasons, the temptation is great, as is the necessity, to promptly resort to pharmacological assistance. Medication in the emergency situation should therefore **generally** be regarded as "**transitional medication**." Documentation of the pharmacological intervention should include indications as to when and how this emergency therapy should be reviewed (and possibly replaced, if necessary) and also information regarding its integration into long-term treatment.

Acute suicidal tendency can also include resistance to any life-preserving medical interventions – in children (this is very rare) and adolescents, however, suicidality is, in most cases, not an expression of a lack of the will to live.

If consent cannot be obtained in the emergency situation because of the general mental state of the patient (lack of insight regarding his/her disorder, acute agitation, acute suicidality), and even the usual explanation of the medication and its use is not possible, monitoring of the condition of the patient (observation of drug effects, including ADRs) is particularly demanding; it is also part of the documentation that consent and explanation of the therapy should be retrospectively undertaken as soon as possible.

Although psychopharmacological therapy is central to the management of emergency situations, the criteria of **psychoeducation** and **psychotherapy** nevertheless still comprise an integrated **component of** the overall **therapeutic concept**. The interaction with the patient,

particularly during the period of acute medication, is an interaction with an acutely vulnerable individual, and the therapeutic approach is not directed against the patient but against the symptoms that place the patient and others in peril and against the disease.

Medication is not a substitute for therapeutic and nursing attention but rather requires sufficient time for the patient as well as a quiet room that provides the opportunity for a discussion with them, free of distractions. The conversation with the physician during the first few minutes of the initial encounter can largely determine whether the patient recognizes the need for treatment as well as their willingness to accept the indicated medication. If possible, the medical history of the patient should also be compiled from other sources; particularly when the patient cannot speak for himself, information supplied by caregivers can assist treatment decisions.

The **documentation** of the **medical procedure includes**.

- A description of the circumstances in which the emergency occurred (initial situation, process of notification),
- psychopathological findings,
- physical/neurological findings,
- laboratory pathological findings (as appropriate).
- If possible, information regarding the patient's medical history (gathered from patient and any other available sources).
- Suspected diagnosis,
- information regarding the therapeutic procedure,
- planning of legal proceedings (committal, involvement of legal authorities).
- Contact details of caregivers.

24.3 Choice of Pharmacotherapy

The following criteria are apposite for the individual decision regarding the choice of medication.

- The physician is familiar with the medication with regard to dosage, effects, ADRs, and interactions with other medications (there is little time available for consulting manuals, and ignorance regarding possible complications should be excluded).
- It should be possible to administer the medication both orally and parenterally (its administration is easy and flexible).
- The medication elicits a rapid response.

> Availability of the following psychopharmacological agents is usually sufficient for the treatment of psychiatric emergencies.
> - A high- and a low-potency antipsychotic
> - A benzodiazepine with anxiolytic and sedative properties
> - An antiepileptic agent

There are no randomized control studies available with regard to the emergency treatment in children and adolescents. The recommendations are based on adult studies, consensus, and our personal clinical experience.

If therapy with psychopharmacological agents is necessary, anxiolytic and sedative agents (e.g., **lorazepam**) and low-potency antipsychotics (e.g., **melperone, thioridazine**) are especially appropriate (see Chaps. 5, 6, and 9). Benzodiazepines such as lorazepam have the advantages that their action is rapid and that they are comparatively well tolerated even in those with preexisting medical conditions or using other medications. Withdrawal of benzodiazepine medication within 4 weeks, however, is desirable in order to avoid habituation and addiction. High doses and intravenous (i.v.) administration of benzodiazepines can cause respiratory depression (see Sect. 6.4.1).

24.4 Treatment Strategies

Table 24.1 provides an overview of the acute pharmacological treatment of psychiatric emergencies.

24.4.1 Suicidality

If therapy with psychopharmacological agents is required in the acute situation (e.g., severe agita-

Table 24.1 Acute pharmacological treatment of psychiatric emergencies

Acute symptoms	Recommended therapy/measures	Repeatability per day	Maximum daily dose (mg)[a]
Severe agitation with pronounced aggression, restlessness, or marked psychotic symptoms	**Haloperidol** 1–10 mg i.v.(or p.o. or i.m.) **plus lorazepam** 0.5–2 mg i.v. (to avoid cramp, inject slowly 2 mg/min)	2–3	Haloperidol (30–60)
		NB: ADRs (see Sects. 5.4.4 and 5.4.5)	Lorazepam (6–7.5)
	Reports of favorable effects with **second-generation antipsychotics**, including	According to tolerance	As for schizophrenia
	Risperidone lingual tablets 0.5/1 mg p.o.		6–8
	Ziprasidone 10 mg p.o. or i.m.		80–160
	Olanzapine 5–10 mg p.o. or i.m.	**NB**: cardiac effects	20
			NB: i.m. administration of a single dose greater than 10 mg not advisable
Mild to moderate agitation with aggression, minor or no psychotic symptoms	**Mid- to low-potency antipsychotics**		
	Levomepromazine 25–50 mg i.m./p.o. (**NB**: cardiovascular and vegetative ADRs, respiratory depression)	2–3	150
	Melperone 12.5–50 mg p.o.	2–4	100 (300 for psychotic agitation)
	Thioridazine 0.5 mg/kg/day p.o.	2–3	3 mg/kg per day
Agitation with pronounced **anxiety** reaction	**Benzodiazepines**		
	Lorazepam 2.5 mg p.o.	3	7.5
Suicidality	**Benzodiazepines**		
	Lorazepam 2.5 mg p.o.	3	7.5
	Mid- to low-potency antipsychotics		
	Melperone 25–50 mg p.o.	2–4	50–100
	Thioridazine 0.5 mg/kg/day p.o.	2–3	3 mg/kg per day
Self-harm, including cutting	**Mid- to low-potency antipsychotics**		
	Melperone 25–50 mg p.o.	2–4	50–100
	Levomepromazine 50 mg i.m./p.o. (see above)	2–3	150
	Thioridazine 0.5 mg/kg/day p.o.	2–3	3 mg/kg per day
	Benzodiazepines		
	Lorazepam 2.5 mg p.o.	3	7.5
Hallucinations and delusions	**Acute**		
	Lorazepam 2.5 mg p.o. until the antipsychotic is effective	3	7.5
	Risperidone lingual tablet 1 mg	6	6
	Olanzapine 5–10 mg buccal or i.m.	1–4	20
	Haloperidol 10 mg i.v. **plus** lorazepam 2 mg i.v. (see above)	2–4	30
		2–4	8
	Longer term		
	Second- or third-generation antipsychotics (Chap. 5)		
Early **dyskinesia**	1–2 ampules (1–2 mg) biperiden (licensed in European countries) i.m. or i.v. applied slowly	1–2	2–6 (8)
	1–2 mg benztropine (FDA-approved) i.m. or i.v.	1–2 **NB**: deliriant conditions if combined with other anticholinergic agents	0.05 per kg body weight

Table 24.1 (continued)

Acute symptoms	Recommended therapy/measures	Repeatability per day	Maximum daily dose (mg)[a]
Neuroleptic malignant syndrome (NMS) NMS is also possible with second- and third-generation antipsychotics, and within therapeutic range	**NB**: life threatening Emergency laboratory parameters: alkaline phosphatase, creatine kinase, and transaminases elevated Implement TDM Internal neurological examination: rigidity, akinesia (EPMS), fever **Therapy**: immediate withdrawal of the antipsychotic, cooling, parenteral fluids; transfer to intensive medical therapy See also Sect. 5.4.4		
Syncope/tetany due to hyperventilation	Breathing into plastic bag Diazepam 5–10 mg p.o. or i.v.	1–2	10
Disturbed consciousness	Initially: somatic investigation except severe agitation (see above)		

[a]Recommended maximal daily dose for children <14 years based on the Prescribing Information: haloperidol from 3 years p.o. 0.025 mg/kg body weight, max. 0.2 mg/kg; levomepromazine 1 mg/kg; lorazepam 0.05 mg/kg
ADRS adverse drug reactions, *EPMS* extrapyramidal motor symptoms, *i.m.* intramuscular, *i.v.* intravenous, *p.o.* per orally, *TDM* therapeutic drug monitoring

tion with an acute tendency to suicide, suicidality with acute psychosis in patients lacking insight into their illness, severe depression, or unresolved conflict without distancing oneself from the possibility of suicide), **benzodiazepines**, particularly lorazepam, are especially useful as anxiolytic or depressant psychopharmacological medications, as are low-potency antipsychotics, such as **melperone** and thioridazine.

Long-term therapy is directed at the underlying disorder. It is important not to prescribe quantities of a preparation that would suffice for a further suicide attempt.

24.4.2 Agitation

Depressant, low-potency antipsychotics (e.g., levomepromazine) have proved useful in the treatment of agitation, whereby one should be alert to ADRs such as orthostatic dysregulation with tendency to collapse and cardiovascular ADRs, such as tachycardia (see Sect. 5.4.4).

For this reason, the vital parameters (respiratory rate, pulse) should be assessed prior to the initiation of therapy and at regular intervals following drug administration and also monitored in the course of therapy. In acute agitation where the patient history is incomplete, it is recommended that a "rapid drug test" be undertaken in every case prior to initiating therapy, as a particular medication may be contraindicated, depending upon the cause of the acute intoxication.

If **agitation** has, for instance, been **triggered by** a **schizophrenic psychosis**, the administration of high-potency antipsychotics, such as **haloperidol**, is possible, although treatment of children and adolescents with first-generation antipsychotics is frequently associated with extrapyramidal motor ADRs. Although quite rare, it can also lead to the potentially life-threatening neuroleptic malignant syndrome. Employment of second-generation antipsychotics, such as **olanzapine** (as a soluble

tablet or as a powder for constitution of an intramuscular [i.m.] injection solution), should therefore also be considered for achieving rapid control in agitated patients. ADRs must also be noted with second-generation antipsychotics, including bradycardia, with or without hypotonia, for which reason constant clinical monitoring is essential.

If the **agitation** appears **colored by anxiety**, the administration of **benzodiazepines**, such as lorazepam – given sublingually, orally, or i.m. – is useful, either alone or together with an antipsychotic agent.

Examples for the treatment of acute aggressive/violent agitation.

- Lorazepam starting dose 0.5 mg (in older youths 1–2 mg) sublingually, orally, i.m., or intravenously (i.v.). Given i.v: inject slowly, 1–2 mg over 2 min. Control respiratory status!
- Haloperidol starting dose 1–5 mg orally, i.m., or i.v.

