Chapter 8
A Multi-Target Drug Treatment in Schizophrenia and Schizoaffective Disorder Using Adjunctive Agents with Non-D_2 Mechanisms of Action

Michael S. Ritsner

Abstract Pharmacologic actions to reduce neurotransmission through the D_2 receptor have been the only proven therapeutic mechanism for schizophrenia (SZ) and schizoaffective (SA) disorder. However, in view of the multifactorial genesis and pathogenesis of these psychoses, it is unlikely that any antipsychotic drug would work equally well against all symptoms and behavioral disturbances. The absence of a single therapeutic target for SZ/SA disorder has prompted the use of *polypharmacy strategies* including *multi-target pharmacotherapy*, consisting of various *add-on medications and supplements*. Multi-target polypharmacy strategies include the off-label prescription of adjunctive agents such as antidepressants, mood stabilizers, and benzodiazepines already in use, and novel potential adjunctive agents (newer molecules or compounds) based on several non-dopaminergic hypotheses (serotonergic, noradrenergic, glutamatergic, gamma-aminobutyric acid related, and cholinergic neurotransmission, neuroprotective mechanisms and brain neuroplasticity). This chapter is an overview of the current state of evidence for the augmentation of antipsychotics with antidepressants, lithium, antiepileptic agents, benzodiazepines, and new molecules and compounds for the treatment of people with SZ/SA disorder with a special focus on research data published within the past 5–7 years. Using these agents for the augmentation of antipsychotics based on a *multi-target drug treatment approach* entails the combination of two or more drugs/agents with different mechanisms of action on the central nervous system in an attempt to enhance efficacy.

Keywords Augmentation • Antidepressants • Mood stabilizers • Lithium • Antiepileptic drugs • Benzodiazepines • Schizophrenia • Schizoaffective disorder • Hormones • Supplements

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_8,

Abbreviations

AMPA	DL-α-NH_2-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid
BDNF	Brain-derived neurotrophic factor
BZD	Benzodiazepines
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CNS	Central nervous system
COX	Cyclo-oxygenase
DA	Dopamine
DHEA	Dehydroepiandrosterone
DHEA(S)	Both DHEA and DHEAS
DHEAS	Dehydroepiandrosterone sulfate
EPA	Eicosapentaenoic acid
FGAs	First generation antipsychotics
GABA	γ-amino-butyric acid
GSK	Glycogen synthase kinase
HPA	Hypothalamic-pituitary-adrenal axis
NMDA	*N*-methyl-D-aspartate
PANSS	Positive and Negative Symptom Scale
PREG	Pregnenolone
PREG(S)	Both PREG and PREGS
PREG(S)/DHEA(S)	Both PREG(S) and DHEA(S)
PREGS	Pregnenolone sulfate
SAMe	S-adenosyl L-methionine
SANS	Scale for the Assessment of Negative Symptoms
SGAs	Second generation antipsychotics
SSRI	Selective serotonin re-uptake inhibitor
SZ/SA	Schizophrenia and schizoaffective disorder

8.1 Introduction

Schizophrenia (SZ) and schizoaffective (SA) disorder are pervasive and debilitating conditions. The biological mechanisms underlying these disorders are not fully understood.

The *dopamine hypothesis* states that there is over activity in the dopamine systems. The hypothesis stems from the finding that all effective anti-psychotic medications block dopamine brain receptors, and that their potency correlates with the strength of binding to dopamine D_2 receptors in the brain. However, the idea that the symptoms of psychosis are caused by the overactivity of dopamine is not supported by currently available evidence [1].

Dopamine (DA) D_2 receptor antagonism is a unifying property of all antipsychotic drugs, while often effective at ameliorating psychosis, these drugs are largely

ineffective in the treatment of negative and cognitive symptoms. In recent years, a variety of new experimental pharmacological approaches have emerged, including compounds that act on targets other than the dopamine D_2 receptor. However, there is still an ongoing debate as to whether drugs selective for singe molecular targets (that is, 'magic bullets') or drugs selectively non-selective for several molecular targets (that is, 'magic shotguns') will lead to more effective new medications for schizophrenia [2]. This has prompted *multifactorial approaches* to the development of new therapeutics, such as polypharmacy and an augmentative strategy known as "*intramolecular polypharmacy*", in which a single drug has the capacity to affect multiple receptor types [3]. These multi-target agents (also called '*multifunctional drugs*' [4]) with more than one putative therapeutic mechanism of action may lead to the development of selective drugs for the treatment of SZ/SA disorder.

The concurrent use of more than one drug to treat syndromes and diseases is common in internal medicine [5, 6]. Wald and Law [7] postulated that using a combination of well known, inexpensive medications in one pill (the "*polypill*") would be a particularly effective treatment against cardiovascular disease. They presented a statistical model which suggested that widespread use of the polypill could reduce mortality due to heart disease and strokes by up to 80%. The treatment is potentially inexpensive, with few side effects (in perhaps 10–15% of recipients) and the research was based on data from many trials relating to the individual components. Increasingly, combined antihypertensive agents are being used in practice to enhance control and improve compliance. In some cases, a combination of relatively low doses has resulted in superior efficacy not only to the components administered alone but to higher doses of the individual components [8]. Systematic reviews and meta-analyses have confirmed that there is evidence that low-dose combination products could provide equal or enhanced efficacy with a potentially reduced adverse effect burden [9]. Mahmud and Feely [10] report a prospective study using a capsule containing four different antihypertensive drug classes, each given in a dose one quarter of the usual dose of the preparation: patients received amlodipine (5 mg), atenolol (50 mg), bendroflumethiazide (2.5 mg), and captopril (50 mg twice daily) or a capsule containing each of the four above at one-quarter dosage in a parallel group design for 4 weeks. This randomized trial indicates that the capsule containing four agents of different classes at a quarter of the usual dose was more effective at lowering blood pressure than any of the individual drugs alone in the usual dose. There is clearly a lot of work to be done before any product could be registered for use in hypertension, but this preliminary report confirms the theoretical basis of the polypill concept and suggests that other multiple drug therapy approaches using low doses may be able to realize benefits at least as great as those predicted from the controlled trials [5]. Thus, a range of combination therapies utilizing medications with differing mechanisms of action have been shown to provide superior blood pressure-lowering efficacy than monotherapy with individual components.

Although the international guidelines recommend antipsychotic monotherapy as the treatment of choice, many of SZ/SA patients receive two or more antipsychotics in clinical practice (antipsychotic polypharmacy). The term "combination" includes virtually all the ways in which one medication may be added to another. The other commonly used

terms are "augmentation" which implies an additive effect of a second medicine added to the initial prescribed drug, an "add on" which implies adding on to an existing, possibly effective treatment which, for one reason or another, cannot or should not be stopped [11]. Experts recommend polypharmacy in a few special clinical situations [12]:

- For augmentation when a patient fails to respond to adequate antipsychotic trials,
- In some instances of failed cross-taper of antipsychotics, and
- Adding an FGA to a SGA for agitation during acute treatment of psychosis.

Interestingly, a myelin-centered model of human brain function suggests that widely used psychotropic treatments share complex signaling pathways such as Akt and glycogen synthase kinase-3 (GSK_3) that affect myelination, its plasticity, and repair [13, 14]. Independent lines of research involving biochemical and behavioral approaches in normal and/or genetically modified mice provide converging evidence for an involvement of the signaling molecules Akt and GSK_3 in the regulation of behavior by DA and 5-HT (5-hydroxytryptamine, serotonin) neurotransmissions [15]. It may also provide a link between the action of these neurotransmitters and gene products, such as those disrupted in schizophrenia one (DISC1) and neuregulin (NRG), that are associated with increased risk for mental disorders [16]. These signaling pathways respond to neurotransmitters, neurotrophins, hormones, and nutrition, underlie intricate neuroglial communications, and may substantially contribute to the mechanisms of action and wide spectra of efficacy of current therapeutics by promoting myelination [17].

The trend of antipsychotic polypharmacy has increased considerably, especially since the introduction of second generation antipsychotics (SGAs) [11, 12]. Pickar and associates [18] reported that only 25% of 200 schizophrenia patients are treated with antipsychotics alone. Nielsen and co-authors [19] using a cohort study of newly diagnosed patients with schizophrenia in Denmark (n = 13,600) reported that between 1996 and 2005 there was increased use and dosing of antipsychotics and antidepressants, as well as more antipsychotic polypharmacy. In contrast, antipsychotic monotherapy of Japanese inpatients with schizophrenia increased from 31.6% in 2007 to 33.8% in 2009 [20].

There are current updates and critical reviews of the pharmacology and clinical profiles of current antipsychotic drugs and preparations that act on novel targets and have the potential to be therapeutic agents in the future [2, 21–26]. This chapter is an overview the current state of evidence of the augmentation of antipsychotics with antidepressants, lithium, antiepileptic agents, benzodiazepines, and new molecules and compounds for the treatment of SZ/SA disorder (Fig. 8.1).

8.2 A Multi-Target Drug Treatment

The aim of augmenting antipsychotics, *multi-target drug treatment approach,* is to combine two or more drugs/agents with different mechanisms of action on the central nervous system in an attempt to enhance efficacy and/or tolerability. There are

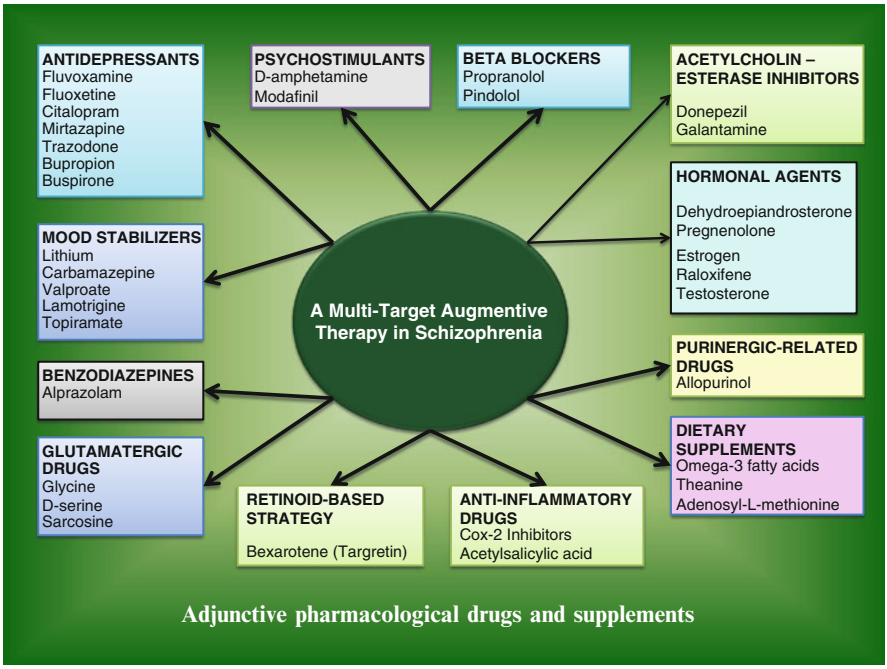

Fig. 8.1 Adjunctive pharmacological drugs and supplements (© M.S. Ritsner (2012) and used by permission)

several possible rationales for a *multi-target drug treatment approach* that is more likely to alleviate core and comorbid symptoms.

- The multifactorial genesis, genetic heterogeneity and pathogenesis of schizophrenia and other functional psychoses/disorders cannot be attributed to any single cause, see, e.g. [27, 28], and Fig. 8.2 [40].
- In light of the clinical polymorphism of these conditions, it is unlikely that any antipsychotic drug would work equally well against positive, negative, and mood symptoms, cognitive, functional and quality of life deficits, and against behavioral disturbances in all patients. Indeed, although clinical guidelines recommend the routine use of a single antipsychotic drug in a standard dose [41, 42], prescriptions for high-dose and combined antipsychotics are common in clinical practice [43].
- Poor treatment response of patients with SZ/SA is a compelling clinical problem. In addition to the poor response of about one-third of SZ/SA patients [44], antipsychotic monotherapy is often inadequate in the management of particularly challenging symptoms such as negative and cognitive disturbances, affective instability, anxiety or insomnia, persistent aggression, functional and quality of life impairments.

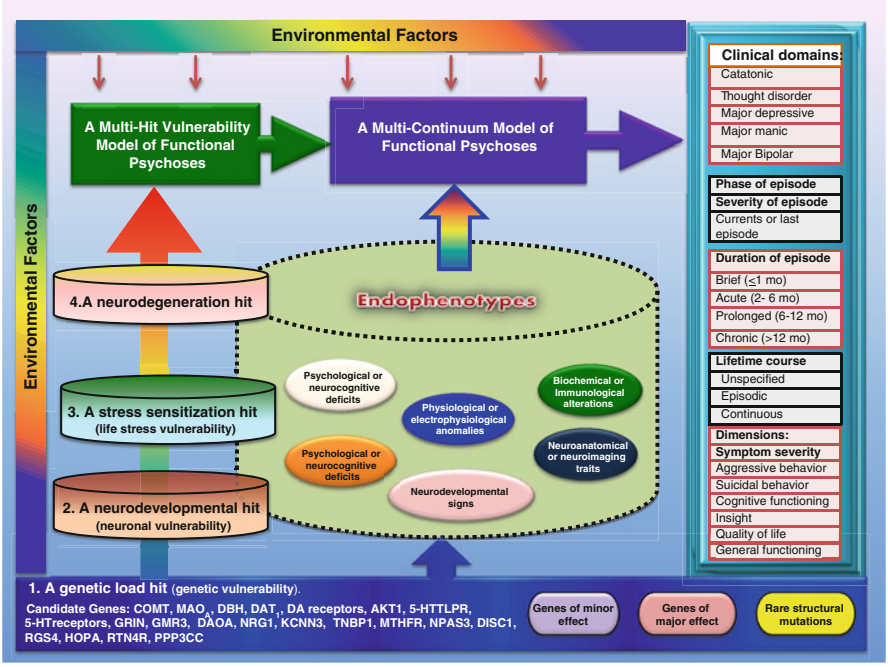

Fig. 8.2 Multidimensional continuum model of functional psychoses for research purposes (Version 1.1) (© M.S. Ritsner [26] and used by permission)

- In addition to dopaminergic, serotonergic, noradrenergic, and glutamatergic pathways, γ-amino-butyric acid (GABA) and acetylcholine dysregulation have also been implicated in the pathogenesis of SZ/SA disorder [45–48].
- Multiple lines of evidence have linked degenerative abnormalities in both post-mortem and brain imaging studies to the pathophysiology of SZ/SA disorder [49]. These changes include ventricle enlargement, volumetric reduction, and atrophy or loss of neurons and glial cells in selective cortical and limbic brain regions [25, 26, 50, 51].
- *Neurotrophic effects* can be considered a therapeutic strategy intended to augment proliferation, differentiation, growth, and regeneration, whereas *neuroprotective effects* slow or halt the progression of neuronal atrophy or cell death following the onset of disease or clinical decline [52]. Available data suggest that psychotropic treatment needs to target brain protective mechanisms [14, 29].
- Antipsychotic agents might be enhanced by co-administration with antidepressants, mood stabilizers, benzodiazepines, and others compounds that act via other, non-dopaminergic mechanisms (e.g., serotonergic, glutamatergic, adrenergic receptors, and others) [23–26].

Thus, elucidation of the contribution of multiple signaling pathways to the action of psychotropic drugs might lead to more efficient *multi-target drug* therapeutics for

SZ/SA disorder, especially for the associated cognitive impairments, negative and mood symptoms.

8.3 Augmentation in the "Real World"

Adjunctive pharmacological agents are extensively used in the treatment of patients with schizophrenia. There are two types of adjunctive agents:

- Off-label prescription of adjunctive agents, such as antidepressants, lithium, antiepileptic drugs, and benzodiazepines that are already in use; and
- Newer molecules or compounds based on several non-dopaminergic hypotheses that are currently being examined.

