Attention-Deficit/Hyperactivity Disorders

12

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Contents

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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.

Literature

AACAP (Official Action (American Association of Child and Adolescent Psychiatry) (2007) Practise parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 46:894–921

Abikoff H, McGough J, Vitiello B, McCracken J, Davies M, Walkup J, Riddle M, Oatis M, Greenhill L, Skrobala A, March J, Gammon P, Robinson J, Lazell R, McMahon DJ, Ritz L; RUPP ADHD/Anxiety Study Group (2005) Sequential pharmacotherapy for children with comorbid attention-deficit/hyperactivity and anxiety disorders. J Am Acad Child Adolesc Psychiatry 44:418–427

Ahmann PA, Theye FW, Berg R, Linquist AJ, Van Erem AJ, Campbell LR (2001) Placebo-controlled evaluation of amphetamine mixture-dextroamphetamine salts and amphetamine salts (Adderall): efficacy rate and side effects. Pediatrics 107:e10

Aman MG, Binder C, Turgay A (2004) Risperidone effects in the presence/absence of psychostimulant medicine in children with ADHD, other disruptive behavior disorders, and subaverage IQ. J Child Adolesc Psychopharmacol 14:243–254

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th edn (DSM-5TM). American Psychiatric Publishing, Washington/London

Angold A, Costello EJ, Erkanli A (1999) Comorbidity. J Child Psychol Psychiatry 40:57–87

Arnsten AF, Scahill L, Findling RL (2007) Alpha-2 adrenergic receptor agonists for the treatment of attention-deficit/hyperactivity disorder: emerging concepts from new data. J Child Adolesc Psychopharmacol 17:393–406

Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, Danckaerts M, Döpfner M, Faraone SV, Rothenberger A, Sergeant J, Steinhausen HC, Sonuga-Barke EJ, Taylor E (2006) Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. Eur Child Adolesc Psychiatry 15:476–495

Banaschewski T, Soutullo C, Lecendreux M, Johnson M, Zuddas A, Hodgkins P, Adeyi B, A Squires L, Coghill D (2013) Health-related quality of life and functional outcomes from a randomized, controlled study of lisdexamfetamine dimesylate in children and

adolescents with attention deficit hyperactivity disorder. CNS Drugs 27:829–840

Benjamin E, Salek S (2005) Stimulant-atypical antipsychotic interaction and acute dystonia. J Am Acad Child Adolesc Psychiatry 44:510–512

Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA) (2011) Canadian ADHD practice guidelines, 3rd edn. CADDRA, Toronto

Charach A, Dashti B, Carson P, Booker L, Lim CG, Lillie E, Yeung E, Ma J, Raina P, Schachar R (2011) Attention deficit hyperactivity disorder: effectiveness of treatment in at-risk preschoolers; long-term effectiveness in all ages; and variability in prevalence, diagnosis, and treatment. Agency for Healthcare Research and Quality (US), Rockville

Coghill DR, Banaschewski T, Lecendreux M, Zuddas A, Dittmann RW, Otero IH, Civil R, Bloomfield R, Squires LA (2013) Efficacy of lisdexamfetamine dimesylate throughout the day in children and adolescents with attention-deficit/hyperactivity disorder: results from a randomized, controlled trial. Eur Child Adolesc Psychiatry (Epub ahead of print). May 25

Cornforth C, Sonuga-Barke E, Coghill D (2010) Stimulant drug effects on attention deficit/hyperactivity disorder: a review of the effects of age and sex of patients. Curr Pharm Des 6:2424–2433

Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, Graham J, Taylor E, Sergeant J (2013) Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. J Child Psychol Psychiatry 54:227–246

Czamara D, Tiesler CM, Kohlböck G, Berdel D, Hoffmann B, Bauer CP, Koletzko S, Schaaf B, Lehmann I, Herbarth O, von Berg A, Müller-Myhsok B, Schulte-Körne G, Heinrich J (2013) Children with ADHD symptoms have a higher risk for reading, spelling and math difficulties in the GINIplus and LISAplus cohort studies. PLoS One 8:e63859

Eggers C, Rothenberger A, Berghaus U (1988) Clinical and neurobiological findings in children suffering from tic disease following treatment with tiapride. Eur Arch Psychiatry Clin N 237:223–229

Findling RL, Newcorn JH, Malone RP, Waheed A, Prince JB, Kratochvil CJ (2007) Pharmacotherapy of aggression in a 9-year-old with ADHD. J Am Acad Child Adolesc Psychiatry 46:653–658

Geller D, Donnelly C, Lopez F, Rubin R, Newcorn J, Sutton V, Bakken R, Paczkowski M, Kelsey D, Sumner C (2007) Atomoxetine treatment for pediatric patients with attention-deficit/hyperactivity disorder with comorbid anxiety disorder. J Am Acad Child Adolesc Psychiatry 46:1119–1127