  If continuous medication is needed:
  i.m. or oral doses given at 1-h interval
- Lorazepam 0.5–2 mg up to 6 mg total within 24 h.
- Haloperidol 1–5 mg up to 30 mg total within 24 h.

New formulations of second- and third-generation antipsychotics also may be helpful, for example, the use of risperidone orally disintegrating tablets (0.25–0.5 mg/day) or olanzapine orally disintegrating tablets (starting dose 2.5–5 mg, maximum 10 mg/day).

Further details concerning the treatment of agitation are contained in Chaps. 9 and 15.

24.4.3 Disturbed Consciousness

In more severe agitation or confusion, benzodiazepines or haloperidol may be indicated. Details concerning the treatment of disturbed consciousness with antipsychotics, anxiolytics, and sedatives are found in Chaps. 5 and 6.

24.4.4 Hallucinations and Delusions

Treatment of hallucinations and delusions that are the most frequent symptoms of paranoid-hallucinatory schizophrenia primarily involves high-potency antipsychotics; in children and adolescents second- and third-generation antipsychotics, such as olanzapine, quetiapine, ziprasidone, aripiprazole, and risperidone, are to be preferred. The second-generation antipsychotic clozapine is highly effective as an antipsychotic agent but may only be prescribed after two other antipsychotics have failed to afford satisfactory relief or have been withdrawn because of severe ADRs (see Sect. 5.4.1). If the patient is highly anxious, the simultaneous employment of benzodiazepines, such as lorazepam, is advisable until the antipsychotic effect has developed.

> Clozapine and benzodiazepines should not be coadministered, as there is a risk of respiratory arrest, particularly where benzodiazepines are administered i.v.

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Schizophrenia

25

Benno G. Schimmelmann, Claudia Mehler-Wex,
and Christoph Wewetzer

Contents

B.G. Schimmelmann, MD (✉)
University Hospital of Child and Adolescent Psychiatry, University of Bern, Bolligenstr. 111, 3000 Bern, Switzerland
e-mail: benno.schimmelmann@gef.be.ch

C. Mehler-Wex, MD
Department of Child and Adolescent Psychiatry and Psychotherapy, University of Ulm, Steinhövelstr. 5, 89075 Ulm, Germany

HEMERA-Klinik, Schönbornstr. 16, 97688 Bad Kissingen, Germany
e-mail: mehler-wex@hemera.de

C. Wewetzer, MD
Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Florentine-Eichler-Str. 1, 51067 Köln, Germany
e-mail: wewetzerc@kliniken-koeln.de

25.1 Definition, Classification, and Target Symptoms

Schizophrenia is characterized by positive and negative psychotic as well as cognitive and mood symptoms in many cases. Positive symptoms include delusions, hallucinations, thought disorder, and movement disorders. Negative symptoms include blunted affect, lack of pleasure and drive, lack of spontaneity and flow of speech and thinking as well as social withdrawal.

According to the International Classification of Diseases, 10th revision (**ICD-10**; World Health Organization 1996), the following important **subtypes** are distinguished (key symptoms in brackets):

- Paranoid schizophrenia (F20.0; stable delusions, frequently acoustic hallucinations, perceptual disturbances)
- Hebephrenic schizophrenia (F20.1; shallow affect, disorganized thought, rambling, incoherent speech, unpredictable and irresponsible behavior)
- Catatonic schizophrenia (F20.2; psychomotor abnormalities with possible alternation between agitated and stuporous states)
- In the rare schizophrenia simplex (F20.6), negative symptoms are presented without prior positive symptomatology. Negative symptoms are also characteristic for chronic courses (schizophrenic residuum).

Accordingly, the **target symptomatology** is accordingly very complex and involves aspects

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of cognitive, affective, psychomotor, and social experiences and behavior.

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (**DSM-5**), has just been published (American Psychiatric Association 2013). One aim of the revision was to emphasize the dimensional nature of psychotic disorders. Thus, among others, the **subtypes of schizophrenia were omitted** due to their limited reliability and validity, and an eight-item tool to assess six dimensions of psychotic disorders (hallucinations/delusions, negative symptoms, cognitive symptoms, motor symptoms, disorganization, and mood symptoms, i.e., depression and mania) was introduced in section III for further research and clinical evaluation. Further, schizophrenia as defined by the DSM-5 differs from the DSM-IV-TR4 by the following: delusions, hallucinations, or disorganized speech are required for diagnosis, and commenting and conversing hallucinations and bizarre delusions are no longer accorded special diagnostic status (McClellan et al. 2013).

25.2 Therapeutic Framework

Prior to therapy, a **diagnosis** of a psychotic disorder must be ascertained and organic etiologies and intoxication excluded (physical-neurologic examination, clinical laboratory, EEG, brain imaging, possibly lumbar puncture).

According to the NICE **guidelines** (National Institute for Health and Clinical Excellence 2013a), the treatment of a first episode and subsequent episodes of a psychotic disorder including schizophrenia-spectrum disorders in children and adolescents involves **antipsychotic medication and psychosocial interventions**. According to the practice parameters of the American Academy of Child and Adolescent Psychiatry (AACAP, McClellan et al. 2013), which is based on the evidence published until 2010, psychosocial interventions should be provided in combination with medication therapies (clinical guideline derived from strong clinical consensus and some empirical evidence).

Psychosocial interventions consist of individual cognitive behavioral therapy, family interventions, psychoeducation, and rehabilitative measures if needed. Psychosocial and rehabilitative interventions also include measures for developing social and communicative skills, stress management, problem solving, and emotion regulation as well as supported employment and coaching for independent living in older adolescents. New data on the efficacy and safety of antipsychotics have been published in the recent years (see Chap. 5), while the **evidence** for psychosocial and rehabilitative interventions is still **meager** (Schimmelmann et al. 2013a).

The **diagnosis** and **treatment** of schizophrenia including the titration of antipsychotic medication can be **undertaken in all treatment settings**, e.g., outpatient, home-treatment, day-treatment, and inpatient child and adolescent psychiatric services. In some countries, specialized community care (mostly outpatient and home-treatment settings) provided by either first-episode services (age 14–25 or 28 years) or child and adolescent mental health services (children) is preferred over inpatient treatment even for acute psychotic episodes in children and adolescents (see NICE guidelines). In other countries, such as Germany and Switzerland, many to most acute psychotic episodes in children and adolescents are treated in an inpatient setting. According to the NICE guidelines, before initiating hospitalization, the (negative) impact of hospitalization on the child or adolescent and his/her parents, carers, or other family members and alternative treatment options should be considered (National Institute for Health and Clinical Excellence 2013a).

Generally, the **initiation of treatment** until remission and/or stabilization of psychotic symptoms within the first 12 months should be provided by **specialized** (secondary) **care teams**, i.e., first-episode services or child and adolescent mental health services. After stabilization, specialized care teams should at least stay involved (NICE guidelines).

For further information regarding the therapy of schizophrenia, we refer to the recent review by Schimmelmann et al. (2013a), the NICE guidelines (National Institute for Health and Clinical Excellence 2013a), the practice parameters of AACAP (McClellan et al. 2013), and Chap. 5.

According to the NICE guidelines, the treatment of psychotic disorders should include antipsychotic medication and psychosocial interventions. In the event that a child/adolescent and his or her parents or carers **wish to try psychosocial interventions alone** (without antipsychotic medication), it should be advised that psychosocial interventions are more effective if delivered in conjunction with antipsychotic medication. If psychosocial interventions alone are still preferred, then individual cognitive behavioral therapy and family interventions should be offered. A time limit (1 month or less) should be agreed upon for reviewing treatment options including introducing antipsychotic medication. Symptoms, level of distress, impairment, level of functioning, educational or occupational engagement, and achievements should be monitored regularly (National Institute for Health and Clinical Excellence 2013a). There is no such recommendation in the AACAP practice parameters (McClellan et al. 2013).

25.3 Pharmacotherapy

For further information regarding the psychopharmacological agents discussed here, including age- and indication-specific aspects of approval status, efficacy studies, recommended dosages, adverse drug reactions (ADRs), drug interactions, contraindications, and special precautions, please refer to the corresponding special Chaps. 4, 5, 6 and 7.

25.3.1 Applied Antipsychotic Pharmacotherapy

25.3.1.1 Choice of Antipsychotic for First-Episode Patients

Antipsychotics are efficacious in the treatment of schizophrenia-spectrum disorders. There is a lack of evidence for efficacy differences between various antipsychotics (except for clozapine for treatment-refractory schizophrenia (see Chap. 5). Thus, a "**primum non nocere**" **principle** is recommended when choosing an antipsychotic in this vulnerable population. To achieve this, data should be taken into account supporting that several ADRs of antipsychotics are more common in early-onset compared to adult-onset schizophrenia and that antipsychotics vary considerably in causing different ADRs (Schimmelmann et al. 2013a). The **NICE guidelines** (National Institute for Health and Clinical Excellence 2013a) state that the choice of an antipsychotic should be made by adolescents and their parents/carers or by parents/carers (if the child is too young). For this, **age-appropriate information** should be **provided** about the benefits, approval status, and possible ADRs of each antipsychotic drug. Importantly, as many patients require careful monitoring, dose adjustments, or switching of antipsychotics, treatment with antipsychotic medication should be considered an explicit individual therapeutic trial.

The **AACAP practice parameters** (McClellan et al. 2013) **recommend** that the choice of antipsychotic medication is based on Food and Drug Administration (FDA) **approval status,** ADR profile, patient and family preferences, clinician familiarity, and cost. The AACAP practice parameters suggest that usage of olanzapine as first-line agent is limited by its risk for weight gain. Furthermore, as the evidence for the efficacy of ziprasidone in this population is limited, ziprasidone should probably not be considered until new data supporting its efficacy are available (McClellan et al. 2013).

25.3.1.2 Dosing Antipsychotics

Information on dosing recommendations for each antipsychotic (i.e., initial dose, titration, and dose range) is provided in Sect. 5.4.3. Generally, dosing should be informed by emerging ADRs or insufficient efficacy and follow the principle "**Start low**, **go slow**, **but go if needed and tolerated**," and the target dose should be the dose with the highest possible efficacy with the most minimal adverse effects.

Importantly, there is no evidence that target doses of antipsychotics should be driven by the patient's body weight (Schimmelmann et al. 2013a). A treatment trial should be carried out at optimum dosage (highest possible efficacy with minimal ADRs) for 4–6 weeks (NICE guidelines), unless there is no efficacy at all (at full adherence) over 2–3 weeks, or intolerable ADRs. Note that a slow response over the first 4–6 weeks alone does not necessarily justify switching to another antipsychotic, because this is expected in many patients with schizophrenia. If higher than recommended doses are used, the reason for this should be discussed and recorded.