There are established practices in "real world" pharmacotherapy. Pickar et al. [18] reported that 70% of 200 schizophrenia patients received an antipsychotic together with medication from another drug class: the most common drug class combinations were antipsychotics and mood stabilizers. A total of 42.5% of patients received more than one antipsychotic drug.

Cascade et al. [53] found that 43% of patients receive one additional class to supplement their antipsychotic medication, and 10% of patients are prescribed two or more classes of drugs in addition to an antipsychotic agent. The most common classes used to supplement antipsychotic medications in the management of schizophrenia include antidepressants (28%), mood stabilizers (18%), sleep aids (5%), and agents to treat extrapyramidal symptoms (7%), according to Dussias et al. [54]—20%, 15%, 7%, and 6%, respectively.

Längle et al. [55] evaluated the effects of different types of psychotropic polypharmacy on clinical outcomes and quality of life in 374 patients with SZ/SA disorder in routine care before discharge and after 6, 12, 18, and 24 months. At baseline 22% of the participants received antipsychotic monotherapy (quetiapine, olanzapine, or risperidone), 20% received more than one antipsychotic drug, 16% received antipsychotics combined with antidepressants, 16% antipsychotics plus benzodiazepines, 11.5% had antipsychotics and mood stabilizers, and 16% received psychotropic drugs from three or more subclasses.

Shinfuku et al. [56] based on a systematic chart review of 300 patients (100 of whom were psychotropic-free prior to their first visit) during a 2-year period, reported that polypharmacy occurred in 79% of the patients, with 2-year rates of the use of hypnotics (56.7%), benzodiazepine derivative anxiolytics (49.7%), anticholinergic drugs (38.3%), antidepressants (21.3%), and mood stabilizers (14.0%). *Once polypharmacy had started, it was continued until their final visit in >70% of the patients*. Himelhoch et al. [57] estimated the receipt of prevalent and incident antidepressant medications in the fiscal year 2007 among 2,412 veterans who received treatment for schizophrenia. They found that 37.4% also received an antidepressant prescription.

In order to determine the frequency of off-label prescriptions for mood stabilizers a cross-sectional survey of inpatients aged 18–65 years at St Andrew's Hospital

(Northampton, UK) was carried out [58]. Thirty percent (75/249) patients were administered one or more *mood stabilizers*, of which 71 were off-label. Sim et al. [59] examined the frequency of mood-stabilizer use and its clinical correlates among hospitalized patients diagnosed with schizophrenia in 2001–2008 in nine Asian regions (China, Hong Kong, India, Korea, Japan, Malaysia, Taiwan, Thailand, and Singapore). Overall, mood stabilizers were given to 20.4% ($n = 1{,}377/6{,}761$) of hospitalized schizophrenia patients, with increased usage over time. Xiang et al. [60] surveyed the use of adjunctive *mood stabilizers* in older Asian schizophrenia patients aged 55 years or more that were extracted from a database that included 1,452 patients from nine Asian countries and territories. The frequency of prescription of *mood stabilizers* was 26.7% in the pooled sample, with 25.5% in 2001, 26.9% in 2004 and 27.7% in 2009. Multiple logistic regression analysis of the whole sample revealed that patients on *mood stabilizers* were younger and more likely to be men and to have extrapyramidal side effects (EPS) and a longer duration of illness.

Guidelines for the prescription of benzodiazepines (BZD) recommend that their use be limited to the short-term relief of severe anxiety or insomnia. However, clinical experience suggests that in psychiatry these drugs might be more broadly prescribed. Haw and Stubbs [61] investigated benzodiazepine prescribing in a specialist UK psychiatric hospital using a structured interview with consultant psychiatrists. Of 412 inpatients, 77 (18.7%) received 90 BZD prescriptions for psychiatric indications. Most prescriptions were for anxiety (45/90; 50.0%), aggression (23/90; 25.6%) and agitation (13/90; 14.4%). Use was commonest for acquired brain injury, schizophrenia (26/77; 33.8%) and personality disorders. Much usage was chronic (only 4.4% prescriptions had been initiated within the previous 4 weeks) and off-label (94.4%). In psychiatry BZD are quite frequently used in the management of a number of groups of difficult-to-treat patients.

The frequency of BZD prescription in nine Asian countries and territories was 20.7% in the pooled sample, with 20.2% in 2001, 18.4% in 2004 and 23.1% in 2009 (the sample included 1,452 hospitalized schizophrenia patients aged 55 years or more). Compared to patients in China, their Korean and Singaporean counterparts were more likely to be on BZD [60]. Use of psychotropic medications (antidepressant, anxiolytic, and sedative/hypnotics) by 1,449 participants in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was documented at each study visit: initiation of new adjunctive agents post baseline period was moderately frequent, 14.6% of patients received antidepressants, 13.7% received anxiolytics, and 11.2% received sedative/hypnotics [62].

Thus, substantial proportions of patients with SZ/SA disorder do not achieve acceptable levels of response with antipsychotic therapy alone, which commonly leads clinical psychiatrists to use augmentive agents. Differences in the use of adjunctive medications may be due to true differences in the frequency of ancillary symptom complexes. For instance, among patients with recognized ancillary symptom complexes, black patients may also be less likely than white patients to receive treatment. This may be due to racial differences in accessibility of mental health care, physician perceptions of patients, and patient beliefs and preferences [63]. Further research is needed to clarify the underlying biases and behaviors that affect use of adjunctive medications among patients with schizophrenia.

8.4 Antidepressants

Depressive symptoms in patients with schizophrenia may be secondary to negative symptoms [64], medications, or neuroleptic-induced movement disorders [65], or a core component of various stages of SZ/SA disorder [66, 67]. At the same time, depressive symptoms are common in older patients with schizophrenia [68]. The most prevalent symptoms cut across several domains of the depressive syndrome: psychological (e.g., depressed mood, depressed appearance, psychic anxiety); cognitive (e.g., guilt, hopelessness, self depreciation, loss of insight); somatic (insomnia, anorexia, loss of libido, somatic anxiety); psychomotor (e.g., retardation and agitation) and functional (diminished work and activities) [69].

Lako et al. [70] investigated the prescribing patterns of antidepressants in relation to the course of depressive symptoms in a cohort of 214 Dutch patients with psychotic disorder patients. Depressive symptoms were prevalent among 43% of the patients. Antidepressants were prescribed for 40% of the patients and the majority (83%) continued this therapy after 1 year.

8.4.1 Mechanism of Action

A common mechanism of action of antidepressant drugs has not been found. Antidepressants are usually classified according to structure (e.g., tricyclic antidepressants, TCAs) or function (e.g., monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, SSRIs). However, it may be more useful to classify them according to the acute pharmacologic effects that are presumed to trigger behavioral improvement. If this is done, the antidepressants can be grouped in four categories [71]:

- Selective blockade of norepinephrine reuptake: desipramine, nortriptyline, amoxapine, maprotiline reboxetine
- Selective blockade of serotonin reuptake (SSRIs): citalopram, fluoxetine, paroxetine, sertraline
- Nonselective enhancement of norepinephrine and 5-HT transmission: imipramine, amitriptyline, phenelzine, tranylcypromine, venlafaxine, mirtazapine
- Unknown potent stimulatory effects on norepinephrine and 5-HT: trimipramine, bupropion, nefazodone, trazodone

The molecular mechanisms underlying the augmentation are unclear. There is increasing evidence suggesting that symptoms of depression and anxiety may be associated with serotonergic dysfunction in schizophrenic patients; significant progress has been made, pointing to some candidate systems which may be involved in SSRI-antipsychotic synergism. While as yet limited in scope, the evidence suggests definable molecular targets which may be implicated in drug development based on SSRI-antipsychotic synergistic actions [72]. Laboratory investigations into the mechanism of this synergism showed that co-administration of SSRIs and

antipsychotics produces changes in the $GABA_A$ receptor and related systems, which differ from the effects of each drug alone. SSRI augmentation of antipsychotics alters the expression of the $GABA_A$ receptor and related genes in peripheral mononuclear cells of schizophrenia patients [73].

8.4.2 Clinical Studies

The antidepressants that are most frequently assessed in clinical trials are those that are specifically targeted to treat persistent negative symptoms [30, 74–78].

8.4.2.1 Fluvoxamine

Published reports of clinical trials revealed that fluvoxamine improved negative symptoms and cognitive deficits in treated chronic schizophrenia [79–81]. Fluvoxamine at dosages up to 100 mg/day is not associated with clinically significant changes in plasma risperidone concentrations. However, higher doses of fluvoxamine may elevate plasma levels. Fluvoxamine increases plasma haloperidol and risperidone concentrations in a dose-dependent manner [82, 83].

8.4.2.2 Fluoxetine

Current evidence indicates that fluoxetine can ameliorate primary negative symptoms in chronic schizophrenic patients treated with first-generation antipsychotics [84]. The combination is well-tolerated, although as antipsychotic drug concentrations may rise, close monitoring of drug doses and possibly drug concentrations is needed.

8.4.2.3 Citalopram

There is contradictory evidence that add-on citalopram to antipsychotic drugs may improve the psychopathological and/or cognitive symptoms in schizophrenia [85–87]. Kasckow et al. [86] conducted a 10-week single-blind trial of citalopram (20–40 mg/day) vs no citalopram augmentation in 19 middle-aged and elderly patients with schizophrenia hospitalized for more than six of the past 12 months. Patients in both groups improved on positive and negative symptoms, but the citalopram group revealed significantly greater improvement in the Hamilton Depression Rating (HAM-D) scale and Clinical Global Impression Scale scores than the control group. Citalopram (40 mg/d) adjunctive treatment to atypical antipsychotics produced no significant cognitive improvement in patients with schizophrenia after 12 weeks of treatment [87]. Citalopram augmentation of antipsychotic treatment in middle aged and older patients with schizophrenia and subsyndromal depression

appears to improve social and mental health functioning as well as quality of life. Among 55 participants with schizophrenia or schizoaffective disorder and baseline suicidal ideation, citalopram reduced suicidal ideation, especially in those whose depressive symptoms responded to treatment [88]. Iancu et al. [75] evaluated the efficacy of escitalopram for the treatment of negative symptoms in patients with schizophrenia. Under double-blind conditions, 40 patients with chronic schizophrenia were randomized to add-on treatment with escitalopram (up to 20 mg) or placebo for 10 weeks. Escitalopram was well tolerated, but was not more effective than placebo in the treatment of negative symptoms in patients with chronic schizophrenia. A double-blind, crossover study demonstrated *anti-aggressive effects* of adjunctive citalopram in chronic schizophrenia [89].

8.4.2.4 Mirtazapine

Evidence that the combination of mirtazapine (remeron), and antipsychotic drugs may improve negative and/or cognitive symptoms in schizophrenia is contradictory [90–98]. Berk et al. [92] using a 6 week, double-blind design, recruited schizophrenia patients that were treated with SGAs plus mirtazapine (30 mg/day) or placebo, and did not find significant differences between mirtazapine and placebo treated participants in Positive and Negative Syndrome Scale (PANSS) scores or any of the secondary outcome measures. Abbasi et al. [93] investigated the effect of mirtazapine (30 mg/day) added to risperidone (6 mg/day) as augmentation therapy in 40 inpatients during the active phase of chronic schizophrenia and prominent negative symptoms in a double-blind randomized clinical trial. The mirtazapine group showed significantly greater improvement in negative symptoms and PANSS total scores over the 8-week trial. Mirtazapine was well tolerated and no clinically important side effects were observed. Other clinical trials suggest that augmentation with mirtazapine can effectively improve both negative and/or cognitive symptoms of schizophrenia [96, 97].

Overall, six randomized, double-blind, placebo-controlled trials assessed add-on mirtazapine to SGAs (four trials), and to first generation antipsychotics (FGAs, two trials). Five of the six trials supported the use of mirtazapine for negative symptoms of schizophrenia [98]. An open-label extension phase to a randomized controlled trial showed that mirtazapine continued to produce significant improvement in negative symptoms over a longer duration of time, when added to FGAs [95]. Mirtazapine appears to be well tolerated and associated with few drug interactions. Although adjunct mirtazapine to antipsychotics has been shown to be effective at doses of 30 mg/day in most of the trials, limitations of these studies include short study duration and small sample sizes.

8.4.2.5 Trazodone

Trazodone used in conjunction with neuroleptics, mildly reduced the severity of negative symptoms in residual schizophrenia (47 patients with an average age of

60 years) and did not exacerbate florid psychosis during a 6-week trial [99]. This conclusion was confirmed by Hayashi et al. [100] in double-blind, placebo-controlled small study (n = 12) with the dose gradually increased from trazodone 50 mg/day to 200 mg/day. Results also indicated a possible beneficial effect of trazodone in the treatment of tardive dyskinesia.

8.4.2.6 Bupropion

Bupropion affects the uptake of the neurotransmitters norepinephrine and dopamine. Englisch et al. [101] reported on a consecutive series of depressed patients with psychotic spectrum lifetime diagnoses who received bupropion extended release for a period of 6 weeks in addition to stable doses of antipsychotic agents. All patients experienced significant improvements of their major depressive episodes. Psychotic positive symptoms remained stably absent, and both negative symptoms and global psychopathology considerably improved. The treatment was generally well tolerated; however, subtle electroencephalographic deteriorations were observed. This case series suggests safe and effective antidepressive treatment with bupropion in SZ patients, if stable antipsychotic medication and electroencephalographic-monitoring are provided. Further randomized studies involving a control group are necessary.

8.4.2.7 Buspirone

Buspirone is a partial agonist at 5-HT_{1A} receptors, and is approved by the US Food and Drug Administration as an anxiolytic. It was tested for use in depression, panic disorder, obsessive-compulsive disorder, and schizophrenia as well [102]. Randomized controlled trials produced mixed results concerning the efficacy of buspirone in the augmentation of antipsychotic drugs [103–105]. For instance, 73 patients with schizophrenia, who had been treated with SGAs for at least 3 months, were randomly assigned to receive either buspirone (30 mg/day), or matching placebo. Attention, verbal fluency, verbal learning and memory, verbal working memory, and executive function, as well as psychopathology, were assessed at baseline, 6 weeks, and 3 and 6 months after baseline. A significant time by group interaction effect was noted on the Digit Symbol Substitution Test, a measure of attention/speed motor performance, with better performance of the buspirone group compared to the placebo group at 3 months [103]. On the contrary, in a 6-week, double-blind, placebo-controlled, independent group study, 18 subjects (14 males, four females) received in random order either placebo or buspirone (15–30 mg/day). There were no statistically significant differences between placebo and buspirone treatments on either of the cognitive function measures or symptom ratings [104]. Another small trial with 23 schizophrenia patients [risperidone (6 mg/day) plus buspirone (60 mg/day)] and 20 patients treated with risperidone plus placebo showed that the buspirone group had significantly greater improvement in the negative symptom and positive general

psychopathology subscales and PANSS total scores over the 8-week trial. Therapy with 60 mg of buspirone per day was well tolerated, and no clinically important adverse effects were observed [105].

8.4.2.8 Meta-analysis

Sepehry et al. [31] performed a meta-analysis of *11 studies* that assessed SSRI add-on therapy for the negative symptoms of schizophrenia. Studies were retained if

- SSRI add-on therapy was compared with antipsychotic monotherapy among schizophrenia spectrum disorder patients;
- The clinical trial was randomized, double-blind, placebo-controlled with a parallel-arm design;
- Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms or the PANSS-Negative subscale.

When studies were divided according to severity of illness, a moderate and significant effect size emerged for the studies involving so-called "chronic patients" (n = 274). *This meta-analysis provides support for augmentation with antidepressants for the treatment of negative and affective symptoms in schizophrenia.*

Singh et al. [32] published a systematic review and meta-analysis of *23 randomised controlled trials* of antidepressant augmentation that included 819 patients with chronic schizophrenia treated with SSRIs (mirtazapine, reboxetine, mianserin, trazodone, and ritanserin). Across the included studies there was a moderate pooled standardized mean difference with an effect size of 0.48. In specific subgroup analyses *fluoxetine, trazodone, and ritanserin* led to significantly greater response rates than placebo.