Greenhill L (2002) Stimulant medication treatment of children with attention deficit hyperactivity disorder. In: Jensen PS, Cooper JR (eds) Attention deficit hyperactivity disorder: state of the science. Best practices. Civic Research Institute, Kingston. pp. 919–927

Greenhill L, Pliszka S, Dulcan MK, Bernet W, Arnold V, Beitchman J et al, American Academy of Child and Adolescent Psychiatry (2002) Practice parameter for the use of stimulant medications in the treatment of children, adolescents and adults. J Am Acad Child Adolesc Psychiatry 41:26–49

Greenhill L, Kollins S, Abikoff H, McCracken J, Riddle M, Swanson J, McGough J, Wigal S, Wigal T, Vitiello B, Skrobala A, Posner K, Ghuman J, Cunningham C, Davies M, Chuang S, Cooper T (2006) Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry 45:1284–1293

Groenman AP, Oosterlaan J, Rommelse N, Franke B, Roeyers H, Oades RD, Sergeant JA, Buitelaar JK, Faraone SV (2013) Substance use disorders in adolescents with attention deficit hyperactivity disorder: a 4-year follow-up study. Addiction 108:1503–1511

Handen BL, Feldman HM, Lurier A, Murray PJ (1999) Efficacy of methylphenidate among preschool children with developmental disabilities and ADHD. J Am Acad Child Adolesc Psychiatry 38:805–812

Hosenbocus S, Chahal R (2009) A review of long-acting medications for ADHD in Canada. J Can Acad Child Adolesc Psychiatry 18:331–339

Jacob CP, Romanos J, Dempfle A, Heine M, Windemuth-Kieselbach C, Kruse A, Reif A, Walitza S, Romanos M, Strobel A, Brocke B, Schäfer H, Schmidtke A, Böning J, Lesch KP (2007) Co-morbidity of adult attention-deficit/hyperactivity disorder with focus on personality traits and related disorders in a tertiary referral center. Eur Arch Psychiatry Clin Neurosci 257:309–317

Jensen PS, Hinshaw SP, Kraemer HC, Lenora N, Newcorn JH, Abikoff HB, March JS, Arnold LE, Cantwell DP, Conners CK, Elliott GR, Greenhill LL, Hechtman L, Hoza B, Pelham WE, Severe JB, Swanson JM, Wells KC, Wigal T, Vitiello B (2001) ADHD comorbidity findings from the MTA study: comparing co-morbid subgroups. J Am Acad Child Adolesc Psychiatry 40:147–158

Koneski JA, Casella EB, Agertt F, Ferreira MG (2011) Efficacy and safety of methylphenidate in treating ADHD symptoms in children and adolescents with uncontrolled seizures: a Brazilian sample study and literature review. Epilepsy Behav 21:228–232

Kratochvil CJ, Vitiello B, Brent D, Bostic JQ, Naylor MW (2006) Selecting an antidepressant for the treatment of pediatric depression. J Am Acad Child Adolesc Psychiatry 45:371–373

Levy F, Young D, Bennett KS, Martin NC, Hay DA (2013) Comorbid ADHD and mental health disorders: are these children more likely to develop reading disorders? Atten Defic Hyperact Disord 5:21–28

Loy JH, Merry SN, Hetrick SE, Stasiak K (2012) Atypical antipsychotics for disruptive behaviour disorders in children and youths. Cochrane Database Syst Rev 9:CD008559

Markowitz JS, Patrick KS (2001) Pharmacokinetic and pharmacodynamic drug interactions in the treatment

of attention-deficit hyperactivity disorder. Clin Pharmacokinet 40:753–771

MTA Cooperation Group (1999a) Multimodal treatment Study of Children with ADHD. A 14 month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 56:1073–1086

MTA Cooperation Group (1999b) Multimodal treatment Study of Children with ADHD. Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 56:1088–1096

MTA Cooperation Group (2004) National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. Pediatrics 113:754–761

National Institute for Health and Clinical Excellence (NICE) (2008) Attention deficit hyperactivity disorder – diagnosis and management of ADHD in children, young people and adults. National Clinical Practice Guideline Number 72. The British Psychological Society and The Royal College of Psychiatrists, London

Pearson DA, Santos CW, Roache JD, Casat CD, Loveland KA, Lachar D, Lane DM, Faria LP, Cleveland LA (2003) Treatment effects of methylphenidate on behavioral adjustment in children with mental retardation and ADHD. J Am Acad Child Adolesc Psychiatry 42:209–216

Pelham WE, Aronoff HR, Midlam JK, Shapiro CJ, Gnagy EM, Chronis AM, Onyango AN, Forehand G, Nguyen A, Waxmonsky J (1999) A comparison of Ritalin and Adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. Pediatrics 103:e43