25.3.1.3 Monitoring During Antipsychotic Treatment

A monitoring schedule is provided in Table 5.11. The NICE guidelines recommend to systematically monitor the following:

- Efficacy (change of core symptoms and behavior)
- ADRs taking into account the potential overlap between certain ADRs and clinical features of schizophrenia (e.g., motor symptoms such as akathisia, cognitive symptoms, vigilance, agitation, or anxiety). The emergence of movement disorders is specifically mentioned by the NICE guidelines, potentially because they are often underestimated as symptoms of psychotic disorders and ADRs of antipsychotics.
- Weight, height, waist/hip circumference, fasting blood glucose, HbA1c, blood lipids, and prolactin levels (see Table 5.11).
- Adherence
- Physical health

With regard to ADRs, we recommend to **explain** to patients and parents/carers that all antipsychotics may have **adverse effects** and which ones are to be expected. This should be done **before starting treatment**, if that is possible at all. It should also be explained that, by close monitoring, most ADRs are temporary or decrease with dose reduction or slowing down of titration, or they can be treated (Schimmelmann et al. 2013a). Of note, the objective severity of and the subjective distress by a given ADR, as perceived by the adolescent, often do not concur. Therefore, both should be addressed (Schimmelmann et al. 2005). We further recommend to explicitly assessing sexual dysfunctions as – from clinical experience – they are commonly underreported but cause significant distress.

With regard to efficacy, we recommend to also **assess psychosocial functioning** and **quality of life/subjective well-being** as well as **comorbidities** such as depression, anxiety disorders, or substance use disorders above the core symptoms of schizophrenia regularly. Apply healthy lifestyle counseling right away, as prevention of weight gain has greater health benefits than the needed treatment of overweight/obesity and related metabolic abnormalities caused by antipsychotics (De Hert et al. 2011).

25.3.1.4 Switching Antipsychotics

Switching antipsychotics may destabilize patients with schizophrenia. Therefore, it is important to attempt stabilization of acutely ill patients with treatment options that are sustainable and acceptable long term. If a switch is indicated, clinicians should consider the potential for pharmacodynamic and pharmacokinetic rebound effects, which is most likely when switching too quickly from an agent that has considerably stronger blockade of a given receptor than the post-switch antipsychotic (Correll 2010).

A **pharmacodynamic rebound** may be caused, for example, by switching from an agent with strong dopamine D2-receptor affinity (e.g., risperidone) to an agent with low dopamine D2-antagonism (e.g., quetiapine, clozapine) or even with partial D2-agonism (aripiprazole). The previously blocked dopamine D2-receptors are generally upregulated or more sensitive and can react to the low D2-antagonism or partial agonism by possibly producing a worsening of psychotic symptoms, agitation, or withdrawal dyskinesia if switching these agents is done too quickly.

Similarly, switching from antipsychotics with strong antihistaminergic properties (e.g., clozapine, olanzapine, quetiapine) to those with low antihistaminergic properties (e.g., aripiprazole, ziprasidone), **histaminergic rebound effects** may occur in case of speedy switching, i.e., anxiety,

insomnia, or restlessness and akathisia. In case of switching to aripiprazole or ziprasidone, for example, plateau cross-titration is strongly recommended and/or temporary comedication with benzodiazepines or antihistaminergics (Correll 2010).

Pharmacokinetic rebounds may occur if the elimination half-life ($t_{1/2}$) or reabsorption/metabolism particularities are not attended to. For example, if ziprasidone is not given with a 500 kcal meal, the absorption is reduced and a relatively lower dose of this medication compared to the dose of the pre-switch antipsychotic can lead to dopaminergic rebound. Similarly, pharmacokinetic dopamine rebound can occur even when using cross-titration when switching from antipsychotics with a very short $t_{1/2}$ of 7–8 h (e.g., quetiapine immediate-release formulation or ziprasidone) to other antipsychotics (that generally have $t_{1/2}$ between 16 and 30 h) or when switching to either aripiprazole or sertindole (that have $t_{1/2}$ of approximately 3 days). Here again, longer overlapping switches or plateau cross-titration can avoid complicating rebound phenomena, unless calming comedications are provided in case a switch needs to be faster (Correll 2010).

25.3.2 Pharmacotherapy with Other Psychopharmacological Agents as Supplementary Medication

Special features of combination therapy with antipsychotics are summarized in Table 5.9.

25.3.2.1 Benzodiazepines

Adjunct medication with benzodiazepines (such as lorazepam, diazepam) may be useful in terms of anxiolysis and acute crisis intervention in agitation states but should be only short term to avoid tolerance development. There are older reports (including Sassim and Grohmann 1988) of problematic interactions between clozapine and benzodiazepines (respiratory depression!). Restraint or special caution should be exercised, although a larger study did not confirm these observations (Naber et al. 1992).

25.3.2.2 Antidepressants

Antidepressants may also be indicated in the course of a schizophrenic disorder for treatment of accompanying depressive, anxious, or compulsive symptoms (Chap. 4). It should be noted that significant **interactions with many antipsychotics** can be expected in the form of altered plasma levels of each agent, particularly when classic tricyclic antidepressants are employed (Table 5.9). SSRIs also inhibit a number of CYP enzymes so that increased plasma antipsychotic levels can occur (see Chap. 5). Close monitoring of plasma levels (TDM, see Sect. 2.3) is advisable (assay of all medications in steady state, i.e., at least five $t_{1/2}$; after the most recent dosage change). For the combination of second- and third-generation antipsychotics with antidepressants, see Table 5.9.

25.3.2.3 Mood Stabilizers

In recurrent psychotic episodes with particularly pronounced accompanying affective symptoms of manic or depressive type (so-called schizoaffective disorders), the use of medication as phase prophylaxis may be advisable. Psychotic and manic symptoms are treated with antipsychotics, depressive symptoms with antidepressants (see Chap. 20). It should be noted, however, that the evidence for treatment guidelines for schizoaffective disorder is sparse. Most studies involved only small subsamples of schizoaffective disorder. Therefore, the abovementioned treatment options for schizoaffective disorder are an extrapolation of studies on schizophrenia or bipolar disorder (Murru et al. 2011).

25.4 Treatment Strategy in Specific Situations

25.4.1 Crisis and Challenging Behavior

The chance to treat schizophrenia of children and adolescents in the least invasive setting is increased if a **plan for critical situations** is developed with parents/carers and the child **before a crisis happens**. Accordingly, the NICE guidelines recommend to adhere to the following

principles (adapted from National Institute for Health and Clinical Excellence 2013a): the possible early warning signs of a crisis should be discussed in advance as well as the potential coping strategies; the available support, where the child or adolescent would be admitted to inpatient or day treatment if needed; and the role of the specialized (secondary care) treatment team as well as of the family in the event of a crisis with/without hospitalization. Information about 24-h access to services should be provided including the name of key clinical contacts.

In case the child or adolescent poses an **immediate risk to him/herself** or others during an acute psychotic episode, **rapid tranquillization and restraint** may be needed. While there is no evidence for a specific medication for such situations, benzodiazepines as well as antipsychotics may be used. It is important to keep in mind that the goal in such situations is rapid tranquillization and not "rapid neuroleptization." Therefore, NICE guidelines recommend to be particularly cautious when high-potency antipsychotics (such as haloperidol) are considered, because of the higher risk of acute dystonic reactions and other extrapyramidal motor symptoms in this age group.

Rapid tranquillization should be communicated to the patient and parents/carers in a brief and clear manner. Patients and parents/carers should be given the opportunity to discuss rapid tranquillization and restraint measures after the emergency situation has been resolved. For further information, the reader may also consult the NICE guidelines "quality standard for self-harm" (National Institute for Health and Clinical Excellence 2013b).

25.4.2 Post-acute Treatment

After the acute episode and (partial) remission of symptoms, plans to support recovery and future care should be made. **Relapse prevention** is of high importance. For this purpose, patients and parents/carers commonly weigh the risks and benefits of antipsychotic treatment again. Many young people do not wish to continue their antipsychotic treatment, because for many patients "being in need of antipsychotics" means to be ill, which they do not accept. **Nonadherence** with medication, often hidden from the treatment team, or nonadherence with any continuous treatment is common. Making sense of certain psychotic symptoms and the crisis as a whole as well as "being in control of the symptoms by identifying early warning signs for relapse" and family/peer support may help the young person with schizophrenia to accept the disorder.

Techniques such as "open dialogue," involvement of former patients ("ExIn"), and an attitude towards recovery as perceived by patients and their family may help to meet the individual needs of the young patients and keep them on track to recovery. Further information on measures to promote recovery is summarized in the NICE guidelines (National Institute for Health and Clinical Excellence 2013b).

If a young person does not wish to continue antipsychotic medication, reduce the dose gradually and monitor for signs of relapse.

25.4.3 Interventions for Nonresponders

In case of nonresponse (unsuccessful 4–6 week antipsychotic trial at recommended target dose), antipsychotics should be switched after the diagnosis has been re-reviewed, adherence with medication has been assessed, and other causes of nonresponse have been ruled out. These may be comorbid disorders (such as substance abuse) or failure of psychosocial interventions including unsuccessful engagement of patient and/or parents into the treatment plan. According to our clinical experience, a negative attitude of parents or peers towards medication and towards the treatment as a whole or the psychotic disorder may have deleterious impact on antipsychotic response and recovery of the young person.

If **switching** the antipsychotic is **considered**, see Sect. 25.3.1.4 for detailed strategies. The NICE guidelines explicitly (National Institute for Health and Clinical Excellence 2013a) recommend a trial

with the third-generation antipsychotic **aripiprazole** in adolescents, aged 15–17 years, whose schizophrenia has not been adequately treated with risperidone.

Clozapine should only be considered **after two full antipsychotic trials** were unsuccessful, and adherence to the precautions necessary for clozapine treatment is likely. Thus, clozapine is indicated in treatment-refractory schizophrenia in children and adolescents. Risks and benefits of clozapine should be weighed against the risks and benefits of antipsychotic polypharmacy.

While there is little evidence for the risks and benefits of antipsychotic **polypharmacy** in children and adolescents, research from adults indicates that the risks of antipsychotic polypharmacy outweigh the benefits despite its common use in clinical practice (Gallego et al. 2012). If antipsychotic polypharmacy is administered, it is recommended to choose a second antipsychotic with a different ADR profile in order to avoid potentiation of certain ADRs (Schimmelmann et al. 2013a).