Watanabe [106] also concluded that fluoxetine, trazodone and ritanserin are more effective than placebo when used as add-on therapies for negative symptoms of schizophrenia. There was no evidence that antidepressant treatment induced a deterioration of psychotic symptoms. Further research is required to address the potential benefits and risks of chronic administration of antidepressants to patients with schizophrenia. Predictors of antidepressant initiation (14.6% of group) in the CATIE study were female gender or white skin color, and a prior diagnosis of depression or symptoms of depression at baseline. Patients with higher positive symptom scores and younger patients were started on antidepressants sooner. Duration of antidepressant treatment was longer in patients with less education and in those with a history of alcohol abuse/dependence [62].

Recently, Tiihonen et al. [107] showed that antidepressant use is associated with decreased suicide deaths among patients with schizophrenia in Finland.

Thus, clinical studies have shown that negative symptoms of schizophrenia unresponsive to antipsychotic monotherapy can improve after augmentation with some antidepressants. Possible explanations for inconsistencies in study findings include small sample sizes, variable duration of treatment, a range of concomitant antipsychotic regimens, and the nature of the inclusion criteria and outcome measures used [108].

8.5 Mood Stabilizers

The term "mood stabilizer" does not describe a mechanism, but rather an effect. Lithium, carbamazepine, valproate, and lamotrigine are recognized mood stabilizers.

8.5.1 Lithium

Lithium, the first mood-stabilizing medication approved by the U.S. Food and Drug Administration for treatment of mania, is often very effective in controlling mania and preventing the recurrence of both manic and depressive episodes.

8.5.1.1 Mechanism of Action

Lithium, affecting each neurotransmitter system within complex interactive neuronal networks, is suggested to restore the balance among aberrant signaling pathways in critical regions of the brain. Evidence from both in vitro and in vivo studies has demonstrated that lithium exerts multiple effects on neurotransmitter/receptor-mediated signaling, ion transport, signal transduction cascades, hormonal and circadian regulation, and profoundly alters gene expression patterns (see, e.g., reviews [109, 110]). Recent molecular studies have revealed the action of lithium on signal transduction mechanisms, such as phosphoinositide hydrolysis, adenylyl cyclase, G protein, glycogen synthase kinase-3beta, protein kinase C, and its substrate myristoylated alanine-rich C kinase substrate [111]. Lithium's main mechanisms of action appear to stem from its ability to inhibit glycogen synthase kinase-3 activity and also to induce signaling mediated by brain-derived neurotrophic factor. Lithium has emerged as a *neuroprotective agent* efficacious in preventing apoptosis-dependent cellular death. Lithium neuroprotection is provided through multiple, intersecting mechanisms; for instance, lithium increases cell survival by inducing brain-derived neurotrophic factor and thereby stimulating activity in anti-apoptotic pathways, including the phosphatidylinositol 3-kinase/Akt and the mitogen-activated protein kinase pathways [112]. Furthermore, there is evidence that demonstrates the action of lithium on cyclic adenosine monophosphate (cAMP)-mediated signal transduction, cAMP response element binding activation, increased expression of brain-derived neurotrophic factor, the phosphatidylinositide cascade, protein kinase C inhibition, glycogen synthase kinase 3 inhibition, and B-cell lymphoma 2 expression [113].

8.5.1.2 Clinical Studies

Lithium has been the subject of more double-blind studies than any other adjunctive treatment. Patients originally treated with placebo added to neuroleptics did not have significantly greater improvement when they received open-label adjunctive

lithium [114]. Findings from another research suggests that lithium might benefit only schizoaffective patients. However, the methodological shortcomings of the trials analyzed limit the impact of the evidence provided [115]. Based on a review of 20 studies with 611 participants, Leucht, Kissling, and McGrath [116] found:

- Three studies that compared lithium with placebo as the sole treatment showed no difference in any of the outcomes;
- In eight studies comparing lithium with antipsychotic drugs as the sole treatment, more participants in the lithium group left the studies early (n = 270);
- Eleven studies examined whether the augmentation of antipsychotic drugs with lithium salts is more effective than antipsychotic drugs alone. More participants who received lithium augmentation had a clinically significant response (n = 244). However, statistical significance became borderline when participants with schizoaffective disorders were excluded in a sensitivity analysis (n = 120, p = 0.07);
- No superior efficacy of lithium augmentation in any specific aspect of the mental state was found; and
- There were no differences between groups for adverse events.

Authors concluded that despite some evidence in favor of lithium augmentation, the overall results are inconclusive. A large trial of lithium augmentation of antipsychotic medications is required in order to detect a benefit of small effect size in patients with schizophrenia but with no affective symptoms.

8.5.2 Anticonvulsants

Anticonvulsant drugs are widely used for psychiatric indications. This includes alcohol and benzodiazepine withdrawal symptoms, panic and anxiety disorders, dementia, schizophrenia, and to some extent personality disorders. Besides pain syndromes, their main domain aside from epilepsy, however, is bipolar disorder [117].

8.5.2.1 Mechanism of Action

When hyper-function of glutamatergic pathways in the frontal cortex of schizophrenic patients was proposed [45], clinical studies provided evidence for glutamate abnormalities in schizophrenia. The majority of antiepileptic drugs have more than one mechanism of action [71]. Antiepileptic drugs are divided by mechanisms of action into the following groups [118]:

- Antiepileptics which block sustained repetitive firing in individual neurons, this effect is mainly due to the blockade of voltage-dependent sodium or calcium channels: carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproate;
- Drugs that enhance inhibitory events mediated by gama-aminobutyric acid (GABA): gabapentin, phenobarbital, topiramate, and valproate;

- The third group practically consists of one drug which blocks T-type calcium channels and is active against absences (ethosuximide); and
- Antiepileptic drugs that reduce events that are mediated by excitatory amino acids: glutamate, phenobarbital, and topiramate [119].

Lamotrigine's anticonvulsant action has been attributed to the increase in GABA release and also antagonism of voltage-gated sodium channels leading to a reduction in glutamate release [120–122]. There is also a glutamatergic hypo-function hypothesis of schizophrenia based on the ability of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, phencyclidine, to induce psycho-mimetic effects in healthy human volunteers indistinguishable from schizophrenia. Phencyclidine mimics the positive and negative symptoms and cognitive dysfunction as well as formal thought disorders and even auditory hallucinations. It could exacerbate psychosis in schizophrenic patients [123, 124]. The two opposing glutamatergic hypo-function and hyper-function theories have been reconciled by the fact that phencyclidine has a glutamate release increasing potential beside its NMDA associated channels blocking properties [46]. Therefore, the psychotic symptoms of phencyclidine could be due to glutamate release potentiation and not due to the reduction of glutamate activity.

Topiramate is an anticonvulsant drug with alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist properties and a GABA potentiating action [123, 124]. Because of these properties, topiramate could be chosen as a novel medication to address downstream consequences of NMDA receptor hypo-function, which are potentiation of GABAergic neurotransmission and antagonism of the excitotoxic actions of glutamate at the AMPA classes of glutamate-gated channels [125, 126].

Thus, conventional antiepileptics generally inhibit sodium currents (carbamazepine, phenobarbital, phenytoin, and valproate) or enhance GABA-ergic inhibition (valproate). Novel antiepileptic drugs mainly associated with an inhibition of voltage-dependent sodium channels are lamotrigine and oxcarbazepine [127].

8.5.2.2 Clinical Studies

Add-on carbamazepine, valproate, lamotrigine and several other antiepileptic drugs to antipsychotic agents have been prescribed with diverging or inconclusive results in SZ/SA disorder [128].

Carbamazepine (Tegretol)

Although the findings of the various clinical trials are very difficult to compare, the results generally indicate beneficial effects particularly if carbamazepine is used as an adjunct to antipsychotic medication [129]. Recently conducted clinical trials indicated that carbamazepine augmentation may be effective for patients with schizophrenia treated with aripiprazole, although carbamazepine dramatically decreases plasma concentrations of aripiprazole [130].

Leucht and associates [131] evaluated the effects of carbamazepine and its derivatives for the treatment of schizophrenia and related psychoses (ten studies, 258 participants). A favorable effect of carbamazepine was found when those who received the antipsychotic (perphenazine) had Parkinsonism. There were no between group differences between the add-on carbamazepine and the add-on placebo groups, regarding acceptability or early termination of study. Carbamazepine augmentation was superior compared with antipsychotics alone in terms of overall global improvement. No data were available for the effects of carbamazepine on subgroups of people with schizophrenia and aggressive behavior, negative symptoms or EEG abnormalities or with schizoaffective disorder. Based on currently available randomized trial-derived evidence, carbamazepine cannot be recommended for routine clinical use for treatment or augmentation of antipsychotic treatment of schizophrenia.

Valproate

There is only limited evidence to support the use of augmentation therapy with valproate *(divalproex sodium)*, including a single small study that revealed less agitation in the valproate augmentation group versus the antipsychotic monotherapy group. A Cochrane review and meta-analysis of only seven randomized studies with 519 participants found no significant benefit of valproate augmentation [132]. A clinical trial with 249 patients hospitalized for acute exacerbation of schizophrenia, in which valproate (a maximum dosage of 30 mg/kg/day) or placebo was added to risperidone (6 mg/day) or olanzapine (15 mg/day), showed improvement from baseline throughout the 28-day treatment period in the two combination therapy and the two antipsychotic monotherapy groups. There were statistically significant treatment differences favoring combination therapy as soon as day 3 for PANSS total score, derived Brief Psychiatric Rating Scale (BPRS) total score, as well as PANSS and BPRS subscales. Treatment with divalproex in combination with an atypical antipsychotic agent resulted in earlier improvement in a range of psychotic symptoms among hospitalized patients with acute schizophrenia [133]. A recent 12-week, randomized, double-blind, parallel-group, multi-center trial with 402 patients failed to show an advantage of valproate augmentation at any of the time points [134].

Citrome et al. [135] compared the specific anti hostility effects of SGAs monotherapy (olanzapine or risperidone) with that of combination treatment with divalproex sodium among 249 inpatients with schizophrenia in a double-blind, 28-day multicenter trial. Combination treatment with risperidone or olanzapine plus divalproex had a significantly greater anti hostility effect at days 3 and 7 than monotherapy. The effect on hostility appears to be statistically independent of antipsychotic effect on other PANSS items reflecting delusional thinking, a formal thought disorder, or hallucinations. Thus, divalproex sodium may be useful as an adjunctive agent in specifically reducing hostility in the first week of treatment with risperidone or olanzapine among schizophrenia patients who are experiencing an acute psychotic episode.

Lamotrigine

A double-blind, placebo-controlled 14 week trial with a cross-over design, assessed the addition of lamotrigine to ongoing clozapine treatment in 34 treatment resistant patients. Lamotrigine was shown to be more effective than placebo in reducing positive symptoms and 'general psychopathological symptoms' measured by the PANSS, but had no significant benefit on negative symptoms [136]. Two multicenter, randomized, double-blind, 12-week, parallel-group trials were conducted to compare flexibly dosed lamotrigine (100–400 mg/d) with placebo as add-on treatment in 429 schizophrenia patients with stable, residual psychotic symptoms. The primary end point was the change in PANSS total score at week 12 [137]. Results from these two studies do not support the use of lamotrigine as an adjunct to atypical antipsychotics in patients with refractory psychosis. It is unclear why positive results from previous lamotrigine trials were not replicated. The positive effect of lamotrigine on cognition in one trial, while of uncertain significance, may merit further study.

Fifty-one treatment-resistant schizophrenic patients treated with clozapine received, either up to 200 mg/day of lamotrigine or placebo in a double-blind design for 24 weeks, [138]. Lamotrigine added to stable clozapine treatment showed a beneficial effect on negative, positive and general psychopathological symptomatology. Regarding cognitive functions, improvement was observed in attentional resistance to interference, verbal fluency and executive functioning. The findings provide evidence that lamotrigine augmentation of clozapine treatment is well tolerated and may be proposed as an effective therapeutic strategy to improve outcome in treatment-resistant schizophrenia.

Glick et al. [139] compared the efficacy of mood stabilizer augmentation of an antipsychotic for patients with schizophrenia who are both stabilized and partially responsive. Adult patients with SZ/SA disorder were enrolled in a 12-week, double-blind randomized trial. They were randomly assigned to one of three adjunctive treatments: (1) lamotrigine, (2) divalproex sodium, or (3) placebo. There were no differences in global outcomes, positive, negative and depressive symptoms, quality of life, or demoralization among the three groups.

A Cochrane review and meta-analysis of five lamotrigine augmentation studies and 537 participants revealed some efficacy on positive and negative symptoms, though results were mixed and not robust [140]. However, in another more recent meta-analysis data were restricted to lamotrigine add-on therapy to clozapine, with clozapine as a proxy for highly likely treatment resistance. In this meta-analysis of five trials and 161 participants a significant effect in favor of lamotrigine was observed [33]. This meta-analysis drew between two and 30 patients for the clozapine and placebo groups from individual trials in which a mixture of baseline antipsychotics was allowed and in which clozapine treatment was not used as a stratification factor. This means that the included patients were not truly randomly assigned to clozapine or placebo, rendering a suggestive analysis. Nevertheless, overall lamotrigine still seems to hold some promise but more studies are needed.

Topiramate

Clinical results suggest that treatment with topiramate may improve negative symptoms and cognitive dysfunction in schizophrenia when added to a stable dose of antipsychotic medication [141–143]; however much of this information is based on open-label studies, case reports and case series [144]. In a randomized, double-blind, placebo-controlled study of SZ patients, the addition of topiramate resulted in a reduction of both positive and negative symptoms compared with patients on antipsychotic monotherapy [143]. A 12-week naturalistic, open study was carried out to examine the potential benefits of topiramate in clozapine-treated schizophrenia patients who exhibited a suboptimal clinical response (20 subjects were enrolled, and 16 completed the study). Topiramate augmentation led to a 14% improvement in total Brief Psychiatric Rating Scale scores ($p=0.0003$), a 2.5% decrease in body weight ($p=0.015$), and was generally well tolerated; paraesthesia was the most common side effect [145]. These findings support topiramate as a viable augmentation strategy in clozapine partial responders.

8.5.2.3 Aggressive Behavior

Antiepileptic drugs may reduce aggression by acting on the CNS to reduce neuronal hyper-excitability associated with aggression. Huband et al. [146] reviewed 14 studies of five different antiepileptic drugs with data from 672 participants. Four antiepileptics (carbamazepine, valproate/divalproex, oxcarbazepine and phenytoin) were effective, compared to placebo, in reducing aggression in at least one study, although for three drugs (valproate, carbamazepine and phenytoin) at least one other study showed no statistically significant difference between treatment and control conditions. The authors considered that the body of evidence summarized in this review was insufficient to allow any firm conclusion to be drawn about the use of antiepileptic medication in the treatment of aggression and associated impulsivity.

Mood-stabilizer use was significantly and independently associated in multivariate logistic modelling with: aggressive behavior, disorganized speech, multiple hospitalizations, less negative symptoms, younger age, and revealed regional variation [59]. Further research is warranted.

8.6 Benzodiazepines

The use of benzodiazepines (BZDs) in schizophrenia was mainly for symptoms such as insomnia, anxiety, agitation, aggression, and psychotic excitement in general and control of florid psychotic symptoms such as hallucinations and delusions in particular [147, 148]. BZDs were further found to be useful in the reduction of neuroleptic-induced side effects such as akathisia or tardive dyskinesia [149].

8.6.1 Mechanism of Action

Benzodiazepines bind to the $GABA_A$ receptor, reducing the quantity of GABA required to open the chloride channel, hyperpolarize the neuron and inhibit neurotransmission [150]. Benzodiazepines also have an effect on the mesoprefrontocortical regions where neuroleptics may be less efficient [151].