Pliszka SR, Crismon ML, Hughes CW, Corners CK, Emslie GJ, Jensen PS, McCracken JT, Swanson JM, Lopez M (2006) Texas consensus conference panel on pharmacotherapy of childhood attention deficit hyperactivity disorder. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 45:642–657

Popper CW (1995) Combining methylphenidate and clonidine – pharmacological questions an news reports about sudden-death. J Child Adolesc Psychopharmacol 5:157–166

Sallee F, Connor DF, Newcorn JH (2013) A review of the rationale and clinical utilization of α2-adrenoceptor agonists for the treatment of attention-deficit/hyperactivity and related disorders. J Child Adolesc Psychopharmacol 23:308–319

Santosh PJ, Taylor E (2000) Stimulant drugs. Eur Child Adolesc Psychiatry 9(Suppl 1):127–143

Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, Arnsten AF, Cohen DJ, Leckman JF (2001) A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry 158:1067–1074

Simonoff E, Taylor E, Baird G, Bernard S, Chadwick O, Liang H, Whitwell S, Riemer K, Sharma K, Sharma SP, Wood N, Kelly J, Golaszewski A, Kennedy J, Rodney L, West N, Walwyn R, Jichi F (2013) Randomized controlled double-blind trial of optimal dose methylphenidate in children and adolescents with severe attention deficit hyperactivity disorder and intellectual disability. J Child Psychol Psychiatry 54:527–535

Sinzig J, Döpfner M, Lehmkuhl G, German Methylphenidate Study Group, Uebel H, Schmeck K, Poustka F, Gerber WD, Günter M, Knölker U, Gehrke M, Hässler F, Resch F, Brünger M, Ose C, Fischer R (2007) Long-acting methylphenidate has an effect on aggressive behavior in children with attention-deficit/hyperactivity disorder. J Child Adol Psychop 4:421–432

Sonuga-Barke EJS, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, Stevenson J, Danckaerts M, van der Oord S, Döpfner M, Dittmann RW, Simonoff E, Zuddas A, Banaschewski T, Buitelaar J, Coghill D, Hollis C, Konofal E, Lecendreux M, Wong ICK, Sergeant J, European ADHD Guidelines Group (2013) Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiat 170:275–289

Spencer TJ, Abikoff HB, Connor DF, Biederman J, Pliszka SR, Boellner S, Read SC, Pratt R (2006) Efficacy and safety of mixed amphetamine salts extended release (adderall XR) in the management of oppositional defiant disorder with or without comorbid attention-deficit/hyperactivity disorder in school-aged children and adolescents: a 4-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, forced-dose-escalation study. Clin Ther 28:402–418

Svanborg P, Thernlund G, Gustafsson PA, Hägglöf B, Schacht A, Kadesjö B (2009) Atomoxetine improves patient and family coping in attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in Swedish children and adolescents. Eur Child Adolesc Psychiatry 18:725–735

Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, Clevenger B, Davies M, Elliott GR, Greenhill LL, Hechtman L, Hoza B, Jensen PS, March JS, Newcorn JH, Owens EB, Pelham WE, Schiller E, Severe JB, Simpson S, Vitiello B, Wells K, Wigal T, Wu M (2001) Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry 40:168–179

Taurines R, Schmitt J, Renner T, Conner AC, Warnke A, Romanos M (2010) Developmental comorbidity in attention-deficit/hyperactivity disorder. Atten Defic Hyperact Disord 2:276–289

Taylor E, Döpfner M, Sergeant J, Asherson P, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Rothenberger A, Sonuga-Barke E, Steinhausen HC, Zuddas A (2004) European clinical guidelines for hyperkinetic disorder-first upgrade. Eur Child Adolesc Psychiatry 13(Suppl 1):17–30

Weisman H, Qureshi IA, Leckman JF, Scahill L, Bloch MH (2013) Systematic review: pharmacological treatment of tic disorders – efficacy of antipsychotic and alpha-2 adrenergic agonist agents. Neurosci Biobehav Rev 37:1162–1171

Wilens TE, McBurnett K, Bukstein O, McGough J, Greenhill L, Lerner M, Stein MA, Conners CK, Duby J, Newcorn J, Bailey CE, Kratochvil CJ, Coury D, Casat C, Denisco MJ, Halstead P, Bloom L, Zimmerman BA, Gu J, Cooper KM, Lynch JM (2006) Multisite controlled study of OROS methylphenidate in the treatment of adolescents with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 160:82–90

Wilens TE, Adler LA, Adams J, Sgambati S, Rotrosen J, Sawtelle R, Utzinger L, Fusillo S (2008) Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. J Am Acad Child Adolesc Psychiatry 47:21–31

World Health Organization (1996) Multiaxial classification of child and adolescent psychiatric disorders. The ICD-10 classification of mental and behavioral disorders in children and adolescents. Cambridge University Press, Cambridge