Apart from optimizing antipsychotic therapy in nonresponders, optimizing need-adapted psychosocial interventions and initiating rehabilitative measures are of high importance. In severe impaired schizophrenia, when medication does not help, electroconvulsive therapy is a treatment option (McClellan et al. 2013).

25.4.4 Treatment of Attenuated Psychotic Symptoms

The clinical validity of attenuated psychotic symptoms or the newly introduced attenuated psychosis syndrome (Section III of DSM-5 for further research) has not been studied in children and young adolescents, while many studies at least included a few adolescents, aged 16 years and above (for a review, see Schimmelmann et al. 2013b). Nevertheless, transient or attenuated psychotic symptoms, not sufficient for a diagnosis of a psychotic disorder, may still be distressing and impairing, may lead to help-seeking, and therefore require intervention. For these patients, the NICE guidelines (National Institute for Health and Clinical Excellence 2013a) recommend to consider individual cognitive behavioral therapy with or without family intervention and the treatment of relevant comorbid conditions such as anxiety disorders or depression according to the respective guidelines. The NICE guidelines explicitly recommend to not offering antipsychotic medication for the treatment of these symptoms or for decreasing the risk of psychosis in children and adolescents.

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Sleep Disorders

26

Andreas Warnke and Christoph Wewetzer

Contents

A. Warnke, MD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: warnke@kjp.uni-wuerzburg.de

C. Wewetzer, MD
Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Florentine-Eichler-Str. 1, 51067 Köln, Germany
e-mail: wewetzerc@kliniken-koeln.de

26.1 Definition, Classification, and Target Symptoms

Sleep disorders are characterized by difficulties with the initiation and maintenance of sleep. Duration, quality, and timing of sleep are abnormal, causing distress (insomnias, dyssomnias). There are also abnormal experiences and behaviors that occur during sleep and are regarded as disturbing by the affected person or by those around them (parasomnias).

Insomnia disorders have been categorized in various ways in different sleep disorder classification systems. The International Classification of Sleep Disorders, 2nd edition (ICSD-2), identifies insomnia as one of eight major categories of sleep disorders (American Academy of Sleep Medicine 2005) and, within this group, lists 12 specific insomnia disorders (Fig. 26.1).

ICSD-2 delineates both general diagnostic criteria that apply to all insomnia disorders, as well as more specific criteria for each diagnosis. Insomnia complaints may also occur in association with comorbid disorders or other sleep disorder categories, such as sleep-related breathing disorders, circadian rhythm sleep disorders, and

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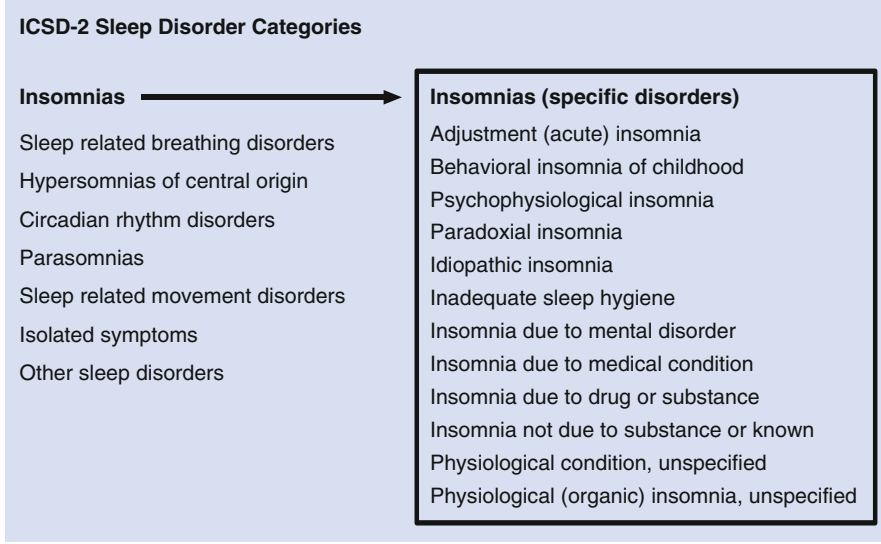

Fig. 26.1 ICSD-2 (International Classification of Sleep Disorders, 2nd Edition) insomnia diagnosis (Schutte-Rodin et al. 2008)

sleep-related movement disorders (Fig. 26.1). According to ICSD-2, an insomnia disorder is defined as a subjective report of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep and that result in some form of daytime impairment (Table 26.1).

Discussion is **limited** in this chapter to the sleep disorders categorized by the International Classification of Diseases, 10th revision (**ICD-10**; World Health Organization 1996), as "nonorganic sleep disorders (F51)." This excludes sleep disorders arising from primary organic disorders and those explained by misuse of psychotropic substances or medications. Nonorganic sleep disorders are diagnosed as distinct disorders if the symptoms caused by the sleep disorder predominate, even where they are symptoms of other mental or physical disorders. The **nonorganic sleep disorders** include according to ICD-10:

- Nonorganic insomnia (F51.0; DSM-5: insomnia disorder 780.52)
- Nonorganic hypersomnia (F51.1; DSM-5: hypersomnolence disorder 780.54)
- Nonorganic disorder of the sleep-wake schedule (F51.2)
- Sleep walking (somnambulism, F51.3; DSM-5: sleep walking type 307.46)

Table 26.1 Diagnostic criteria for insomnia

- A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early or sleep that is chronically non-restorative or poor in quality
- The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep
- At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the patient:
  1. Fatigue or malaise
  2. Attention, concentration, or memory impairment
  3. Social or vocational dysfunction or poor school performance
  4. Mood disturbance or irritability
  5. Daytime sleepiness
  6. Motivation, energy, or initiative reduction
  7. Proneness for errors/accidents at work or while driving
  8. Tension, headaches, or gastrointestinal symptoms in response to sleep loss
  9. Concerns or worries about sleep

According to the American Academy of Sleep Medicine (2005)

- Sleep terrors (night terrors, pavor nocturnus, F51.4; DSM-5: sleep terror type 307.46 of "non-rapid eye movement sleep arousal disorders")
- Nightmares (F51.5; DSM-5: nightmare disorder 307.47)

In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (**DSM-5**), sleep disorders are classified under "sleep-wake disorders" (American Psychiatric Association 2013). The classification refers partially to the ICD-10 medical conditions classification (nonpsychiatric listings) G47 (sleep disorders), partially to the F51 classification, and also to the ICSD-2. The intention is that the classification should be useful for general mental health as well as for medical clinicians. The differential diagnosis would necessitate a multidimensional approach because of possibly co-occurring nonorganic mental, medical, and neurological conditions. The chapter on "sleep-wake disorders" in DSM-5 includes ten "disorder groups": insomnia disorder (corresponding to nonorganic insomnia F51.0), hypersomnolence disorder (F51.2), narcolepsy (G47.4), breathing-related sleep disorders, circadian rhythm sleep-wake disorders, non-rapid eye movement (NREM) sleep arousal disorders (sleep walking F 51.3, sleep terrors F51.4), nightmare disorder (F51.5), rapid eye movement (REM) sleep behavior disorder, restless legs syndrome, and substance-/medication-induced sleep disorder. Associated daytime distress and impairment are core features of all these disorder groups.

The **target symptoms** depend upon the type of sleep disorder. We refer to the nonorganic sleep disorders with regard to ICD-10 (F51). These are:

- in nonorganic insomnia, disturbance of sleep initiation and maintenance, the disturbed sleep-wake schedule.
- In nonorganic hypersomnia, the increased need for sleep,
- in sleep terrors and sleep walking, the rarely severe impairment of daily life and the risk of harm to self or others resulting from agitation or motor activity during sleep.

For further information regarding the diagnosis and therapeutic interventions of sleep disorders in children, adolescents, and adults, the reader is referred to reviews published on these topics (Buford and Nemeroff 2012; Dahl and Harvey 2008; Olson et al. 2008; Owens and Mindell 2011; Mindell et al. 2006; Schutte-Rodin et al. 2008; Smith et al. 2011).

26.2 Therapeutic Framework

The **diagnosis** is made by interviewing the patient and their caregivers regarding:

- bedtime habits (sleep hygiene),
- the duration of and behavior during periods when the patient cannot fall asleep and during waking phases,
- total sleep duration and sleep behavior during the day,
- adverse consequences of the sleep disorder,
- the reactions of those around the patient to the sleep disorder.

For parasomnias, information regarding symptoms, frequency, duration, and ability to remember the parasomnia should be gathered. Information relevant to explaining insomnias is derived from the patient's developmental history, external disorder-relevant factors (parenting behavior, mental stressors, physical complaints), and questioning regarding psychiatric comorbidity (anxiety disorder, depression, ADHD, affective disorders, posttraumatic stress disorder, drug abuse). Clinical and pathological laboratory examination (EEG for patients with sleep terrors and sleep walking, sleep laboratory, and assessment of respiratory function in hypersomnias) and psychological testing (intelligence assessment, diagnostic tests for determination of psychiatric comorbidity) are appropriate in individual cases. The differential diagnosis must exclude thyroid gland dysfunction, pain syndromes, and respiratory disorders.

Therapeutic interventions are based upon comprehensive counseling and, where required, behavioral therapeutic and pharmacological interventions. **Counseling** includes explanation of the features of normal age-appropriate sleep, the elements of good sleep hygiene (regular bedtimes, falling asleep rituals, avoiding hunger and thirst), as well as supportive parenting (no unnecessary sleep phases during the day, no rewarding reinforcement of delayed bedtime or waking). **Behavioral therapeutic measures** are based upon extinction procedures, stimulus control (no daytime sleep, bed used only for sleeping), and in older children and adolescents on relaxation methods, cognitive techniques, and conflict- or stress-oriented psychotherapy (further details:

Dahl and Harvey 2008; Olson et al. 2008; Owens and Mindell 2011; Schutte-Rodin et al. 2008).