8.6.2 Clinical Studies

The use of various types of BZDs as adjunct therapy to neuroleptics in the treatment of symptoms such as agitation and psychotic excitement in general and control of florid psychotic symptoms such as hallucinations and delusions in particular is well known [152–155]. For instance, about half of the 48 alprazolam-treated patients with schizophrenia demonstrated clinically significant improvement in both positive and negative symptoms [154]. The positive symptoms appear to be significantly reduced by BZDs in some but not all studies [156]. These suggest that there could be a group of patients who respond to BZDs. Diazepam was reported to be effective in treating prodromal and early signs of schizophrenia [155].

Multivariate logistic regression and multivariate linear regression analyses were performed to assess predictors of benzodiazepine use and dose, respectively, in Asian patients with schizophrenia [157]. Overall, 54% of the patients received adjunctive BZDs at an average daily dose equivalent to 30.3 mg diazepam, with minor changes over the years sampled. Benzodiazepine use was highest in Taiwan and Japan, lowest in Thailand and China, and was associated with shorter duration of illness, presence of delusions, hallucinations, disorganized speech, social or occupational dysfunction, and use of mood stabilizers, anti-parkinsonian or antidepressant drugs, and lower doses of antipsychotics.

As reviewed by Volz et al. [158], a meta-analysis of 31 randomized studies with 2,454 participants did not reveal significant superiority for BZDs compared with placebo. Nevertheless, a number of methodological problems such as insufficient data or the use of different outcome criteria hampered the meta-analytic process. The sedative effects of benzodiazepines in schizophrenia could be shown, but there is much room for randomized studies on the decisive question whether BZDs improve or at least hasten the amelioration of positive symptoms.

Tiihonen et al. [107] using national databases of mortality and medication prescriptions among a complete nationwide cohort of 2,588 patients hospitalized in Finland investigated if the use of benzodiazepines, antidepressants, or multiple concomitant antipsychotics is associated with increased mortality among patients with schizophrenia. Authors concluded that BZD use was associated with a marked increase in mortality among patients with schizophrenia, whereas the use of an antidepressant or several concomitant antipsychotics was not.

Predictors of anxiolytic initiation (13.7% of group) in the CATIE study were not being African-American, younger age, higher body mass index, and akathisia. Time to anxiolytic initiation was shorter in patients who were separated or divorced and

in patients with better neurocognitive functioning. Duration of anxiolytic treatment was shorter for African Americans and longer in patients with better instrumental role functioning. Predictors of sedative/hypnotic use (11.2% of group) were depressive symptoms and prior diagnosis of an anxiety disorder. Time to initiation of sedative/hypnotics was longer for those with depressive symptoms and shorter for those with a history of alcohol abuse or dependence [62].

Thus, BZDs, in conventional doses, can enhance the antipsychotic effect of neuroleptics in schizophrenics who did not respond satisfactorily to neuroleptics alone. This effect is more conspicuous regarding hallucinations, and improvement has also been observed for delusions, thought disturbances, some negative symptoms, anxiety and tension. Some BZDs may be more effective than others in schizophrenia, but this has not been clearly determined. Benzodiazepines combined with clozapine clearly increases the frequency of cardiovascular and respiratory accidents [151].

8.7 Glutamatergic Drugs

8.7.1 Mechanism of Action

NMDA receptors are a major subtype of glutamate receptors and mediate slow excitatory postsynaptic potentials. The glutamate hypothesis of schizophrenia is based on the ability of NMDA receptor antagonists to induce schizophrenia-like symptoms. There are strong lines of evidence indicating that dysfunction of NMDA receptors may explain the pathophysiology of schizophrenia [107, 159, 160]. Research over the past two decades has highlighted promising new targets for drug development based on potential pre- and postsynaptic, and glial mechanisms leading to NMDA receptor dysfunction. Reduced NMDA receptor activity on inhibitory neurons leads to disinhibition of glutamate neurons increasing synaptic activity of glutamate, especially in the prefrontal cortex [161].

8.7.2 Clinical Studies

Presently, glutamatergic drugs are not available for clinical use [162].

Much interest has surrounded the use of agonists at the NMDA-glycine site (D-serine, glycine, D-alanine and D-cycloserine) and glycine transporter-1 (GlyT-1) inhibitor (sarcosine) in order to improve the symptoms of stable chronic schizophrenia patients receiving concurrent antipsychotics.

8.7.2.1 Glycine

This therapeutic approach for the treatment of schizophrenia aimed to increase synaptic glycine levels with add-on oral glycine to antipsychotic agents. Clinical trials provided clinical support for this approach. For instance, in a double-blind,

placebo-controlled fashion 14 medicated patients with chronic schizophrenia were treated with glycine. Significant improvement in negative symptoms occurred in the group given glycine but not in the group given placebo, suggesting that potentiation of NMDA-receptor-mediated neurotransmission may represent an effective treatment for neuroleptic-resistant negative symptoms in schizophrenia [163]. High glycine dose studies replicated and extended initial findings by demonstrating improvements in positive, negative, and cognitive symptoms of the disorder [164–166]. High variability of clinical efficacy of glycine adjuvant therapy (ranging from 20 to 70%) should be noted.

8.7.2.2 D-cycloserine

Thirty eight stable adult schizophrenia outpatients (87% completed the trial) treated with any antipsychotic except clozapine were randomized to a double-blind, 8-week add-on trial of d-cycloserine 50 mg or placebo. Once-weekly dosing with d-cycloserine for 8 weeks produced persistent improvement of negative symptoms compared to placebo, although statistical significance was, in part, the result of worsening of negative symptoms with placebo [167]. These results must be considered preliminary since a number of outcomes were examined without correction for multiple tests. Preliminary studies with once-weekly administration of D-cycloserine supported its benefit on negative symptoms, memory consolidation, and facilitation of cognitive behavioral therapy for delusions [168].

8.7.2.3 D-serine

The mammalian brain contains unusually high levels of D-serine. In the last few years, studies from several groups have demonstrated that D-serine is a physiological co-agonist of the NMDA type of glutamate receptor—a key excitatory neurotransmitter receptor in the brain [169, 170]. Heresco-Levy et al. [171] assessed the efficacy and safety of D-serine adjuvant treatment for 39 schizophrenia patients treated with SGAs (risperidone- or olanzapine) using a double-blind, placebo-controlled, 6-week crossover trial with 30 mg/kg/day D-serine. D-serine administration induced increased serine serum levels ($p<0.001$) and resulted in significant ($p<0.001$) improvement in negative, positive, cognitive, and depression symptoms, as measured by the PANSS. D-serine was well tolerated, and no detrimental changes in clinical laboratory parameters were noted. These findings indicate that risperidone and olanzapine efficacy might be augmented with D-serine adjuvant treatment, and confirm D-serine efficacy against main schizophrenia symptom domains.

Kantrowitz et al. [172] performed a 4-week, open-label trial of adjunctive D-serine (30, 60 or 120 mg/kg/day) with 42 antipsychotic-stabilized patients with SZ/SA disorder. On the PANSS, improvement was observed for positive ($p=0.006$; $d=0.46$), negative ($p<0.001$; $d=0.68$), general psychopathology ($p=0.001$; $d=0.53$), and total ($p<0.0001$; $d=0.74$) symptoms. Furthermore, increases in

plasma levels correlated with improved symptomatic and neuropsychological function. Thus, findings support a double-blind investigation of D-serine at doses 60 mg/kg/d, and suggest effectiveness in treatment of both persistent symptoms and neurocognitive dysfunction. However, when Lane et al. [173] compared D-serine, and sarcosine with placebo in the treatment of 60 patients using a double-blind, placebo-controlled design, D-serine did not differ significantly from placebo on any measure (symptoms, functioning, and quality of life).

8.7.2.4 Sarcosine

A glycine transporter-I inhibitor is a small molecule that enhances the NMDA neurotransmission and has been shown to be beneficial as adjuvant therapy for schizophrenia. In one study, 65 risperidone-treated in-patients with acute exacerbations of schizophrenia were given adjuvant sarcosine (a glycine transporter inhibitor) 2 g/day, DSR 2 g/day, or placebo in a 6-week, randomized, double-blind trial. The sarcosine group showed significantly more symptom improvement than the other two groups [174]. In a 6-week, controlled trial with chronic schizophrenia patients, sarcosine 2 g/day adjuvant treatment led to 17% ($P<0.0001$), 14% ($P<0.0001$), and 13% ($P<0.0001$) reductions in positive, negative, and cognitive symptoms, respectively, without inducing any significant side effects [174]

Lane, Huang, Wu et al. [175] examined the effects of sarcosine adjuvant therapy for schizophrenic patients among 20 schizophrenic inpatients enrolled in a 6-week double-blind, placebo-controlled trial of sarcosine (2 g/day) which was added to their stable doses of clozapine. Sarcosine produced no greater improvement when co-administered with clozapine than placebo plus clozapine at weeks 2, 4, and 6. Sarcosine was well tolerated and no significant side-effects were noted. Thus, unlike patients treated with other antipsychotics, patients who received clozapine exhibited no improvement with the addition of sarcosine or agonists at the NMDA-glycine site. In a replication study sarcosine was shown to be superior to placebo on all four outcome measures of PANSS total score ($p=0.005$), Scale for the Assessment of Negative Symptoms (SANS) ($p=0.021$), Quality of Life (QOL) ($p=0.025$), and Global Assessment of Functioning (GAF) ($p=0.042$) [173].

8.7.2.5 Meta-analysis

Tiihonen and Wahlbeck [176] analysed 18 short-term trials with 358 randomised participants. All trials were short-term trials with a maximum duration of 12 weeks. In all of these trials, glycine, D-serine, and D-cycloserine was used to augment the effect of antipsychotic drugs. D-cycloserine, a partial agonist of NMDA receptors' glycine site, seemed ineffective towards the symptoms of schizophrenia. NMDA receptor co-agonists glycine and D-serine showed some effects in reducing the negative symptoms of schizophrenia ($n=132$, $p=0.0004$), but the magnitude of the effect was moderate. In general, all glutamatergic drugs appeared to be ineffective in

further reducing positive symptoms of the disease when added to the ongoing antipsychotic treatment. Glycine and D-serine may somewhat improve negative symptoms when added to regular antipsychotic medication, but the results were not fully consistent and data are too few to allow any firm conclusions. Many participants in the included trials were treatment-resistant which may have reduced treatment response. Additional research on glutamatergic mechanisms of schizophrenia is needed.

In a meta-analysis Tsai and Lin [34] included about 800 subjects from 26 studies. Overall, the NMDA-enhancing molecules were effective in most schizophrenic symptom domains with an effect size of total psychopathology of 0.40. Glycine, D-serine, and sarcosine treatments significantly improved multiple symptom domains, whereas D-cycloserine did not improve any symptom domain. Moderator analysis revealed that glycine, D-serine and sarcosine were better than D-cycloserine in improving overall psychopathology. Patients that received risperidone or olanzapine, but not clozapine, improved. No significant side effect or safety concern was noted.

Another meta-analysis was based on 29 trials with 1,253 participants [35]. Subgroup analysis revealed medium effect sizes for D-serine and N-acetyl-cysteine for negative and total symptoms, and for glycine and sarcosine for total symptoms. When added to clozapine, none of the drugs demonstrated therapeutic potential, and addition of glycine worsened positive symptoms. Taking into consideration the number of trials and sample sizes in subgroup analyses, D-serine, N-acetyl-cysteine and sarcosine as adjuncts to non-clozapine antipsychotics revealed therapeutic benefit in the treatment of negative and total symptoms of chronic schizophrenia.

Recently de Bartolomeis et al. [177] critically updated preclinical and clinical data on the modulation of glutamate NMDA receptor activity by NMDA-receptors co-agonists, glycine transporters inhibitors, AMPAkines, mGluR5 agonists, NMDA-receptors partial agonists. Though promising preclinical findings have been reported for virtually all compounds, clinical efficacy has not been confirmed for D-cycloserine. Contrasting evidence has been reported for glycine and D-serine that may however have a role as add-on agents. More promising results in humans have been reported for glycine transporter inhibitors.

Thus, although hypofunction of NMDA receptor-mediated neurotransmission is proposed to play an important role in the pathophysiology of schizophrenia, results of clinical trials of small molecules that enhance the NMDA function are inconsistent.

8.8 Hormonal Agents

It is a well-established fact that schizophrenia, and related psychoses may have a significant hormonal, mainly neuroprotective, component in the pathogenesis of the disease. Findings from the current literature support the role of neurosteroids and the estrogen protection hypotheses.

8.8.1 Neurosteroids

Neurosteroids such as dehydroepiandrosterone (DHEA), pregnenolone (PREG), and their sulfates (DHEAS and PREGS) display multiple effects on the central nervous system.

After discovering that PREG and DHEA are produced in the brain Baulieu [178] introduced the term "neurosteroids". Current knowledge concerning PREG and DHEA metabolism, the enzymes mediating these reactions, and their localization was recently summarized [179, 180]. Clinical studies revealed low levels of PREG in individuals with major depression [181], generalized anxiety disorder [182], generalized social phobia [183], and chronic medicated schizophrenia patients [184]. Comparisons of the values of blood DHEA and DHEAS levels of schizophrenia patients with healthy controls were found to differ among studies, ranging from normal, to low, and to high levels [185–193]. A meta-analysis of differences in mean concentrations of serum DHEA(S) between schizophrenia patients and control subjects shows a significant non-zero effect ($p<0.001$), and significant heterogeneity of data ($p<0.001$; [194]).

Alterations in PREG(S) and DHEA(S) in schizophrenia may be associated with impaired stress-response. Several lines of evidence have shown that a variety of stressors result in a shift in the balance of cortisol and DHEA(S), in that there is an increase in cortisol synthesis and a decrease in androgen synthesis. During acute psychological stress, stimulation of adrenal steroid release is accompanied by a shift towards DHEA release [195]. Furthermore, DHEA(S) were shown as mediators of the HPA axis adaptation to extreme stress and the psychiatric symptoms associated with posttraumatic stress disorder [196]. PREG is increased in rodent brain and plasma after HPA activation by acute stress or ethanol administration [197]. The antiglucocorticoid properties of DHEA [198] and neuromodulatory effects of DHEA(S) on GABA, NMDA and sigma receptors in the brain [199–201] may contribute to symptom severity, including behavioral functions such as response to stress, anxiety, aggressive behavior, learning and memory [202]. This, in turn, may lead to dysregulation in neurotransmission, and neuroprotective mechanisms and result in chronic and progressive deterioration in emotional, cognitive, and psychosocial functions of patients.

8.8.1.1 Mechanism of Action

Experimental and clinical observations suggest that PREG, DHEA and their sulfates (PREGS, DHEAS) [together abbreviated as PREG(S) and DHEA(S)] display multiple effects on the central nervous system (CNS) such as modulation of neurotransmitter receptors [203–205], anti-stress effects [206], neuroprotective properties [207], cognitive-enhancing effects [208, 209], androgenic, estrogenic activities, and neuropsychopharmacological effects [210, 211]. In particular, they regulate the growth of neurons, enhance myelinization and synaptogenesis in the CNS, affect

synaptic functioning, and thus may be effective as brain protectors [212, 213]. In elderly populations they are reduced to 20–30% of the peak levels of young adulthood [214, 215]. Studies in experimental animals revealed important roles of neuroactive steroids in the control of central nervous system functions in physiological and pathological conditions, suggesting that they may represent good candidates for the development of neuroprotective strategies for neurodegenerative and psychiatric disorders [216]. Specifically, neurosteroids have various functions associated with neuroprotection, response to stress, mood regulation and cognitive performance. In addition, neurosteroid levels are altered in stress-related neuropsychiatric disorders, see review, e.g., [36].

8.8.1.2 Clinical Studies

Several randomized, double-blind, placebo-controlled clinical trials were conducted with PREG [217, 218] and DHEA [219–224] for the treatment of schizophrenia and schizoaffective patients. Comparative critical analyses of these clinical trials were published [36, 225]. Overall, the results of these clinical trials with two neurosteroids are based on 117 patients who received DHEA and 34 patients treated with PREG. The clinically significant benefits of both DHEA and PREG augmentation remain unclear. Limitations of the studies reviewed include small sample sizes. It is crucial to replicate these trials with larger samples of schizophrenia or schizoaffective patients, and for a longer duration of treatment.

In summary, experimental and clinical observations support the speculation that neurobiological alterations in PREG(S)/DHEA(S) neurosteroids are related to the pathophysiology of schizophrenia and other neuropsychiatric disorders. Based on the accumulated evidence, it is also possible to conclude that PREG(S)/DHEA(S) might play a relevant role in the expressions of stress response, anxiety, and cognitive deficit in schizophrenia. Finally, these insights underscore the need for development of novel treatment strategies such as neuroprotective strategies using neurosteroids and other compounds, to help overcome the limitations of current antipsychotic drugs and to improve the cognitive deficits and negative symptoms, as well as functioning and quality of life outcomes of people affected by schizophrenia. Pilot clinical trials indicate that PREG and DHEA augmentation may improve some clinical symptoms and neurocognitive response in schizophrenia. Clinical trials for the evaluation of these neurosteroids pose a few challenges, and further investigation of neurosteroid treatment in schizophrenia and related disorders is warranted.

8.8.2 Estrogen, Raloxifene and Testosterone

There is a wealth of historical and circumstantial evidence to suggest that female patients with schizophrenia may suffer from a deficit in estrogenic function [226]. Epidemiological and life-cycle data point to significant differences in the incidence

and course of schizophrenia between men and women, suggesting a protective role of estrogen. In-vitro and in-vivo preclinical research has confirmed estradiol's interactions with central neurotransmitter systems implicated in the pathogenesis of schizophrenia [227, 228].

8.8.2.1 Mechanism of Action of Estrogen

Estrogen is known to have diverse *neuroprotective properties*; in particular, estrogenic compounds can protect brain cells against injury from excitotoxicity, oxidative stress, inflammation and apoptosis [229–231]. They can also enhance neurogenesis, angiogenesis, synaptic density, plasticity and connectivity, axonal sprouting and remyelination and expression of neurotrophic factors [232, 233]. Furthermore, estradiol has been found to significantly interact with the dopaminergic, serotonergic and glutamatergic systems, giving it properties similar to those of FGAs [234, 235].

8.8.2.2 Clinical Studies

Estrogen has recently been used as an adjunct to standard antipsychotic medication in quite a few studies of female schizophrenia patients [236, 237]. Cochrane review and meta-analysis summarized four studies with a total of 108 women and concluded that adjunctive estrogen with or without progesterone does not appear to offer convincing advantages over placebo [238]. In men, consideration of estrogen therapy has been impacted by concerns of feminising side effects, however, clinical trials of the use of estrogen in treating prostate cancer, bone density loss and even aggression and psychosis in dementia or traumatic brain injury, show this to be a safe and effective therapy. A 14-day randomised placebo-controlled trial involving 53 men with schizophrenia was conducted to evaluate the efficacy of 2 mg oral estradiol valerate as an adjunct to FGAs [239]. Results demonstrated a more rapid reduction in general psychopathology that occurred in the context of greater increases in serum estrogen levels and reductions in FSH and testosterone levels in participants that received estradiol. Approximately 28% of the estradiol participants did not achieve an increase (at least a 50% from baseline) in serum estrogen suggesting that further research is needed to refine the type, dose and administration route for estrogen therapy in men.

Raloxifene

Another therapeutic strategy may be related to add-on raloxifene hydrochloride. It is a selective estrogen receptor modulator that acts as an estrogen antagonist in breast tissue and may have agonistic actions in the brain, potentially offering mental health benefits with few estrogenic side effects [240]. Kulkarni et al. [241] examined

the effect of a therapeutic dose of adjunctive raloxifene (120 mg/day, n = 13) versus oral placebo (n = 13) in postmenopausal women with schizophrenia. Analysis of variance found significant interaction effects for total and general PANSS scores. The demonstrated benefit of adjunctive treatment with 120 mg/day raloxifene hydrochloride offers support for the potential role of this selective estrogen receptor modulator in treating postmenopausal women with schizophrenia.

Usall et al. [242] conducted a 12-week, double-blind, randomized, placebo-controlled study with 33 postmenopausal women with schizophrenia who exhibited prominent negative symptoms. The addition of raloxifene (60 mg/day) to regular antipsychotic treatment significantly reduced negative ($p = 0.044$), positive ($p = 0.031$), and general psychopathological ($p = 0.045$) symptoms during the 12-week trial as compared to the add on placebo group. If more extensive and longer-term studies confirm and expand upon these positive results, the use of raloxifene could be recommended in postmenopausal patients with schizophrenia.

Testosterone

To explore the therapeutic effect of *testosterone augmentation* of antipsychotic medication on symptoms in male patients with schizophrenia, Ko, Lew, Jung et al. [243] performed a placebo-controlled, double-blind trial with 30 schizophrenic men, using either 5 g of 1% testosterone gel or a placebo added to a fixed dosage of antipsychotic medication over a period of 4 weeks following a 2-week washout period. Results indicated a significant improvement of negative symptoms in both the last observation carried forward and the completer analyses and a nonsignificant trend for the improvement of depressive symptoms in completers. There were no significant changes in serum hormone levels except total and free testosterone. The findings of this study suggest that testosterone augmentation may be a potential therapeutic strategy in patients with schizophrenia.

8.9 Retinoid-Based Strategy

Retinoids are a family of molecules that are derived from vitamin A. Several studies reported that retinoids are involved in neurodevelopment [244] and regulation of genes thought to be important in the pathogenesis of schizophrenia [245]. It has been suggested that retinoid dysregulation might be involved in the pathogenesis of schizophrenia. It is hypothesized that the availability in the brain of retinoid acid, the final product of the retinoid metabolic cascade, influences the onset of the disease [246, 247]. Defects in retinoid acid signaling have been implicated in several neurological diseases, including schizophrenia, movement disorders, and motor neuron disease [246, 248]. Because the retinoid acid level is controlled by genes involved in retinoid acid synthesizing, metabolizing and transporting, Chunling Wan et al. [249] investigated the polymorphisms of seven genes involved in these functions to reveal the possible role of retinoid acid in schizophrenia.

8.9.1 Mechanism of Action

There are two types of retinoid nuclear hormone receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Both belong to the corticosteroid receptor superfamily and co-exist in most cells. The alpha, beta, and gamma subtypes of the RARs and RXRs have distinct and conserved amino and carboxy terminal domains. Each receptor subtype has a specific pattern of expression during embryonal development and a different distribution in adult tissues. This differential expression of receptor subtypes is thought to regulate the expression of distinct sets of genes. Heterodimers of the RARs and RXRs bind and regulate a specific DNA sequence known as the retinoic acid response element, which is located in the promoter region of genes such as the *RAR-b2* gene, reviewed in [250].

Retinoids modulate neurotransmission. The expression of D_2 receptors been shown to be regulated by retinoid acid [251], and single and compound null mutations for the RARB, RXRB 8 and RXRG in mice result in reduced expression of D_1 and D_2 receptors and impaired dopamine signaling [252]. Retinoid analogs have therefore been proposed as candidates for the treatment of schizophrenia [253, 254].

8.9.2 Clinical Study

Bexarotene (Targretin) belongs to the group of synthetic medicines derived from vitamin A (retinoid). Its chemical name is 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid [255]. To date this medication has been exclusively used as treatment of neoplastic or dermatological diseases. Adverse events potentially related to bexarotene include lipid abnormalities, hypothyroidism, headache, asthenia, rash, leucopenia, anemia, nausea, and increased risk of infection, peripheral edema, abdominal pain, dry skin, dizziness, hyperesthesia, hypoesthesia, and neuropathy. Based on the retinoid hypothesis in schizophrenia, our group conducted a 6-week open label trial in two mental health centers [256]. It was assumed that the combined effect of antipsychotic agents and bexarotene would have a beneficial effect in treatment of psychopathological symptoms in chronic schizophrenia patients. Since high daily doses of bexarotene can produce numerous adverse effects, the first trial was aimed to examine safety and preliminary efficacy of a low daily dose (75 mg/day) of bexarotene in an open label pilot study. Twenty-five patients with chronic schizophrenia received a low dose of bexarotene (75 mg/day) augmentation. Significant improvement from baseline to endpoint was observed on the total PANSS score, general psychopathology, and on the positive and the dysphoric mood factor scores. Low doses of bexarotene were well tolerated. Bexarotene was found to be a safe medication as measured by all laboratory parameters with the exception of increased total cholesterol serum levels. This short-term pilot study supports bexarotene as a potential valuable adjunct in the management of schizophrenia. A double-blind controlled study is currently underway to replicate these preliminary results.

8.10 Nonsteroidal Anti-inflammatory Drugs (NSAID)

This strategy is based on the hypothesis that immune-mediated glutamatergic-dopaminergic dysregulation may lead to the clinical symptoms of schizophrenia, and, consequently, to the use of anti-inflammatory drugs (cyclo-oxygenase-2 inhibitors, acetylsalicylic acid) [257, 258].

8.10.1 Mechanism of Action

A literature search identified more than 100 articles pertaining to suspected immunologic influences on schizophrenia published over the past 15 years [259]. Evidence suggests that a (prenatal) infection is involved in the pathogenesis of schizophrenia. Due to an early sensitization process of the immune system or to a (chronic) infection, which is not cleared through the immune response, an immune imbalance between the type-1 and the type-2 immune responses takes place in schizophrenia [257]. For instance, the differential activation of the enzyme indoleamine 2,3-dioxygenase and of the tryptophan/kynurenine metabolic pathway, resulting in the increased production of kynurenic acid in schizophrenia, and a possible increase in quinolinic acid in depression, also may play a key role in these diseases. Such differences are associated with an imbalance in glutamatergic neurotransmission that may contribute to increased levels of NMDA agonism in depression and NMDA antagonism in schizophrenia. In addition, immunological imbalance results in the increased production of prostaglandin E_2 in schizophrenia and depression, as well as increased cyclooxygenase-2 (COX-2) expression in schizophrenia [260].

8.10.2 Clinical Studies

8.10.2.1 Cox-2 Inhibitors

The selective cyclooxygenase-2 inhibitor (celecoxib) is a non-steroidal anti-inflammatory drug that selectively targets the COX-2 enzyme. A study of 50 patients undergoing acute exacerbation of their symptoms reported a significant improvement in their PANSS total score using 400 mg/d for 5 weeks; a reanalysis showed that it had the most effect in patients with an illness of less than 2 years' duration [261]. A follow-up study of 40 patients using 400 mg/d for 8 weeks reported no overall effect; however, a reanalysis showed that patients with recent-onset illness showed the most improvement [262]. One study of 35 patients with chronic schizophrenia, average duration of illness 20 years and using 400 mg/d for 8 weeks, reported negative results [263], but another trial of 60 patients with chronic schizophrenia, average duration of illness 8 years and "in an active phase of illness," also

using 400 mg/d for 8 weeks, reported a significant improvement in positive and total symptoms on PANSS [264]. Most recently, a study of 49 individuals with first-episode schizophrenia, using 400 mg/day for 6 weeks, reported significant improvement in negative and total symptoms on PANSS [265].

8.10.2.2 Acetylsalicylic Acid

Laan et al. [266] reported findings from a randomized (aspirin 1,000 mg/d or placebo), double-blind, placebo-controlled study with 70 antipsychotic-treated inpatients and outpatients with a DSM-IV-diagnosed schizophrenia spectrum disorder from ten psychiatric hospitals. Patients were randomized to adjuvant treatment with aspirin 1,000 mg/d or placebo. The authors report a mean modest reduction of the PANSS total score. Effect size was approximately 0.5. Aspirin did not significantly affect cognitive function. No substantial side effects were recorded.

Sommer et al. [37] summarized five double-blind, randomized, placebo-controlled trials, with a total of 264 patients. Four studies applied celecoxib, and one used acetylsalicylic acid. Authors found a mean effect size of 0.43 ($p=0.02$) in favor of NSAIDs on total symptom severity. For positive and negative symptom severity, the mean standardized difference was about 0.3 ($p<0.05$). These results suggest that NSAID augmentation could be a potentially useful strategy to reduce symptom severity in schizophrenia. Since these initial studies were conducted on small samples, the obtained results should be interpreted with caution.

8.11 Acetilcholinesterase Inhibitors

Alterations in the central cholinergic system of patients with schizophrenia such as reduced numbers of muscarinic and nicotinic receptors in the cortex and hippocampus may contribute to the cognitive impairment associated with schizophrenia [267]. Furthermore, several lines of evidence suggest that cholinergic deficits may contribute to the pathophysiology of schizophrenia, depression, and dementia [268, 269]. Therefore, pharmacological treatments that enhance central cholinergic function may be useful as cognitive enhancers in schizophrenia.

8.11.1 Mechanism of Action

To understand the underlying mechanism for the clinical effectiveness of, for example, galantamine, neuropharmacological studies have been performed in animal models of several psychiatric disorders. These studies suggest that the nicotinic receptor-modulating properties as well as muscarinic receptor activation contribute to the galantamine's antipsychotic effect and contribution to the improvement of

cognitive dysfunction [270]. Donepezil is an acetylcholinesterase inhibitor that appears to enhance cognitive functioning in patients with dementia [268].

8.11.2 Clinical Studies

8.11.2.1 Donepezil

In a randomized placebo-controlled add-on trial, schizophrenia patients were randomly assigned to donepezil titrated up to 10 mg/day or placebo for 12 weeks (donepezil, n = 121; placebo, n = 124). Donepezil did not improve performance on any cognitive test compared to placebo and was associated with worsening of negative symptoms [271].

8.11.2.2 Galantamine

Add-on galantamine to the FGAs of patients with schizophrenia did not produce a change in the cognitive function or state of psychopathology [272]. Lindenmayer and Khan [273] performed a 52-week double-blind, randomized study of treatment with long-acting injectable risperidone (25 mg or 50 mg every 2 weeks). Adjunctive galantamine (up to 24 mg/day) or placebo treatment was administered from month 6–12. Galantamine showed no ameliorative effects on cognitive measures in this 6 month trial.

8.11.2.3 Meta-analysis

Ribeiz et al. [274] conducted a literature search (up to December 2008) for randomized, double-blind, placebo-controlled trials with donepezil, rivastigmine or galantamine in patients with SZ/SA disorder. The meta-analysis of 13 double-blind studies (four with rivastigmine, six with donepezil and three with galantamine) suggests that specific cognitive deficits (memory, and the motor speed and attention part of executive function) of patients with SZ/SA disorder respond to rivastigmine, donepezil and galantamine as adjunctive therapy.

Recently, Singh, Kour, and Jayaram [269] evaluated the clinical effects, safety and cost effectiveness of acetylcholinesterase inhibitors by analyzine all clinical randomized trials comparing acetylcholinesterase inhibitors with antipsychotics or placebo either alone, or in combination, for schizophrenia and schizophrenia-like psychoses. The acetylcholinesterase inhibitor plus antipsychotic showed benefit over antipsychotic and placebo in the following outcomes: PANSS negative and general psychopathology, improvement in depressive symptoms, cognitive domains—attention, visual memory, verbal memory and language and executive functioning. Confirmatory studies are needed to determine the clinical utility of this treatment strategy.

8.12 Purinergic-Related Drugs

A purinergic hypothesis of schizophrenia postulates that increased adenosinergic transmission reduces the affinity of dopamine agonists for dopamine receptors [275]. This model also addresses the systemic aspects of schizophrenia, based on peripheral roles of purines, such as modulation of the immune system.