Indications for pharmacotherapy are provided by:

- Treatment of causal psychiatric or organic disorders
- Nonorganic insomnias
- Nonorganic hypersomnias
- Sleep terrors
- Sleep walking

Prior to **prescribing** sleep-inducing medication, the **following principles must be observed**:

- Consideration of the type of sleep disorder (the primary complaints, e.g., disorders of sleep initiation and/or maintenance, frequent awakenings, disorder of sleep-wake schedule, parasomnia).
- Consideration of the duration and severity of the sleep disorder.
- Consideration of everyday complaints and of the extent to which daytime performance might be affected by medication.
- Consideration of the age of the patient.
- Consideration of prior medication and treatment.
- Consideration of a primary psychiatric or other organic disorder, such as pervasive developmental disorder, ADHD, psychosis, depression, anxiety disorder, or suicidality, chronic pain, and blindness.
- Explanation of therapy for the patient and parents, with particular regard to time limits for medication, potential withdrawal reactions, avoidance of alcohol, and possible impairments of daily life arising from medication.
- Avoidance of high dosages (lowest possible dosage according to product information).
- Only short-term medication (days to 2 weeks), intermittent where possible.
- No abrupt withdrawal if medication has been continuous for 2 weeks.
- Avoidance of sedation extending into the day – unless such sedation is desirable (suicidality, for instance).
- Setting the exact dosage.
- Clarify to what extent a repeat treatment is from the outset indicated and feasible.
- The total amount of the prescribed medication for outpatients should not exceed what is required for 3–4 weeks' standard dosage. A further appointment should be scheduled for within 2–4 weeks.
- Consideration of contraindications.
- Exclusion of drug abuse in at-risk patients.

26.3 Choice of Pharmacotherapy

Because no medications, except chloral hydrate, are currently labeled by the US Food and Drug Administration (FDA) for the treatment of insomnia in children and adolescents, the use of these medication in practice settings appears to be based largely on clinical experience, empirical data derived from adults, or small case series of sedative-hypnotics in pediatric population (Owens and Mindell 2011). Table 26.2 summarizes FDA-approved drugs for insomnia in adults as well as dosages and elimination half-lifes.

The clinical guidelines for the evaluation and management of chronic insomnia in adults are generally appropriate also for younger adults (Schutte-Rodin et al. 2008) but not generally for children. **Most** of primary **sleep disorders** in children do **not need any medication**. If medication is believed to be potentially therapeutically beneficial in a given clinical situation (i.e., appropriately implemented behavioral interventions are not fully effective), the choice of sleep medication is dependent upon the target symptomatology and the attendant circumstances.

26.3.1 Benzodiazepines

The **first-choice** pharmacological treatment for primary insomnia is short-term use of **short- to intermediate-acting** benzodiazepines: examples

Table 26.2 US Food and Drug Administration (FDA)-approved medication for insomnia in adults

Drugs	Dose range (mg)	Elimination half-life (h)
Benzodiazepines		
Estazolam	1–2	10–24
Eszopiclone	2–3	6
Flurazepam	15–30	24–100
Lorazepam	2–4	10–20
Quazepam	7.5–15	25–41
Temazepam	7.5–30	8–15
Triazolam	0.125–0.5	1.5–5.5
Zaleplon	5–20	1
Zolpidem	5–10 (immediate release)	2.5
Zopiclone	3.75–7.5	3.5–6.5
Other anxiolytics and sedative-hypnotics		
Diphenhydramine (antihistamine)	25–100	8.5
Doxepin (tricyclic antidepressant)	1–6	8–24
Ramelteon (melatonin receptor agonist)	8	1–2.6

According to Buford and Nemeroff (2012)

are eszopiclone, temazepam, triazolam, zaleplon, and zolpidem (see Sect. 6.7 and Table 26.2). Eszopiclone and zolpidem demonstrated continued efficacy in adults without significant complications for 6 months, and in open-label studies for 12 months or longer (see Sect. 6.4.1). The benzodiazepines have positive effects on sleep latency, total sleep time, and/or waking after sleep onset. However, a single published clinical trial of zolpidem in children failed to show efficacy (Owens and Mindell 2011).

According to a **FDA black box warning**, benzodiazepines have been associated with reports of disruptive sleep-related behaviors including sleep walking and driving. Patients should be informed about the need of allowing appropriate sleep time and avoiding the combination of benzodiazepines with alcohol, other sedatives, and sleep restriction.

26.3.2 Sedating Antidepressants

Sedating antidepressants such as doxepin, mirtazapine, nefazodone, and trazodone, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants are used in clinical practice to treat insomnia in adult and pediatric populations. An analysis of 2002 prescribing practices in the USA found that three of four medications prescribed for insomnia were antidepressants such as amitriptyline, mirtazapine, and trazodone (Walsh 2004). However, due to the occurrence or potentially significant adverse drug reactions (ADRs) such as daytime residual sedation, orthostatic hypotension, cardiac arrhythmias, and anticholinergic effects, these drugs **should not be used in nonpsychiatric patients**. According to the clinical guideline for the evaluation and management of chronic insomnia in adults that are reported to be generally appropriate also for younger adults (Schutte-Rodin et al. 2008), sedating low-dose antidepressants may be **considered only** when **insomnia** is accompanied **with comorbid depression** or in the case of other treatment failures. Examples of these drugs include amitriptyline, doxepin, mirtazapine, and trazodone.

26.3.3 Melatonin and Ramelteon

Melatonin, a nutritional substance and over-the-counter medication, and ramelteon, a FDA-approved (treatment of insomnia characterized by difficulty with sleep onset) melatonin receptor agonist (MT_1 and MT_2) with an entirely new mechanism of action that is different from classic hypnotics, have been reported to be potentially useful in the pediatric population (Coppola et al. 2004; Liu and Wang 2012; Smits et al. 2001, 2003).

Melatonin is a hormone endogenously produced by the pineal gland that plays a key role in the regulation of the sleep-wake cycle. The efficacy of melatonin supplementation has been tested in a large number of clinical trials. Meta-analyses have demonstrated that melatonin has small effects on sleep latency, with little effect on wake time after sleep onset or total sleep time. Therefore, it is **not recommended** in the treatment of **chronic insomnia** (Schutte-Rodin et al. 2008). However, there are studies in children and adolescents with insomnia accompanied with comorbid disorders showing efficacy (Smits et al. 2001, 2003; Stigler et al. 2006). For example, a randomized, placebo-controlled study

found that melatonin improves wake-sleep disorders in children with intellectual deficits (Coppola et al. 2004; for sleep disorders in children with intellectual disability, see Chap. 23). The results in the study of Smits et al. (2001) showed that melatonin, 5 mg administered at 6 p.m., was relatively safe to take in the short term, and significantly more effective than placebo in advancing sleep onset and increasing sleep duration in elementary school children with chronic sleep-onset insomnia. Sustained attention was not affected. Smits et al. (2003) found again that melatonin improved health status and advanced the sleep-wake rhythm in children with idiopathic chronic sleep-onset insomnia. In addition, melatonin was shown to be effective in reducing sleep latency in children with ADHD (van der Heijden et al. 2006).

26.3.4 Other Pharmacological Agents

Second-generation **antipsychotics** such as quetiapine and olanzapine are **only** suitable for patients with **comorbid insomnia**. Because of the significant ADRs, their use is not recommended in the treatment of insomnia in the general population (see Sects. 26.4.4 and 26.4.5).

Antihistamines (e.g., hydroxyzine, diphenhydramine) are widely used in pediatric psychiatric practice as a sedative in patients with insomnia (Zito et al. 2000). But according to the clinical guideline for the evaluation and management of chronic insomnia in adults, antihistamines are **not recommended** for long-term use (Schutte-Rodin et al. 2008).

26.3.5 Herbal Medicine

The most commonly employed herbal hypnotics include extracts of valerian (*V. officinalis*), *Melissa officinalis*, and hops. Numerous simple and combination preparations with differing dosages are commercially available, facilitating their frequent use. In contrast to medications, makers of herbal supplements do not have to get approval from the US FDA before putting their products on the market. They fall under a category called dietary supplements and are available as either over-the-counter drugs or dietary supplements.

The **efficacy** of phytotherapeutic preparations in sleep disorders has, however, **not** been compellingly **demonstrated** (Fernandez-San-Martin et al. 2010; Sarris et al. 2011; Smith et al. 2011). As a rule, a placebo effect of about 50 % of the patients medicated can be assumed in the medication of sleep disorders. *V. officinalis* is the only botanical with sufficient research of adequate rigor in the area of insomnia (Sarris et al. 2011). Meta-analyses and reviews by Fernandez-San-Martin et al. (2010) and Sarris et al. (2011) reveal that the evidence concerning the soporific plant medicine is quite varied and currently does not support its use in treating insomnia. For example, one of the meta-analysis which included 16 eligible randomized and controlled trials on Valeriana spp. monotherapy or in combination with other herbal medicines found that 9 out of 16 studies did not have positive outcomes in regard to improvement of sleep quality (Sarris et al. 2011). The safety profile of Valeriana spp. appears good; however, traditional pharmacopoeias caution it as a "cerebral stimulant" (see Sarris et al. 2011); thus, it may not consistently provide somnolence.

26.4 Treatment Strategy

26.4.1 Sleep Initiation and Sleep Maintenance Disorders in the First Half of the Night

Sedative-hypnotics with a short duration of action are appropriate here (Table 26.2), for example, zolpidem administered 30 min prior to bedtime (adult dose 5–10 mg/day). Estazolam is used for short-term treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. For adults, the recommended dose is 1 mg at bedtime.

26.4.2 Sleep Maintenance Disorders

Sedative-hypnotics with short or medium durations of action (Table 26.2), such as **benzodiazepines** (e.g., lorazepam) or **antihistamines** (e.g., diphenhydramine), are used in clinical practice.

Lorazepam is administered in adult insomnia due to anxiety or transient situational stress as a single daily dose of 0.5–2.5 mg, usually about half an hour before bedtime. In children, lower doses are recommended. In order to avoid a hangover effect, it should not, however, be given after 3 a.m.

When **employing benzodiazepines**, the following points should be noted:

- Sleepiness and slowness continuing into the day (hangover).
- Impairment of learning performance because of concentration difficulties.
- Sleep disturbance and anxiety as rebound phenomena during withdrawal.
- Respiratory depression as possible ADR, particularly with existing respiratory disorders.
- Paradoxical reaction, particularly in children with ADHD or intelligence deficits.
- The medication should essentially be employed only for very short periods because of the potential tolerance and dependence.

There are no specific dosing guidelines for **antihistamines** in children and adolescents with sleep disorders. Diphenhydramine is administered orally at doses of 25–50 mg two to three times a day. Doxylamine is administered orally at doses of 12.5 mg two to four times a day. Hydroxyzine is administered orally for anxiety disorders at doses of 25–75 mg, broken into two to three individual doses.

26.4.3 Sleep Disorders in Depression

When insomnia is accompanied with comorbid depression or in the case of other treatment failures, sedating low-dose antidepressants may be considered. Examples of these drugs include amitriptyline, doxepin, mirtazapine, and trazodone. If a sedating antidepressant drug is used as monotherapy for a patient with comorbid depression and insomnia, the dose should be that recommended for treatment of depression (see Chap. 4). In many cases, this dose will be higher than the typical dose used to treat insomnia alone (Schutte-Rodin et al. 2008).