8.12.1 Mechanism of Action

Allopurinol, a xanthine oxidase inhibitor, may increase circulating pools of adenosine and may have antipsychotic and anxiolytic effects [276].

8.12.2 Clinical Studies

8.12.2.1 Allopurinol

Clinical trials show that adjuvant allopurinol may benefit treatment refractory schizophernia patients. Allopurinol is well tolerated by most patients [276]. In another trial, 59 schizophrenia outpatients (51 patients completed the trial) were randomly assigned to receive adjunctive allopurinol 300 mg bid or identical placebo for 8 weeks after a 2-week placebo run-in [277]. A total of 4 of 31 in the allopurinol group and 0 of 28 in the placebo group had at least a 20% reduction in total PANSS score at the final study visit ($p = 0.049$). Among the completers ($n = 51$), individuals in the allopurinol group rated themselves as more improved than those in the placebo group ($p = 0.025$). Allopurinol was well tolerated. Allopurinol may be an effective adjunctive medication for some patients with persistent schizophrenia.

Weiser et al. [278] performed a multicenter, 8-week randomized clinical trial of allopurinol vs. placebo added to anti-psychotic medications in 248 patients with SZ/SA disorder. Both groups showed improvement in the PANSS (effect size = 1.13) and in clinical and cognitive measures. No between group differences were observed in any outcome measures. These findings do not support allopurinol as a treatment for schizophrenia.

8.13 Psychostimulants

8.13.1 Mechanism of Action

Psychostimulants increase the release of dopamine and norepinephrine and are a well-established treatment for attentional disorders.

8.13.2 Clinical Studies

8.13.2.1 D-amphetamine

In schizophrenia patients treated with haloperidol, D-amphetamine was found to enhance prefrontal cortical activation during performance of the Wisconsin Word Sort Test and to improve processing speed, whereas performance on memory and attentional tasks did not improve significantly [279]. Barch and Carter [280] found that, compared to placebo, D-amphetamine improved reaction times on spatial memory and Stroop tests, working memory accuracy, and language production when added to first generation antipsychotics. Healthy subjects displayed a similar pattern of cognitive improvement, though there was no change in working memory accuracy. Pietrzak and colleagues [281] reported improvement in executive function, attention, and speed of processing with D-amphetamine compared to placebo in chronic schizophrenia patients.

8.13.2.2 Modafinil

Modafinil is a Food and Drug Administration—approved medication with wake-promoting properties. Pre-clinical studies of modafinil suggest a complex profile of neurochemical and behavioral effects, distinct from those of amphetamines. In addition, modafinil shows initial promise for a variety of off-label indications in psychiatry, including treatment-resistant depression, attention-deficit/hyperactivity disorder, substance-dependence, and schizophrenia [282–284].

Compared to placebo, modafinil achieves positive but mainly variable results on different clinical and cognitive measures. Several studies have shown promising preliminary results in clinical domains when modafinil was added to antipsychotic treatment regimens [285, 286]. However, other clinical trials did not reveal any effect of modafinil on negative symptoms [287, 288] or wakefulness/fatigue or cognition compared to placebo [288, 289]. In a 4-week study, adjunctive armodafinil was not associated with an improvement in cognitive measures, and the negative symptoms of schizophrenia [290].

There were no significant differences in neurocognitive measures between adjunctive armodafinil (150 mg/d) and placebo in this 6-week study in 60 patients with schizophrenia or schizoaffective disorder. However, armodafinil was associated with significant improvement in the Scale for the SANS anhedonia-asociality ($F_{1,41}=4.1$, $p=0.05$), but not other negative symptom domains [291]. Scoriels et al. [292] aimed to establish modafinil's role in the adjunctive treatment of cognitive impairments. Forty patients with first episode psychosis participated in a randomized, double-blind, placebo-controlled crossover design study to assess the effects of a single dose of 200 mg modafinil on measures of executive functioning, memory, learning, impulsivity and attention. *Modafinil improved verbal working memory, spatial working memory errors and strategy use*. It also reduced discrimination

errors in a task testing impulsivity. Modafinil showed no effect on impulsivity measures, sustained attention, attentional set-shifting, learning or fluency. Thus, modafinil selectively enhances working memory in first episode psychosis patients. Modafinil significantly improved the recognition of sad facial expressions in first episode psychosis, while there was no effect of modafinil on subjective mood ratings, on tasks measuring emotional sensitivity to reward or punishment, or on interference of emotional valence on cognitive function [293]. Thus, evidence for the use of modafinil or armodafinil as add-on therapy to antipsychotic drugs in schizophrenia is inconclusive owing to small sample sizes and methodological differences of the various trials (cognitive testing). Adverse events include insomnia, headache, nausea, nervousness and hypertension. Further research is required to address the potential benefits and risks of chronic administration of modafinil to patients with schizophrenia.

8.14 Beta Blockers

8.14.1 Mechanism of Action

Propranolol is a non-selective beta-adrenergic receptor blocking agent. It has no other autonomic nervous system activity. Propranolol is a competitive antagonist which specifically competes with beta-adrenergic receptor stimulating agents for available beta-receptor sites. The most serious adverse effects that may be encountered with propranolol are congestive heart failure and bronchospasm.

8.14.2 Clinical Studies

8.14.2.1 Propranolol

High dose propranolol up to 1,200 mg/day has been shown to augment antipsychotic efficacy in treatment refractory schizophrenia. Reported beneficial effects include an ability to treat akathisia, increase antipsychotic serum levels, and decrease anxiety symptoms [38]. The latest Cochrane review and meta-analysis included only five studies with 117 patients and did not support the efficacy of antipsychotic augmentation with beta-blockers [294].

8.14.2.2 Pindolol

Treatment of aggression in schizophrenic patients is a major challenge. Caspi et al. [295] examined the efficacy of augmentation of antipsychotic treatment with

pindolol in the amelioration of aggression. Thirty male inpatients meeting DSM-IV criteria for schizophrenia, aged 20–65 years involved in four or more aggressive incidents in the two previous months, were enrolled in a double-blind crossover study. Aggression was evaluated per incident, with the Overt Aggression Scale. Patients received either pindolol or placebo augmentation 5 mg × three times a day until crossover, and then switched. revealed a significantly decline in the number According to Overt Aggression Scale scores, pindolol, with its dual beta and 5-HT_{1A} blocking effect ameliorated both number of aggressive incidents (0.59 versus 1.46, $p < 0.02$; 1.96 versus 3.23, $p < 0.05$, respectively).and severity of incidents towards objects and other persons (0.89 versus 3.58, $p < 0.0001$; 2.89 versus 6.85, $p < 0.004$, respectively). Influence on severity may be associated with a 5-HT_{1A} antagonistic effect.

8.15 Dietary Supplements

There is considerable scientific disagreement about the possible effects of dietary supplements on mental health and SZ/SA disorder.

8.15.1 Omega-3 Fatty Acids

Decreased n-3 fatty acid levels have been reported in patients with depression, schizophrenia, and Alzheimer's disease. Recently, eicosapentaenoic acid (EPA) was used to treat several psychiatric and neurodegenerative diseases due to its anti-inflammatory and neuroprotective effects [296, 297]. Published results are conflicting, and the antipsychotic efficacy of such augmentation strategies is not well established. A Cochrane review and meta-analysis included six short-term trials with 353 participants. The results were contradictory, leading the study authors to conclude that this treatment still needs further investigation [298]. A recent meta-analysis included double-blind, randomized, placebo-controlled studies using purified or EPA-enriched oils in schizophrenia: the database included 167 schizophrenic subjects under the placebo arm matched with 168 schizophrenic subjects in the EPA arm. The meta-analysis did not show a consistent significant beneficial effect for EPA augmentation on psychotic symptoms in schizophrenia [39].

8.15.2 L-Theanine

L-theanine is a unique amino acid present almost exclusively in the tea plant. It possesses neuroprotective, mood-enhancing, and relaxation properties.

8.15.2.1 Mechanism of Action

L-theanine is a water-soluble amino acid. L-theanine has been shown to have a direct influence on brain activity, such as reducing stress [299, 300]. At high doses (higher than usual doses found in a cup of black tea about 20 mg), it has the ability to relax the mind without causing drowsiness. Thirty-five participants were given either 50 mg of L-theanine or placebo. Electroencephalogram tests were done at baseline and then at specified times afterwards (45, 60, 75, 90, and 105 min). Researchers found that there was a greater increase in alpha activity in those who took L-theanine compared to placebo, demonstrating that the amino acid had an effect on the participants' general state of mental alertness and arousal.

8.15.2.2 Clinical Study

Ritsner et al. [301] conducted a first study designed to evaluate the efficacy and tolerability of L-theanine augmentation of antipsychotic treatment of 60 patients (40 patients completed the study protocol) with chronic SZ/SA disorder during an 8-week, double-blind, randomized, placebo-controlled study. 400 mg/day of L-theanine was added to ongoing antipsychotic treatment. Compared with placebo, L-theanine augmentation was associated with reduction of anxiety ($p = 0.015$) and positive ($p = 0.009$) and general psychopathology ($p < 0.001$) scores (measured by the PANSS 3-dimensional model). According to the 5-dimension model of psychopathology, L-theanine produced significant reductions on PANSS positive ($p = 0.004$) and activation factor ($p = 0.006$) scores compared to placebo. The effect sizes (Cohen *d*) for these differences ranged from modest to moderate (0.09–0.39). L-theanine was found to be a safe and well-tolerated medication. Regression models among L-theanine-treated patients indicate that circulating levels of brain-derived neurotrophic factor (BDNF) and cortisol-to-DHEAS*100 molar ratios were significantly associated with the beneficial clinical effects of L-theanine augmentation [302]. Variability of serum BDNF levels accounted for 26.2% of the total variance in reduction of dysphoric mood and 38.2% in anxiety scores. In addition, the changes in cortisol-to-DHEAS*100 molar ratio accounted for 30–34% of the variance in activation factor and dysphoric mood scores and for 15.9% in anxiety scores. Regression models among placebo-treated patients did not reach significant levels ($p > 0.05$). Thus, L-theanine augmentation of antipsychotic therapy can ameliorate positive, activation, and anxiety symptoms in SZ/SA disorder patients. Furthermore, results indicate that circulating BDNF and cortisol-to-DHEAS*100 molar ratio may be involved in the beneficial clinical effects of L-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients. Long-term studies of L-theanine are needed to substantiate the clinically significant benefits of L-theanine augmentation.

8.15.3 S-Adenosyl-L-methionine

S-adenosyl L-methionine (SAMe) is the natural, universal methyl group donor, participating in transmethylation reactions, known and commonly used as a dietary supplement since 1952 [303]. It plays an important role in the synthesis of neuromediators and melatonin and mechanisms of epigenetic regulation. Since SAM-e is involved in several metabolic processes, its administration may have a role in the amelioration of several disorders.

8.15.3.1 Mechanism of Action

SAM-e is able to cross the blood-brain barrier. SAM-e's predominant function is as a primary methyl group donor for a wide range of compounds including catecholamines, membrane phospholipids, fatty acids, nucleic acids, porphyrins, choline carnitine and creatinine. Following release of its methyl group, SAM-e is converted to S-adenosyl-homocysteine which, in turn, acts as a competitive inhibitor of SAM-e-mediated methylation reactions. An important function of SAM-e involves methylation of certain phospholipids, particularly phosphatidylethanolamine, and proteins which aid in the maintenance/control of the fluidity and microviscosity of cell membranes. Intact SAM-e metabolism is also considered vital for myelin maintenance [304].

8.15.3.2 Clinical Study

The efficacy of SAM-e in managing schizophrenia symptomatology in patients with a low activity catechol-*O*-methyltransferase polymorphism was investigated in a pilot study [305]. Eighteen patients with chronic schizophrenia were randomly assigned to receive either SAM-e (800 mg) or placebo for 8 weeks in a double-blind fashion. Results indicated some reduction in aggressive behavior and improved quality of life following SAM-e administration. Female patients showed improvement of depressive symptoms. Clinical improvement did not correlate with serum SAM-e levels. Two patients that received SAM-e exhibited some exacerbation of irritability. This preliminary pilot short-term study cautiously supports SAM-e as an adjunct in management of aggressive behavior and quality of life impairment in schizophrenia.

8.16 Conclusions and Future Directions

Development of new antipsychotic drugs over the last decade has not produced dramatic improvement in the treatment of schizophrenia. To find better alternatives to the existing antipsychotics, novel receptors are being targeted to develop third-generation antipsychotic agents [306–308]. Other less classic pathways are also under study and have led to some agents that are in very early stages of development

Table 8.1 Possible improvement in schizophrenia dimensions after add-on adjunctive agents or supplements [22, 29–39]. *DHEA* dehydroepiandrosterone

Augmentative agents	Positive symptoms	Negative symptoms	General symptoms	Depressive symptoms	Cognitive deficit	Aggression, excitement	Functioning & Quality of life
Mood stabilizers	Lamotrigine Topiramate	Valproate	Valproate			Carbamazepine	
Antidepressants		Fluvoxamine Fluoxetine Mirtazapine Citalopram		Fluvoxamine Mirtazapine	Mirtazapine	Fluoxetine Citalopram	Citalopram
Anti-Anxiety agents	Alprazolam	Alprazolam					
Neuroendocrine agents	Estradiol	Pregnenolone DHEA			Pregnenolone DHEA		
	Sarcosine D-serine	Glycine Sarcosine D-serine	Sarcosine	Glycine D-serine	Glycine Sarcosine D-serine		Glycine
Anti-inflammatory strategy	Aspirin		Celecoxib				
Cholinesterase inhibitors					Rivastigmine Donepezil Galantamine		
Miscellaneous agents or supplements	Allopurinol Propranolol Omega-3 fats L-Theanine Bexarotene	Allopurinol Omega-3 fats	Allopurinol Omega-3 fats	Omega-3 fats L-Theanine	Amphetamine Modafinil Omega-3 fats	Propranolol Pindolol	Modafinil

Possible improvement in schizophrenia dimensions after add-on adjunctive agents or supplements [22, 42, 64, 97, 98, 133,171, 172, 213, 264, 292, 298]

such as those acting on sigma receptors, cholecystokinin antagonists, neurotensin agonists, neurokinin receptor antagonists, GABAergic enhancers, and cannabinoid receptor modulators [309].

Despite the availability of different classes of drugs for the treatment of SZ/SA disorder, there remains a high prevalence of drug resistance, partial response, subsyndromal symptomatology, and relapse. When treating patients who did not adequately respond to their first antipsychotic therapy, there are three additional options: (1) switch to a different antipsychotic; (2) combine two antipsychotics; or (3) augment the current drug treatment with a non- antipsychotic agent. In present clinical practice non-dopaminergic drugs are usually prescribed in order to gain an enhanced therapeutic effect when the response to antipsychotic monotherapy has been disappointing.

There is a range of potential augmenting agents in SZ/SA disorder, each with varying available evidence regarding efficacy and tolerability. The rationale behind the augmentation strategy is to simultaneously target different brain functions in the hope of providing symptom relief. It is increasingly evident that various non-dopaminergic receptors have an important role in the clinical profile of schizophrenia—with noradrenergic, glutamatergic and serotonergic receptors involved in the pathogenesis of positive and negative symptoms. These agents include multiple antidepressants, lithium, antiepileptic agents, hormone, stimulants, and others. Table 8.1 summarizes some evidence regarding improvement in the specific

dimension of schizophrenia after add-on adjunctive agents or supplements while no adjunctive agent has been clearly demonstrated to be markedly efficacious. Although there is an increasing volume of augmentation trials, some of the available studies reveal conflicting results, and recommendations are based upon theoretical assumptions rather than upon evidence-based knowledge. Augmentation is generally considered the best option when a first drug provides partial relief but does not completely alleviate symptoms [38, 310]. Disadvantages of this strategy include cost of additional treatment and (if drug augmentation is used) increased likelihood of side effects, drug interactions, and the general lack of evidence for effectiveness.

Acknowledgements I wish to express gratitude to Ms. Rena Kurs, B.A. (Shaar-Menashe Mental Health Center, Hadera, Israel) for editorial assistance.

References

1. Moncrieff J (2009) A critique of the dopamine hypothesis of schizophrenia and psychosis. Harv Rev Psychiatry 17:214–225
2. Miyamoto S, Miyake N, Jarskog LF, et al (2012) Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. Mol Psychiatry (15 May 2012) doi:10.1038/mp.2012.47
3. Kim DH, Maneen MJ, Stahl SM (2009) Building a better antipsychotic: receptor targets for the treatment of multiple symptom dimensions of schizophrenia. Neurotherapeutics 6(1):78–85
4. Stahl SM (2009) Multifunctional drugs: a novel concept for psychopharmacology. CNS Spectr 14:2
5. Reid JL (2007) Fall and rise of polypharmacy? Hypertension 49:266–267. doi:10.1161/01.HYP.0000254485.43156.02
6. Volpe M, Chin D, Paneni F (2010) The challenge of polypharmacy in cardiovascular medicine. Fundam Clin Pharmacol 24(1):9–17
7. Wald NJ, Law MR (2003) A strategy to reduce cardiovascular disease by more than 80 %. BMJ 326:1419–1424
8. Myers MG, Asmar R, Leenen FH, Safar M (2000) Fixed low-dose combination therapy in hypertension—a dose response study of perindopril and indapamide. J Hypertens 18:317–325
9. Law MR, Wald NJ, Morris JL, Jordan RE (2003) Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ 326:1427–1435
10. Mahmud A, Feely J (2007) Low-dose quadruple antihypertensive combination: more efficacious than individual agents-a preliminary report. Hypertension 49:272–275
11. Goodwin G, Fleischhacker W, Arango C et al (2009) Advantages and disadvantages of combination treatment with antipsychotics ECNP Consensus Meeting, March 2008, Nice. Eur Neuropsychopharmacol 19(7):520–532
12. Gardos G (2005) Antipsychotic polypharmacy or monotherapy? Neuropsychopharmacol Hung 7(2):72–77
13. Bartzokis G, Altshuler L (2005) Reduced intracortical myelination in schizophrenia. Am J Psychiatry 162(6):1229–1230
14. Bartzokis G (2011) Neuroglialpharmacology: white matter pathophysiologies and psychiatric treatments. Front Biosci 17:2695–2733

15. Beaulieu JM, Gainetdinov RR, Caron MG (2009) Akt/GSK3 signaling in the action of psychotropic drugs. Annu Rev Pharmacol Toxicol 49:327–347
16. Beaulieu JM (2012) A role for Akt and glycogen synthase kinase-3 as integrators of dopamine and serotonin neurotransmission in mental health. J Psychiatry Neurosci 37(1):7–16
17. Bartzokis G (2012) Neuroglialpharmacology: myelination as a shared mechanism of action of psychotropic treatments. Neuropharmacology 62(7):2136–2152
18. Pickar D, Vinik J, Bartko JJ (2008) Pharmacotherapy of schizophrenic patients: preponderance of off-label drug use. PLoS One 3(9):e3150
19. Nielsen J, le Quach P, Emborg C, Foldager L, Correll CU (2010) 10-year trends in the treatment and outcomes of patients with first-episode schizophrenia. Acta Psychiatr Scand 122(5):356–366
20. Yoshio T, Inada T, Uno J et al (2012) Prescription profiles for pharmacological treatment of Japanese inpatients with schizophrenia: comparison between 2007 and 2009. Hum Psychopharmacol 27(1):70–75
21. Stahl SM (2002) Essential psychopharmacology of antipsychotics and mood stabilizers. Cambridge University Press, New York
22. Stahl SM (2008) Psychosis and Schizophrenia. In: Grandy MM (ed) Stahl's essential psychopharmacology, 3rd edn. Cambridge University Press, New Delhi, p 293
23. Rosenberg JM, Salzman C (2007) Update: new uses for lithium and anticonvulsants. CNS Spectr 12(11):831–841
24. Zink M, Englisch S, Meyer-Lindenberg A (2010) Polypharmacy in schizophrenia. Curr Opin Psychiatry 23(2):103–111
25. Ritsner MS (ed) (2010) Brain protection in schizophrenia, mood and cognitive disorders. Springer, New York, p 663
26. Ritsner MS (ed) (2011) Handbook of schizophrenia spectrum disorders. Vol. I, II, III. Springer Science+Business Media B.V.
27. Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 160(4):636–645
28. Fatemi SH, Folsom TD (2009) The neurodevelopmental hypothesis of schizophrenia, revisited. Schizophr Bull 35(3):528–548
29. Ritsner MS (2010) Is a neuroprotective therapy suitable for schizophrenia patients? In: Ritsner MS (ed) Brain protection in schizophrenia, mood and cognitive disorders. Springer Science+Business Media B.V., pp 343–395
30. Silver H, Barash I, Aharon N et al (2000) Fluvoxamine augmentation of antipsychotics improves negative symptoms in psychotic chronic schizophrenic patients: a placebo-controlled study. Int Clin Psychopharmacol 15:257–261
31. Sepehry AA, Potvin S, Elie R et al (2007) Selective serotonin reuptake inhibitor (SSRI) add-on therapy for the negative symptoms of schizophrenia: a meta-analysis. J Clin Psychiatry 68:604–610
32. Singh SP, Singh V, Kar N et al (2010) Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. Br J Psychiatry 197:174–179
33. Tiihonen J, Wahlbeck K, Kiviniemi V (2009) The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis. Schizophr Res 109:10–14
34. Tsai GE, Lin PY (2010) Strategies to enhance N-methyl-D-aspartate receptor-mediated neurotransmission in schizophrenia, a critical review and meta-analysis. Curr Pharm Des 16(5):522–537
35. Singh SP, Singh V (2011) Meta-analysis of the efficacy of adjunctive NMDA receptor modulators in chronic schizophrenia. CNS Drugs 25(10):859–885. doi:10.2165/11586650-000000000-00000
36. Ritsner MS (2011) The clinical and therapeutic potentials of dehydroepiandrosterone and pregnenolone in schizophrenia. Neuroscience 191:91–100
37. Sommer IE, de Witte L, Begemann M, Kahn RS (2012) Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? a meta-analysis. J Clin Psychiatry 73(4):414–419

38. Johns C, Thompson J (1995) Adjunctive treatments in schizophrenia: pharmacotherapies and electroconvulsive therapy. Schizophr Bull 21(4):607–619
39. Fusar-Poli P, Berger G (2012) Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies. J Clin Psychopharmacol 32(2):179–185
40. Ritsner MS (ed) (2009) The handbook of neuropsychiatric biomarkers, endophenotypes, and genes. Volumes I-IV. Springer, New York
41. Herz MI, Liberman RP, Lieberman JA et al (1997) Practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 154(suppl 4):1–63
42. National Institute for Clinical Excellence (NICE) (2003) The treatment and management of schizophrenia in primary and secondary care (Core Interventions)
43. Paton C, Barnes TR, Cavanagh MR et al (2008) High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by p.r.n. prescribing. Br J Psychiatry 192:435–439. doi:10.1192/bjp.bp.107.042895
44. Freedman R (2003) Drug therapy: schizophrenia. N Engl J Med 349:1738–1749
45. Deakin JFW, Slater P, Simpson MD, Gilchrist AC, Skan WJ, Royston AJ et al (1989) Frontal cortical and left temporal glutamatergic dysfunction in schizophrenia. J Neurochem 52:1781–1786
46. Moghaddam B, Adams BW (1998) Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science 281:1349–1352
47. Yamamoto K, Hornykiewicz O (2004) Proposal for a noradrenaline hypothesis of schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 28(5):913–922
48. Remington G (2008) Alterations of dopamine and serotonin transmission in schizophrenia. Prog Brain Res 172:117–140
49. Lieberman JA (1999) Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. Biol Psychiatry 46:729–739
50. Harrison PJ (2000) Postmortem studies in schizophrenia. Dialogues Clin Neurosci 2(4):349–357
51. Shenton ME, Dickey CC, Frumin M, McCarley RW (2001) A review of MRI findings in schizophrenia. Schizophr Res 49(1–2):1–52
52. Hunsberger J, Austin DR, Henter ID, Chen G (2009) Dialogues. Clin Neurosci 11(3):333–348
53. Cascade EF, Kalali AH, Buckley PF (2008) Current management of schizophrenia: antipsychotic monotherapy versus combination therapy. Psychiatry (Edgmont) 5(5):28–30
54. Dussias P, Kalali AH, Citrome L (2010) Polypharmacy of schizophrenia. Psychiatry (Edgmont) 7(8):17–19
55. Längle G, Steinert T, Weiser P, et al. (2012) Effects of polypharmacy on outcome in patients with schizophrenia in routine psychiatric treatment. Acta Psychiatr Scand 2012 Feb 9. doi:10.1111/j.1600-0447.2012.01835.x. [Epub ahead of print] PubMed PMID: 22321029
56. Shinfuku M, Uchida H, Tsutsumi C, et al. (2011) How psychotropic polypharmacy in schizophrenia begins: a longitudinal perspective. Pharmacopsychiatry. 2011 Dec 15. [Epub ahead of print] PubMed PMID: 22174025
57. Himelhoch S, Slade E, Kreyenbuhl J et al (2012) Antidepressant prescribing patterns among VA patients with schizophrenia. Schizophr Res 136:32–35
58. Haw C, Stubbs J (2005) A survey of the off-label use of mood stabilizers in a large psychiatric hospital. J Psychopharmacol 19(4):402–407
59. Sim K, Yong KH, Chan YH et al (2011) Adjunctive mood stabilizer treatment for hospitalized schizophrenia patients: Asia psychotropic prescription study (2001–2008). Int J Neuropsychopharmacol 14:1157–1164. doi:1157
60. Xiang YT, Dickerson F, Kreyenbuhl J, et al (2012) Adjunctive mood stabilizer and benzodiazepine use in older Asian patients with schizophrenia, 2001–2009. Pharmacopsychiatry 45(6):217–222. doi:10.1055/s-0031-1301292
61. Haw C, Stubbs J (2007) Benzodiazepines—a necessary evil? A survey of prescribing at a specialist UK psychiatric hospital. J Psychopharmacol 21(6):645–649

62. Chakos M, Patel JK, Rosenheck R et al (2011) Concomitant psychotropic medication use during treatment of schizophrenia patients: longitudinal results from the CATIE study. Clin Schizophr Relat Psychoses 5(3):124–134
63. Mallinger JB, Lamberti SJ (2007) Racial differences in the use of adjunctive psychotropic medications for patients with schizophrenia. J Ment Health Policy Econ 10(1):15–22
64. Wood K, Harris MJ, Morreale A, Rizos AL (1988) Drug induced psychosis and depression in the elderly. Psychiatr Clin North Am 11:167–193
65. Van Putten T, May PRA (1978) "Akinetic depression" in schizophrenia. Arch Gen Psychiatry 35:1101–1107
66. Bandelow B, Muller P, Gaebel W et al (1990) Depressive syndromes in schizophrenic patients after discharge from the hospital. Eur Arch Psychiatry Clin Neurosci 240:113–120
67. Paulsen JS, Romero R, Chan A et al (1996) Impairment of the semantic network in schizophrenia. Psychiatry Res 63:109–121
68. Zisook S, McAdams LA, Kuck J et al (1999) Depressive symptoms in schizophrenia. Am J Psychiatry 156:1736–1743
69. Zisook S, Nyer M, Kasckow J et al (2006) Depressive symptom patterns in patients with chronic schizophrenia and subsyndromal depression. Schizophr Res 86(1–3):226–233
70. Lako IM, Taxis K, Bruggeman R, et al. (2012) The course of depressive symptoms and prescribing patterns of antidepressants in schizophrenia in a one-year follow-up study. Eur Psychiatry 27(4):240–244
71. Lenox RH, Frazer A (2002) Mechanism of action of antidepressants and mood stablizers. In: Davis KL, Charney D, Coyle JT, Nemeroff C (eds) Neuropsychopharmacology: the fifth generation of progress. Philadelphia: Lippincott Williams & Wilkins, pp 1139–1163
72. Chertkow Y, Weinreb O, Youdim MB, Silver H (2009) Molecular mechanisms underlying synergistic effects of SSRI-antipsychotic augmentation in treatment of negative symptoms in schizophrenia. J Neural Transm 116(11):1529–1541
73. Silver H, Susser E, Danovich L et al (2011) SSRI augmentation of antipsychotic alters expression of GABA(A) receptor and related genes in PMC of schizophrenia patients. Int J Neuropsychopharmacol 14(5):573–584
74. Mulholland C, Lynch G, King DJ, Cooper SJ (2003) A double-blind, placebo-controlled trial of sertraline for depressive symptoms in patients with stable, chronic schizophrenia. J Psychopharmacol 17:107–112
75. Iancu I, Tschernihovsky E, Bodner E et al (2010) Escitalopram in the treatment of negative symptoms in patients with chronic schizophrenia: a randomized double-blind placebo-controlled trial. Psychiatry Res 179:19–23
76. Cho SJ, Yook K, Kim B et al (2011) Mirtazapine augmentation enhances cognitive and negative symptoms in schizophrenia patients treated with risperidone: a randomized controlled trial. Prog Neuropsychopharmacol Biol Psychiatry 35:208–211
77. Barnes TRE (2011) Schizophrenia Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 25:567–620
78. Dawes SE, Palmer BW, Meeks T, Golshan S, Kasckow J, Mohamed S, Zisook S (2012) Does antidepressant treatment improve cognition in older people with schizophrenia or schizoaffective disorder and comorbid subsyndromal depression? Neuropsychobiology 65(3):168–172
79. Silver H, Nassar A (1992) Fluvoxamine improves negative symptoms in treated chronic schizophrenia. An add on double blind placebo controlled study. Biol Psychiatry 31:698–704
80. Silver H, Aharon N, Kaplan A (2003) Add-on fluvoxamine improves primary negative symptoms: evidence for specificity from response analysis of individual symptoms. Schizophr Bull 29(3):541–546
81. Niitsu T, Shirayama Y, Fujisaki M, Hashimoto K, Iyo M (2010) Fluvoxamine improved cognitive impairments in a patient with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 34(7):1345–1346