26.4.4 Insomnias in Which Benzodiazepines and Antidepressants are Contraindicated

In nonpsychotic patients with insomnia, where benzodiazepines are contraindicated (dependence risk, medication misuse) or antidepressants are ineffective or contraindicated, low-potency antipsychotics are used in pediatric population. According to our experience, options include levomepromazine (15–30 mg/day) and melperone (20–75 mg/day) administered 30 min before bedtime as a single dose.

26.4.5 Insomnias in Context of a Psychosis

Where high-potency antipsychotics that have excellent antipsychotic but only minor sleep-promoting effects (such as haloperidol, risperidone, olanzapine, quetiapine) do not afford sufficient sleep in acute insomnia, the following alternatives are available (for dosages of antipsychotics, see Sect. 5.4.3): combination of high-potency antipsychotics with benzodiazepines (e.g., risperidone or olanzapine with lorazepam) or combination with low-potency antipsychotics (such as levomepromazine).

26.4.6 Mild Sleep Initiation Disorders, Rejection of Primarily Indicated Sleep-Promoting Agents, or Ancillary Measures for Behavioral Therapeutic Intervention: Phytotherapeutic Preparations

Herbal preparations are indicated for mild sleep initiation disorders without consequences for daily life, where the usually prescribed sleep-promoting medications are rejected by the patient or their parents, and as support

for psychoeducative and psychotherapeutic sleep therapy measures. The most commonly employed herbal hypnotics include extracts of valerian, *Melissa officinalis*, and hops. Numerous simple and combination preparations with differing dosages are commercially available. The alcohol content of some preparations should be noted.

26.4.7 Treatment of Disorders of the Sleep-Wake Schedule

Melatonin and ramelteon are employed for this indication. The recommended dose of ramelteon in adults is 8 mg taken within 30 min of going to bed. According to our personal clinical experiences, sleep disorders can be effectively treated with **melatonin**, particularly in cases where disturbances of the sleep-wake cycle are evident in children and in adolescents with visual or multiple handicaps (blindness, autism). In order to achieve a sleep-promoting effect, according to our own clinical experience, it is sufficient in many cases to take one to a maximum of 5 mg 30–60 min before retiring. The necessary dosage in an individual should be titrated in 1 mg increments.

26.4.8 Parasomnias

Nightmares do not require pharmaceutical therapy. Alcohol and the following medications can, however, induce nightmares: β-blockers, tricyclic antidepressants, barbiturates, and benzodiazepines. If the magnitude of the nightmare problem has a significantly negative impact on daily life, dosage reduction or a change of medication, if possible, may be appropriate in the case of medication-induced nightmares, and the patient should refrain from consuming alcohol.

26.4.9 Sleep Terrors and Sleep Walking

Pharmacological treatment should be preceded by psychoeducation, whereby the following should be considered:

- Sleep terrors do not represent a serious psychiatric or neurological disorder.
- Adequate nighttime sleep must be ensured.
- Safety measures should be undertaken to prevent the child from hurting itself during sleep terror episodes (closing of windows and doors; blocking of stairs by mesh).
- The child should be woken before the time point at which the sleep terrors normally occur.

It should be noted that **sleep terrors** can be **induced by** various **medications**, including lithium salts and desipramine. The decision as to whether dosage reduction or change of medication is required must be made on a case-by-case basis. Prior to pharmacological intervention, other possible triggers (sleep apnea, gastrointestinal reflux, cerebral seizures) should be excluded.

Medication is indicated only if there is **danger of physical injury** to the child, the family has caused significant distress by the severity and frequency of the sleep terrors, and the child suffers negative consequences in their daily life. Benzodiazepines and tricyclic antidepressants have proved helpful (Burstein and Burstein 1983; Cooper 1987; Fisher et al. 1973). Imipramine and diazepam can be recommended. Diazepam can be administered as a single dose of 6–10 mg to school-age children and adolescents before going to sleep. It should be noted, however, that sleep terrors can return after discontinuation of medication.

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Tic Disorders

27

Veit Roessner and Aribert Rothenberger

Contents

V. Roessner, MD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, TU Dresden, Schubert Str. 42, 01307 Dresden, Germany
e-mail: veit.roessner@uniklinikum-dresden.de

A. Rothenberger, MD
Clinic for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Medical Center Göttingen, von-Siebold-Str. 5, 37075 Göttingen, Germany
e-mail: arothen@gwdg.de

27.1 Definition, Classification, and Target Symptoms

Tics are sudden, abrupt, short, nonrhythmic, repetitive, involuntary movements or vocal productions that serve no recognizable purpose. They wax and wane spontaneously over time and look like fragments of normal movements. Their frequency may increase in situations of stress or challenge and during emotional excitement. The symptomatology is attenuated during sleep and by goal-oriented behavior/concentration. Tics can be voluntarily suppressed for limited periods of time; the sensory-motor phenomena before a tic may be used as signal. Apart from simple movements and vocal impulses, more complex motor (e.g., slapping oneself, hopping, copropraxia = obscene gesturing, echopraxia = imitation of others) and linguistic discharges (such as coprolalia = use of obscene language, palilalia = repetition of the most recently spoken syllables or words and echolalia = repetition of words spoken by others) can also occur. The combination of chronic (lasting longer than a year) vocal and multiple motor tics is termed **Tourette syndrome** (TS).

Motor tics are usually first manifested from the age of 7 years, vocal tics from 11 years, and coprolalia from approximately 15 years; from the age of 18 years, the symptomatology of many patients decreases, independent of treatment (Cath et al. 2011; Roessner et al. 2011; Verdellen et al. 2011). The International Classification of Diseases, 10th revision (**ICD-10**), distinguishes the following **subtypes** (World Health Organisation 1996):

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- Transient tic disorder (F95.0; DSM-5: provisional tic disorder 307.21)
- Chronic motor or vocal tic disorder (F95.1; DSM-5: persistent chronic motor or vocal tic disorder 307.22)
- Combined vocal and multiple motor tic disorder (TS, F95.2; DSM-5: Tourette disorder 307.23)

According to the criteria outlined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (**DSM-5**), to make a diagnosis of definite TS (American Psychiatric Association 2013; Cath et al. 2011):

- Both multiple motor and one or more phonic tics must be present at some time during the illness, although not necessarily concurrently.
- The tics may wax and wane in frequency but have persisted throughout a period of more than 1 year since the first tic onset.
- The onset must be before age 18 years.
- The disturbance must not be due to the direct physiological effects of a substance (e.g., psychostimulants) or another medical condition (e.g., Huntington disease or postviral encephalitis).

Tic disorders are frequently associated with attention-deficit/hyperactivity disorder (ADHD, 50–75 %) and obsessive-compulsive disorders (30–65 %). Further, they are often accompanied by learning difficulties, affective disorders, anxiety disorders, sleep disorders, self-injurious behavior, and restless legs syndrome (Freeman 2007; Rothenberger and Roessner 2013).

Target symptoms are the motor and vocal tics, but the commonly comorbid disorders (about 80 % of cases with TS), such as ADHD and compulsions, frequently also require attention or even higher priority with respect to therapy, because of psychosocial impairment.

27.2 Therapeutic Framework

Diagnostic prerequisite are a detailed **assessment** with **symptom history** based on interviews with the parents of the child and other caregivers, structured behavioral observation, and a tic record prepared under normal living conditions (Yale Tourette syndrome symptom list). A physical-neurological examination and a psychological-psychiatric **diagnosis** focusing on frequently occurring comorbidities should be undertaken and the EEG assessed (to exclude epilepsy).

The tendency to spontaneous remission (from the age of 14–16 years) as well as the only minor impairment of psychosocial development in many cases means that informing the affected person and their family in the sense of **psychoeducation** is **often sufficient** to allow better understanding of the tic symptomatology and thus to enable them to deal with it adequately. Personal contact with other affected persons in the context of self-help groups often achieves a positive effect in the sense of coming to terms with the disease.

Appropriate **psychotherapeutic approaches** include instruction in relaxation techniques (preferably Jacobson progressive muscle relaxation) and cognitive-behavioral strategies for controlling symptoms. Awareness training, relaxation, voluntary movements that are incompatible with the target tic, and the corresponding automation and generalization are trained in the framework of a behavioral therapeutic program for habit reversal, with the ultimate goal of self-management (Verdellen et al. 2011). This may also include neurofeedback (Gevensleben et al. 2014).

The **indication for pharmacotherapy** depends upon the severity of the symptomatology, objective psychosocial impairment, and the significant subjective distress associated with the disorder, usually only if a chronic course (longer than 12 months) is present. Treatment should be adjusted according to any comorbid psychiatric disorders. For further information regarding the therapy of tic disorders including pharmacological treatment, behavioral and psychosocial interventions, and deep brain stimulation, the reader is referred to the published reviews (Jankovic and Kurlan 2011a; Mogwitz et al. 2013; Müller-Vahl et al. 2011b; Roessner et al. 2011, 2013; Verdellen et al. 2011).

The **guidelines** of the European Society for the Study of Tourette Syndrome (ESSTS) **differ** somewhat from the recommendations for the treatment of tics published by authors from the USA (e.g., Jankovic and Kurlan 2011a). Jankovic

and Kurlan (2011a) recommend pharmacotherapy as first-choice treatment followed by habit reversal training. In contrast, ESSTS experts do not prioritize behavioural treatment (habit reversal training or exposure and response prevention) or pharmacotherapy in addition to psychoeducation (Roessner et al. 2011; Verdellen et al. 2011). They only refer to availability or preference of the family as selection criterion and recommended switching in case of refractoriness. Given the scarcity of randomized controlled studies on the treatment of tics, it was concluded that recommendations heavily depend on experts' experiences and preferences rather than scientific evidence (Jankovic and Kurlan 2011b; Mogwitz et al. 2013; Müller-Vahl et al. 2011a; Roessner et al. 2011).

27.3 Choice of Pharmacotherapy

On the basis of our interpretation of evidence-based literature (Roessner and Rothenberger 2013) and our own experience, the following hierarchy of pharmacotherapy with second- and third-generation antipsychotics (see Chap. 5) is recommended:

First-Line Medication

Tiapride: maximum of 1,200 mg/day, divided into 3 doses, increased by 50–200 mg/week, starting with about 2.5 mg/kg body weight per day, increase to usual dose of 5 mg/kg body weight per day and if necessary up to 10 mg/kg body weight per day

Second-Line Medication

Risperidone: 0.5–4 mg/day, divided into 1–2 doses (greater dose in the evening), increasing steps by 0.25–0.5 mg/week

Aripiprazole: maximum of 40 mg/day, divided into 2 doses, increased by 2.5–5 mg/week

First-line medication if **tics** are **combined with** stress-sensitivity, emotional symptoms, and obsessive-compulsive traits.

Sulpiride: maximum of 900 mg/day, divided into 3 doses, increased by 50–200 mg/week; for steps, see tiapride, i.e., 2.5–10 mg/kg body weight per day

This **recommendation** of pharmacotherapy **differs** from Jankovic and Kurlan (2011a) and the ESSTS (e.g., Roessner et al. 2011). The **US** authors have recommended guanfacine and tetrabenazine as first-choice treatment followed by fluphenazine, risperidone, and other second-generation antipsychotics, clonazepam, topiramate, and botulinum toxin. In contrast, **ESSTS** experts have recommended risperidone as first-choice treatment followed by tiapride, sulpiride, and aripiprazole (e.g., Roessner et al. 2011).

Interestingly, none of the recommended drugs were approved by the US Food and Drug Administration (FDA) for the treatment of TS. Only haloperidol (children ≥3 years, adolescents, and adults) and pimozide (12 years and older) are labeled by the FDA for the treatment of TS.

The **differences in the treatment algorithm** seem to largely reflect differences in regional drug supply and experience (Jankovic and Kurlan 2011b; Müller-Vahl et al. 2011a). For example, guanfacine is used very rarely in Europe because it has been withdrawn from the market in several European countries; tetrabenazine, a monoamine-depleting drug that does not cause tardive dyskinesia, is used relatively infrequently in Europe, whereas tiapride and sulpiride are not available in the USA but are used relatively frequently in Europe. According to a questionnaire asking for treatment preferences of tics among ESSTS members, tetrabenazine is the eighth and guanfacine the 15th choice (among 17 different drugs; Roessner et al. 2011). Most European TS experts would opt for risperidone followed by clonidine, aripiprazole, pimozide, sulpiride, tiapride, and haloperidol (Roessner et al. 2011).

27.3.1 Tiapride as First-Line Medication

Tiapride, a selective antagonist of dopamine D2 receptors (Table 27.1) with weak antipsychotic properties, is used commonly in Europe for the treatment of tics because of positive clinical experience with this agent since decades. There has, however, been only one placebo-controlled, double-blind study that has clinically examined the efficacy of tiapride in the treatment of tic disorders in children and adolescents (Eggers

Table 27.1 Tiapride: pharmacological properties and recommended dosages

Pharmacodynamic properties	Second-generation antipsychotic; dopamine D2-receptor antagonist, attenuation of dopamine-mediated effects
Pharmacokinetic properties	t_{max} approximately 1 h, $t_{1/2}$ 2,6–4 h; protein binding, not known; bioavailability 75 % Elimination almost exclusively renal
Indications	Neuroleptic-induced tardive dyskinesia. It is widely available outside of the USA It is not intended for treatment in children Off-label: treatment of tic disorders
Dosages	Tic disorder (based on our clinical experience) Maximum of 1,200 mg/day, divided into 3 doses, increased by 50–200 mg/week, starting with about 2.5 mg/kg body weight per day, increase to usual dose of 5 mg/kg body weight per day and if necessary up to 10 mg/kg body weight per day
Adverse drug reactions (ADRs)	Weight gain, tiredness, sleep disturbances, headache, vertigo, increased prolactin levels Extrapyramidal motor ADRs rare
Drug Interactions	Intensification of CNS depressants, reduced efficacy of anticholinergic agents and dopamine receptor agonists, alcohol increases sedation
Contraindications	Seizures, renal dysfunction, prolactin-dependent tumors
Monitoring	Until third treatment month: monthly blood picture, creatinine, transaminases; then quarterly or semiannually blood picture Monitor ECG and EEG in the first month, then semiannually; check pulse and blood pressure

The summaries are based upon information included in the Summary of Product Characteristics of tiapride
t_{max} time point at which the maximal blood concentration (c_{max}) is reached, $t_{1/2}$ elimination half-life

et al. 1988): Enrolling 27 children with TS, at doses ranging from 4 to 6 mg/kg/day, it was found that tiapride is superior to placebo and produces a 44 % decrease in videotaped tic counts.

Table 27.1 summarizes important key pharmacological data and dosage recommendations. Tiapride is a second-generation antipsychotic (see Chap. 5) that is generally well tolerated and is associated with only a low risk of extrapyramidal motor adverse drugs reactions (ADRs). Cardiovascular effects, tiredness, and depressive mood may be observed. In individual cases, serum prolactin levels may be increased, the effects of which can include galactorrhea. No other endocrinological effects have been observed.

27.3.2 Risperidone and Aripiprazole as Second-Line Medications

The second-generation antipsychotic risperidone has established itself as a second-choice medication, found by double-blind studies to be efficacious (e.g., Scahill et al. 2003, see also Chap. 5). Further, combination therapy with risperidone (low dosage) and a selective serotonin reuptake inhibitor (SSRI) favorably influences both tic disorders and comorbid compulsive behavior (Bloch et al. 2006). Because of the risk of extrapyramidal motor ADRs, a daily dosage of 4 mg risperidone should not be exceeded. Key pharmacological data as well as dosage recommendations are summarized in Sect. 5.7.16.

A special position is occupied by the third-generation antipsychotic aripiprazole because of its unusual mechanism of action (partial agonist at the dopamine D2-receptor family; see Sect. 5.3). It achieved considerable improvement of tic symptomatology in many cases where pharmacological therapy had previously been inadequate, together with a favorable relationship between efficacy and ADRs. Evidence, however, is currently limited to prospective case studies, several open trials and one multicenter, randomized, double-blind, placebo-controlled study (Seo et al. 2008; Yoo et al. 2007, 2013). However, efficacy in the treatment of tics and good safety has been reported in a total of about 260 cases (for a review see Roessner et al. 2011). Section 5.7.1 summarizes the key pharmacological data as well as dosage recommendations.

27.3.3 Third-Line Medications

Haloperidol, a classical, first-generation antipsychotic (see Sect. 5.2), is labeled by the FDA for the treatment of TS (from the age of 3 years). Numerous clinical studies have indicated that dosages of up to 10 mg/day achieve significant improvement of tic symptoms; the more frequent presentation of extrapyramidal motor ADRs and QTc prolongation, however, is a problem (see Sect. 5.4.4). Haloperidol is better tolerated at lower doses (up to 4 mg/day) and is a third-line treatment alternative for tic disorders.

A placebo-controlled, double-blind study of the first-generation antipsychotic **pimozide** found that its clinical efficacy was greater than that of haloperidol; further, the ADR profile of pimozide was also much more favorable (Sallee et al. 1997). Clinically relevant cardiac ADRs have not been described in published clinical studies (Robertson and Stern 2000). Despite the better clinical study situation and the FDA-approved indication for the treatment of TS, pimozide is regarded as a third-line medication for the treatment of tic disorders (Jankovic and Kurlan 2011; Roessner and Rothenberger 2013; Roessner et al. 2011). Key pharmacological data and dosage recommendations are summarized in Sect. 5.7.14).

There is only limited evidence and clinical experience regarding a positive effect upon tics of other antipsychotics including olanzapine, quetiapine, and amisulpride. Reports to date have found that clozapine does not improve tic symptoms; indeed, daily dosages of up to 150 mg have induced temporary increases in tic frequency (Schmider and Hoff 1998). There is currently no indication for clozapine in the treatment of tic disorders.

The efficacy and safety of **ziprasidone**, a second-generation antipsychotic, were shown in a randomized, placebo-controlled trial in children and adolescents with TS. In a 56-day study with 28 subjects (aged 7–17 years), ziprasidone (initiated at a dose of 5 mg/day and flexibly titrated to a maximum of 40 mg/day) was superior to placebo in reducing the Global Severity and Total Tic Scores on the Yale Global Tic Severity Scale (Sallee et al. 2000). No clinically significant effects were observed on specific ratings of extrapyramidal motor symptoms, akathisia, or tardive dyskinesia.

A number of **further medications** are regarded as third-choice agents in the therapy of tic disorders as only positive findings in smaller patient case studies and individual reports are available (review: Robertson and Stern 2000; Roessner et al. 2011; Roessner and Rothenberger 2013). These include pergolide (a dopamine D1/D2-receptor agonist; NB: dyskinesias, psychotic symptoms), botulinum toxin (for persistent [years], localized, painful tics, per injection into affected muscle groups; for severe coprolalia, unilateral into the vocal cord), naltrexone (opioid receptor antagonist; NB: dependence risk and tic exacerbation following withdrawal), nicotine (potentiation of tic-reducing effects of antipsychotics) in a placebo-controlled, double-blind study by Howson et al. 2004), and cannabis (Müller-Vahl et al. 2003). Diazepam and clonazepam (**benzodiazepines**; NB: dependence risk) are primarily employed for **short periods** in cases where self-injuring or extremely painful tics have intensified.

Despite the good evidence level, the adrenergic α_2-receptor agonist **clonidine** is also a third-line medication, as reduction of tic symptoms in practice has not corresponded with the expectations raised by clinical studies. Although many authors report that the ADRs may tend to be mild and transient, this view is not fully supported by others and the clinical practice, especially when moderate to severe tics require a higher dosage of clonidine (Roessner et al. 2011). **Dosages** of up to 0.3 mg/day have been employed (**NB**: gradual titration in 0.025–0.050 mg increments every 5–7 days, daily dosage divided into 3–4 doses). Its employment appears particularly useful with comorbid ADHD as clonidine improves associated symptoms, such as irritability, reduced frustration tolerance, disturbed impulse control, and aggressive tension (see Chap. 8).

NB: When employing clonidine, pulse, blood pressure, and ECG should be regularly monitored!

Guanfacine, a further adrenergic α_2-receptor agonist, exhibited good efficacy in an open-label study of the treatment of tics in children with comorbid ADHD (dosage: 1.5 mg/day; Robertson and Stern 2000). In two placebo-controlled, double-blind studies in children with TS, it was efficacious in one trial (Scahill 2009), however, non-efficacious in the other one (Cummings et al. 2002). With regard to **ADR profiles**, guanfacine can be regarded as **superior to clonidine** in that it has no hypotensive or sedative effects. Interestingly, a recent meta analysis reported only minimal benefit of adrenergic α_2-receptor agonists in tic patients without comorbid ADHD (Weisman et al. 2013).

The full efficacy of adrenergic α_2-receptor agonists such as clonidine and guanfacine in the treatment of tic disorders is manifested only after as long as 10–12 weeks!

As streptococcal infections have been discussed as initiators not only of tics but also of compulsive disorders – at least in a subgroup of patients (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections; PANDAS) – treatment with antibiotics, plasmapheresis, and intravenous immunoglobulins has been investigated. Results regarding the etiology and treatment of PANDAS are still inconsistent (Kurlan et al. 2008).

27.4 Treatment Strategy

Tic symptoms only require pharmacological intervention when everyday competences are compromised in the longer term (i.e., apart from brief tic bursts), there is marked distress, and pure behavioral therapeutic measures (control and self-management techniques, relaxation techniques, and possibly social competence training) are not sufficient (Roessner et al. 2011).

The natural course of tic disorders mentioned above must be borne in mind when deciding for a pharmacological therapy or assessing its efficacy, both to avoid unnecessary or premature therapy on the one hand and to allow valid evaluation of the efficacy of intervention on the other (see Fig. 27.1). Apart from specific ADRs, weight gain associated with long-term antipsychotic therapy represents the major problem.

27.4.1 Duration of Pharmacological Therapy

Treatment (if effective and safe) should be continued for at least 12 months. Trial reductions should be carefully undertaken in small steps. The risk of antipsychotic-induced tardive dyskinesias during tiapride and sulpiride therapy is generally minor in patients with tic disorders.

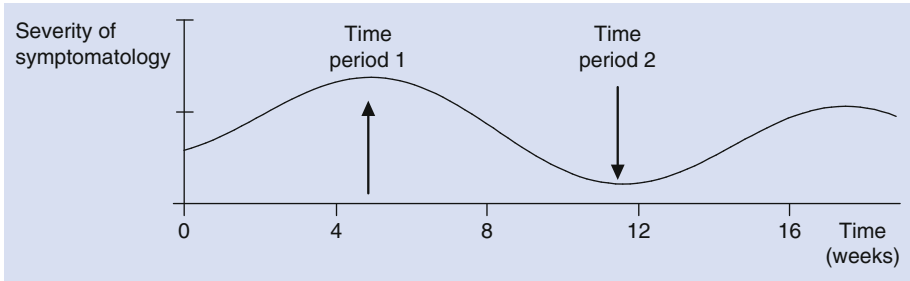

Fig. 27.1 Issues in the evaluation of the efficacy of interventions in tic disorders according to the spontaneously waxing and waning of tics (from Roessner et al. 2004). An intervention at time point 1 (e.g., methylphenidate, tiapride, behavioral therapy) can be followed by a reduction in tics despite the potential induction of tics or potential absence of efficacy. Primarily responsible is not the effectiveness of the intervention, but natural variability in the expression of tic symptomatology. Conversely, an intervention at time point 2 can, despite the well-established efficacy of the intervention, be followed by an increase in tic frequency, possibly in less intense form. **Conclusion**: Confident evaluation of efficacy is possible only after a more extended period of observation

NB: Rebound effects when withdrawing antipsychotics.

27.4.2 Strategy with Comorbid Mental Disorders

Comorbid psychiatric disorders are **treated in disorder-specific manner**. The most common comorbid diagnoses made in patients with tic disorders are ADHD (Cath et al. 2011; Rothenberger and Roessner 2013) and obsessive-compulsive disorders (Roessner et al. 2005). Treatment with psychostimulants (ADHD) or SSRIs (obsessive-compulsive disorders) might achieve some indirect effects (e.g., via improvement of attention and self-regulation) with respect to tic symptoms in some cases.

Psychostimulants (methylphenidate, amphetamine, see Chap. 8) are employed for the disorder-specific treatment of ADHD. For long time, it was controversial whether this agent group exacerbated or even triggered comorbid tics (see Sect. 8.4.1.4). While the induction of the initial manifestation of tics could be excluded for both short (Roessner et al. 2006) and long-acting psychostimulant preparations (Palumbo et al. 2004; Bloch et al. 2009), a placebo-controlled study indicated that psychostimulants did not influence already existing tics in children with ADHD (Tourette Syndrome Study Group 2002). Experience indicates, however, that in very small subgroups of patients an increase or decrease of tics can ensue (Cortese et al. 2013; Kurlan 2003).

Sulpiride, a further second-generation antipsychotic (like tiapride, from the benzamide group), proved in a double-blind study to be efficacious in the therapy of tic disorders, particularly with comorbid compulsive-anxious symptoms (Robertson and Stern 2000). Its antidepressive efficacy was also good. At lower dosages, there is barely any risk for ADRs such as extrapyramidal motor symptoms. Because of the broad clinical experience with sulpiride, it is valuable for the pharmacological treatment of the frequent combination of tics and compulsive-anxious symptoms. Galactorrhea is more common than with tiapride. Table 27.2 summarizes the key pharmacological data as well as dosage recommendations.

Table 27.2 Sulpiride: pharmacological properties and dosage recommendations

Pharmacodynamic properties	Classical, first-generation antipsychotic; dopamine D2-receptor antagonist, attenuation of dopamine-mediated effects
Pharmacokinetic properties	t_{max} 2–6 h, $t_{1/2}$ 6–8 h; protein binding less than 40 %, bioavailability 25–40 % Elimination <95 % renal
Indications	The treatment of acute and chronic schizophrenia. Available only in Europe Not recommended for children under 14 years of age Off-label: treatment of tic disorders
Daily dosages	Tic disorders (based on our clinical experience) Maximum of 900 mg/day, divided into 3 doses, increased by 50–200 mg/week; for steps see tiapride, i.e., 2.5–10 mg/kg body weight per day
Adverse drugs reactions (ADRs)	Elevated prolactin levels, weight gain, restlessness, sleep disorders, headache, vertigo, tachycardia, hypo-/hypertonia, gastrointestinal complaints, micturition disturbances Below 300 mg extrapyramidal motor ADRs seldom
Drug interactions	Enhancement of CNS depressants; reduction of anti-hypertonic agent effects; **NB**: hypertensive crisis! Appetite suppressants and asthma medication can increase restlessness!
Contraindications	Seizures, organic psychosyndrome, mania, prolactin-dependent tumors, pheochromocytoma, hyper-/hypotonia, cardiac disease, renal dysfunction, depression
Monitoring	Until the third treatment month: monthly blood picture, creatinine, transaminases; then quarterly or semiannually blood picture Monitor ECG and EEG in first month, then semiannually; check pulse and blood pressure!

The summaries are based upon information included in the Summary of Product Characteristics of sulpiride
t_{max} time point at which the maximal blood concentration (c_{max}) is reached, $t_{1/2}$ elimination half-life

Of the **antidepressants** (Chap. 4), **SSRIs**, on the basis of their more favorable ADR profile, are **preferred** to the tricyclic antidepressants (anticholinergic effects, cardiovascular disorders, sedation, reduced seizure threshold in some cases). Although fluoxetine achieved no improvement of tic symptomatology in a double-blind, placebo-controlled study in 14 patients with TS (Scahill et al. 1997), it is observed in clinical practice that patients with tic disorders treated with an antidepressant, apart from an improvement of comorbid compulsive behavior, also exhibit a sometimes marked amelioration of overall psychopathology, including tic symptomatology.

The combination of an antipsychotic and SSRIs has proved useful in patients with tics and obsessive-compulsive disorders (approval for fluvoxamine for treatment of compulsions in children from age to 8 years) or depression (approval for fluoxetine for the treatment of depression in children from 8 years). Dosage of the antidepressant is based upon the actual target symptom.

NB: The effects of antidepressants may not be manifested for up to 6 weeks.

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Laurence L. Greenhill, M.D.
Laurence L. Greenhill, M.D., Ruane Professor of Child and Adolescent Psychiatry, Columbia University in New York, has received research grants from the National Institute of Mental Health and from the National Institute of Drug Addiction (NIDA). He has received honoraria from the American Academy of Child and Adolescent Psychiatry when he was President of that Association. Over the past ten years, he has

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received travel support from Rhodes Pharmaceutical and BioBDX Quotient. He serves as the ADHD section editor for the Journal of Child and Adolescent Psychopharmacology.

Beate Herpertz-Dahlmann, M.D.
Prof. Dr. Herpertz-Dahlmann has received industry research funding from Medice and Vifor.

Veit Roessner, M.D.
Prof. Dr. Veit Roessner participated in the last two years in pharmaceutical registration trials of children and adolescents from Shire, Novartis, and Otsuka. He has also received honoraria from Shire, Novartis, and Actelion. He has served as junior-editor of European Child and Adolescent Psychiatry.

Marcel Romanos, M.D.
Prof. Dr. Marcel Romanos has received research grants pertaining to pharmacovigilance in children and adolescents from the German Federal Institute for Drugs and Medical Devices.

Aribert Rothenberger, M.D.
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Benno Schimmelmann, M.D.
Prof. Dr. Benno G. Schimmelmann has received research grants from Swiss National Research Foundation and National Health and Medical Research Council (NHMRC) Australia. He received honoraria from Eli Lilly and Shire Switzerland. He serves as junior-editor of European Child and Adolescent Psychiatry and as coeditor of Early Intervention in Psychiatry and the Zeitschrift für Kinder- und Jugendpsychiatrie.

Klaus Schmeck, M.D.
Prof. Dr. Klaus Schmeck is member of the Jury of the Lundbeck Institute (Switzerland) Psychiatry Award.

Rudolf Stohler, M.D.
Dr. Stohler has received a research grant from Reckitt Benckiser related to opioid maintenance treatment in Switzerland. He has also received honoraria for consultancy from the city of Zurich, Lundbeck, and Reckitt Benckiser.

Alexander von Gontard, M.D.
Prof. Dr. Alexander von Gontard has received honoraria for two talks by Eli Lilly Germany and has been on an advisory board of Otsuka Pharmaceuticals.

Susanne Walitza, MSc, M.D.
Prof. Dr. Walitza has received lecture honoraria from Janssen-Cilag, AstraZeneca, and Eli Lilly in the last 5 years. Her work was partially supported in the last 10 years by the Swiss National Science Foundation (SNF), Deutsche Forschungsgemeinschaft, EU FP7, Hochspezialisierte Medizin of the Kanton Zurich, Switzerland, Vifor, and BMBF Germany.

The following authors have no competing interests:

Tomasz Jarczok, M.D.
Prof. Dr. Claudia Mehler-Wex, M.D.
Dr. Silke Rothenhöfer, M.D.
Dr. Jürgen Seifert, M.D.
Dr. Regina Taurines, M.D.
Prof. Dr. Andreas Warnke, M.D.
Prof. Dr. Christoph Wewetzer, M.D.

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