82. Yasui-Furukori N, Kondo T, Mihara K et al (2004) Fluvoxamine dose-dependent interaction with haloperidol and the effects on negative symptoms in schizophrenia. Psychopharmacology (Berl) 171(2):223–227
83. D'Arrigo C, Migliardi G, Santoro V et al (2005) Effect of fluvoxamine on plasma risperidone concentrations in patients with schizophrenia. Pharmacol Res 52(6):497–501
84. Silver H (2004) Selective serotonin re-uptake inhibitor augmentation in the treatment of negative symptoms of schizophrenia. Expert Opin Pharmacother 5(10):2053–2058
85. Salokangas RK, Saarijärvi S, Taiminen T et al (1996) Citalopram as an adjuvant in chronic schizophrenia: a double-blind placebo-controlled study. Acta Psychiatr Scand 94(3):175–180
86. Kasckow JW, Mohamed S, Thallasinos A et al (2001) Citalopram augmentation of antipsychotic treatment in older schizophrenia patients. Int J Geriatr Psychiatry 16(12):1163–1167
87. Friedman JI, Ocampo R, Elbaz Z et al (2005) The effect of citalopram adjunctive treatment added to atypical antipsychotic medications for cognitive performance in patients with schizophrenia. J Clin Psychopharmacol 25(3):237–242
88. Zisook S, Kasckow JW, Lanouette NM et al (2010) Augmentation with citalopram for suicidal ideation in middle-aged and older outpatients with schizophrenia and schizoaffective disorder who have subthreshold depressive symptoms: a randomized controlled trial. J Clin Psychiatry 71(7):915–922
89. Vartiainen H, Tiihonen J, Putkonen A et al (1995) Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. Acta Psychiatr Scand 91(5): 348–351
90. Delle Chiaie R, Salviati M, Fiorentini S, Biondi M (2007) Add-on mirtazapine enhances effects on cognition in schizophrenic patients under stabilized treatment with clozapine. Exp Clin Psychopharmacol 15(6):563–568
91. Joffe G, Terevnikov V, Joffe M et al (2009) Add-on mirtazapine enhances antipsychotic effect of first generation antipsychotics in schizophrenia: a double-blind, randomized, placebo-controlled trial. Schizophr Res 108(1–3):245–251
92. Berk M, Gama CS, Sundram S et al (2009) Mirtazapine add-on therapy in the treatment of schizophrenia with atypical antipsychotics: a double-blind, randomised, placebo-controlled clinical trial. Hum Psychopharmacol 24:233–238
93. Abbasi SH, Behpournia H, Ghoreshi A et al (2010) The effect of mirtazapine add on therapy to risperidone in the treatment of schizophrenia: a double-blind randomized placebo-controlled trial. Schizophr Res 116:101–106
94. Terevnikov V, Stenberg JH, Joffe M et al (2010) More evidence on additive antipsychotic effect of adjunctive mirtazapine in schizophrenia: an extension phase of a randomized controlled trial. Hum Psychopharmacol 25(6):431–438
95. Terevnikov V, Stenberg JH, Tiihonen J, et al. (2011) Add-on mirtazapine improves depressive symptoms in schizophrenia: a double-blind randomized placebo-controlled study with an open-label extension phase. Hum Psychopharmacol 26(3):188–193
96. Stenberg JH, Terevnikov V, Joffe M et al (2010) Effects of add-on mirtazapine on neurocognition in schizophrenia: a double-blind, randomized, placebo-controlled study. Int J Neuropsychopharmacol 13(4):433–441
97. Stenberg JH, Terevnikov V, Joffe M et al (2011) More evidence on proneurocognitive effects of add-on mirtazapine in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 35(4):1080–1086
98. Phan SV, Kreys TJ (2011) Adjunct mirtazapine for negative symptoms of schizophrenia. Pharmacotherapy 31(10):1017–1030
99. Decina P, Mukherjee S, Bocola V et al (1994) Adjunctive trazodone in the treatment of negative symptoms of schizophrenia. Hosp Community Psychiatry 45(12):1220–1223
100. Hayashi T, Yokota N, Takahashi T et al (1997) Benefits of trazodone and mianserin for patients with late-life chronic schizophrenia and tardive dyskinesia: an add-on, double-blind, placebo-controlled study. Int Clin Psychopharmacol 12(4):199–205
101. Englisch S, Inta D, Eer A, Zink M (2010) Bupropion for depression in schizophrenia. Clin Neuropharmacol 33(5):257–259

102. Harvey KV, Balon R (1995) Augmentation with buspirone: a review. Ann Clin Psychiatry 7(3):143–147
103. Sumiyoshi T, Park S, Jayathilake K et al (2007) Effect of buspirone, a serotonin1A partial agonist, on cognitive function in schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr Res 95(1–3):158–168
104. Piskulić D, Olver JS, Maruff P, Norman TR (2009) Treatment of cognitive dysfunction in chronic schizophrenia by augmentation of atypical antipsychotics with buspirone, a partial 5-HT(1A) receptor agonist. Hum Psychopharmacol 24(6):437–446
105. Ghaleiha A, Noorbala AA, Farnaghi F et al (2010) A double-blind, randomized, and placebo-controlled trial of buspirone added to risperidone in patients with chronic schizophrenia. J Clin Psychopharmacol 30(6):678–682
106. Watanabe N (2011) Fluoxetine, trazodone and ritanserin are more effective than placebo when used as add-on therapies for negative symptoms of schizophrenia. Evid Based Ment Health 14(1):21
107. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P (2012) Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Arch Gen Psychiatry 69(5):476–483
108. Barnes TRE, Paton C (2011) Do antidepressants improve negative symptoms in schizophrenia? BMJ 342:d3371. doi:10.1136/bmj.d3371
109. Williams RS, Harwood AJ (2000) Lithium therapy and signal transduction. Trends Pharmacol Sci 21:61–64
110. Manji HK, Lenox RH (2000) Signaling: cellular insights into the pathophysiology of bipolar disorder. Biol Psychiatry 48:518–530
111. Lenox RH, Hahn CG (2000) Overview of the mechanism of action of lithium in the brain: fifty-year update. J Clin Psychiatry 61(Suppl 9):5–15
112. Rowe MK, Chuang DM (2004) Lithium neuroprotection: molecular mechanisms and clinical implications. Expert Rev Mol Med 6(21):1–18
113. Quiroz JA, Machado-Vieira R, Zarate CA Jr, Manji HK (2010) Novel insights into lithium's mechanism of action: neurotrophic and neuroprotective effects. Neuropsychobiology 62(1):50–60
114. Schulz SC, Thompson PA, Jacobs M et al (1999) Lithium augmentation fails to reduce symptoms in poorly responsive schizophrenic outpatients. J Clin Psychiatry 60(6):366–372
115. Kontaxakis VP, Ferentinos PP, Havaki-Kontaxaki BJ, Roukas DK (2005) Randomized controlled augmentation trials in clozapine-resistant schizophrenic patients: a critical review. Eur Psychiatry 20(5–6):409–415
116. Leucht S, Kissling W, McGrath J (2007) Lithium for schizophrenia. Cochrane Database Syst Rev (3):CD003834
117. Grunze HC (2010) Anticonvulsants in bipolar disorder. J Ment Health 19(2):127–141
118. Deckers CLP, Czuczwar SJ, Hekster YA et al (2000) Selection of antiepileptic drug polytherapy based on mechanism of action: the evidence reviewed. Epilepsia 41:1364–1374
119. Czuczwar SJ, Patsalos PN (2001) The new generation of GABA enhancers. CNS Drugs 15:339–350
120. Anand A, Charney DS, Oren DA et al (2000) Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: Support for hyperglutamatergic effects of N-methyl-daspartate receptor antagonists. Arch Gen Psychiatry 57:270–276
121. Dursun SM, Deakin JF (2001) Augmenting antipsychotic treatment with lamotrigine or topiramate in patients with treatment-resistant schizophrenia: a naturalistic case-series outcome study. J Psychopharmacol 15:297–301
122. Williams HJ, Zamzow CR, Robertson H, Dursun SM (2006) Effects of clozapine plus lamotrigine on phencyclidine-induced hyperactivity. Prog Neuropsychopharmacol Biol Psychiatry 30:239–243
123. Deutsch SI, Rosse RB, Billingslea EN et al (2002) Topiramate antagonizes MK-801 in an animal model of schizophrenia. Eur J Pharmacol 449:121–125
124. Konradsson A, Marcus MM, Sitzia R et al (2007) Adjuvant treatment with the anticonvulsant drug topiramate in schizophrenia. Eur Neuropsychopharmacol 17:S33–S34

125. Deutsch SI, Schwartz BL, Rosse RB et al (2003) Adjuvant topiramate administration: a pharmacologic strategy for addressing NMDA receptor hypofunction in schizophrenia. Clin Neuropharmacol 26:199–206
126. Frau R, Orru M, Fa M et al (2007) Effects of topiramate on the prepulse inhibition of the acoustic startle in rats. Neuropsychopharmacology 32:320–331
127. Czapinski P, Blaszczyk B, Czuczwar SJ (2005) Mechanisms of action of antiepileptic drugs. Curr Top Med Chem 5:3–14
128. Johannessen Landmark C (2008) Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. CNS Drugs 22(1):27–47
129. Simhandl C, Meszaros K (1992) The use of carbamazepine in the treatment of schizophrenic and schizoaffective psychosis: a review. J Psychiatry Neurosci 17:1–14
130. Nakamura A, Mihara K, Nagai G et al (2009) Pharmacokinetic and pharmacodynamic interactions between carbamazepine and aripiprazole in patients with schizophrenia. Ther Drug Monit 31(5):575–578
131. Leucht S, Kissling W, McGrath J, White P (2007) Carbamazepine for schizophrenia. Cochrane Database Syst Rev (3):CD001258
132. Schwarz C, Volz A, Li C, et al. (2008) Valproate for schizophrenia. Cochrane Database Syst Rev (3):CD004028
133. Casey DE, Daniel DG, Wassef AA et al (2003) Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. Neuropsychopharmacology 28(1):182–192
134. Casey DE, Daniel DG, Tamminga C et al (2009) Divalproex ER combined with olanzapine or risperidone for treatment of acute exacerbations of schizophrenia. Neuropsychopharmacology 34:1330–1338
135. Citrome L (2004) Antipsychotic polypharmacy versus augmentation with anticonvulsants: the U.S.perspective(presentation).Paris:CollegiumInternationaleNeuro-Psychopharmacologicum (CINP), June 2004 [abstract in Int J Neuropsychopharmacol 2004; 7(suppl 1):S69]
136. Tiihonen J, Hallikainen T, Ryynanen OP et al (2003) Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled trial. Biol Psychiatry 54(11):1241–1248
137. Goff DC, Keefe R, Citrome L et al (2007) Lamotrigine as add-on therapy in schizophrenia: results of 2 placebo-controlled trials. J Clin Psychopharmacol 27:582–589
138. Zoccali R, Muscatello MR, Bruno A et al (2007) The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. Schizophr Res 93(1–3):109–116
139. Glick ID, Bosch J, Casey DE (2009) A double-blind randomized trial of mood stabilizer augmentation using lamotrigine and valproate for patients with schizophrenia who are stabilized and partially responsive. J Clin Psychopharmacol 29(3):267–271
140. Premkumar TS, Pick J (2006) Lamotrigine for schizophrenia. Cochrane Database Syst Rev (4):CD005962
141. Drapalski AL, Rosse RB, Peebles RR et al (2001) Topiramate improves deficit symptoms in a patient with schizophrenia when added to a stable regimen of antipsychotic medication. Clin Neuropharmacol 24:290–294
142. Hosak L, Libiger J (2002) Antiepileptic drugs in schizophrenia: a review. Eur Psychiatry 17:371–378
143. Afshar H, Roohafza H, Mousavi G et al (2009) Topiramate add-on treatment in schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. J Psychopharmacol 23: 157–162
144. Arnone D (2005) Review of the use of topiramate for treatment of psychiatric disorders. Ann Gen Psychiatry 4:5
145. Hahn MK, Remington G, Bois D, Cohn T (2010) Topiramate augmentation in clozapine-treated patients with schizophrenia: clinical and metabolic effects. J Clin Psychopharmacol 30(6):706–710
146. Huband N, Ferriter M, Nathan R, Jones H (2010) Antiepileptics for aggression and associated impulsivity. Cochrane Database Syst Rev (2):CD003499

147. Lingjaerde O (1991) Benzodiazepines in the treatment of Schizophrenia: an update survey. Acta Psychiatr Scanol 84:453–459
148. Wolkowitz OM, Pickar D (1991) Benzodiazepines in the treatment of schizophrenia: a review and re-appraisal. Am J Psychiatry 148:714–726
149. Bobruff A, Gardos G, Tarsy D et al (1981) Clonazepam and phenobarbital in tardive dyskinesia. Am J Psychiatry 138:189–193
150. Nutt DJ, Malizia AL (2001) New insights into the role of the GABAA—benzodiazepine receptor in psychiatric disorder. Br J Psychiatry 179:390–396
151. Gaillard R, Ouanas A, Spadone C et al (2006) Benzodiazepines and schizophrenia, a review of the literature. Encephale 32(6 Pt 1):1003–1010
152. Jimerson DC, Van Kammen DP, Post RM (1982) Diazepam in schizophrenia: a preliminary double-blind trial. Am J Psychiatry 139:489–491
153. Nestoros JN, Nair NP, Pulman JR (1983) High doses of diazepam improve neuroleptic resistant chronic schizophrenic patients. Psychopharmacology 81:42–47
154. Wolkowitz OM, Turetsky N, Rues VI, Hargreaves W (1992) Benzodiazepine augmentation of neuroleptics in treatment-resistant schizophrenia. Psychopharmacol Bull 28:291–295
155. Carpenter WT Jr, Buchanan RW, Kirkpatrick B, Breier AF (1999) Diazepam treatment of early signs of exacerbation in schizophrenia. Am J Psychiatry 156:299–303
156. Lingjaerde O (1991) Benzodiazepines in the treatment of schizophrenia: an updated survey. Acta Psychiatr Scand 84(5):453–459
157. Tor PC, Ng TP, Yong KH et al (2011) Adjunctive benzodiazepine treatment of hospitalized schizophrenia patients in Asia from 2001 to 2008. Int J Neuropsychopharmacol 14(6):735–745
158. Volz A, Khorsand V, Gillies D, Leucht S (2007) Benzodiazepines for schizophrenia. Cochrane Database Syst Rev (1):CD006391
159. Javitt DC, Zukin SR (1991) Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148(10):1301–1308
160. Heresco-Levy U, Javitt DC, Ebstein R et al (2005) D-serine efficacy as add-on pharmacotherapy to risperidone and olanzapine for treatment refractory schizophrenia. Biol Psychiatry 57:577–585
161. Moghaddam B, Javitt D (2012) From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. Neuropsychopharmacology 37(1):4–15
162. Lin CH, Lane HY, Tsai GE (2012) Glutamate signaling in the pathophysiology and therapy of schizophrenia. Pharmacol Biochem Behav 100(4):665–677
163. Javitt DC, Zylberman I, Zukin SR et al (1994) Amelioration of negative symptoms in schizophrenia by glycine. Am J Psychiatry 151(8):1234–1236
164. Javitt DC, Silipo G, Cienfuegos A et al (2001) Adjunctive high-dose glycine in the treatment of schizophrenia. Int J Neuropsychopharmacol 4:385–391
165. Heresco-Levy U, Ermilov M, Lichtenberg P et al (2004) High-dose glycine added to olanzapine and risperidone for the treatment of schizophrenia. Biol Psychiatry 55:165–171
166. Tsai GE, Yang P, Chang YC, Chong MY (2006) D-alanine added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 59:230–234
167. Goff DC, Cather C, Gottlieb JD et al (2008) Once-weekly D-cycloserine effects on negative symptoms and cognition in schizophrenia: an exploratory study. Schizophr Res 106(2–3): 320–327
168. Goff DC (2012) D-Cycloserine: an evolving role in learning and neuroplasticity in schizophrenia. Schizophr Bull 2012 Feb 23. [Epub ahead of print] PubMed PMID
169. Wolosker H, Dumin E, Balan L, Foltyn VN (2008) D-amino acids in the brain: D-serine in neurotransmission and neurodegeneration. FEBS J 275(14):3514–3526
170. Nishikawa T (2011) Analysis of free D-serine in mammals and its biological relevance. J Chromatogr B Analyt Technol Biomed Life Sci 879(29):3169–3183
171. Heresco-Levy U, Javitt DC, Ebstein R et al (2005) D-serine efficacy as add-on pharmacotherapy to risperidone and olanzapine for treatment-refractory schizophrenia. Biol Psychiatry 57(6):577–585
172. Kantrowitz JT, Malhotra AK, Cornblatt B et al (2010) High dose D-serine in the treatment of schizophrenia. Schizophr Res 121(1–3):125–130

173. Lane HY, Lin CH, Huang YJ et al (2010) A randomized, double-blind, placebo-controlled comparison study of sarcosine (N-methylglycine) and D-serine add-on treatment for schizophrenia. Int J Neuropsychopharmacol 13(4):451–460
174. Tsai G, Lane HY, Yang P et al (2004) Glycine transporter 1 inhibitor N-methylglycine (sarcosine) added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 55:452–456
175. Lane HY, Huang CL, Wu PL et al (2006) Glycine transporter I inhibitor, N-methylglycine (sarcosine), added to clozapine for the treatment of schizophrenia. Biol Psychiatry 60(6):645–649
176. Tiihonen J, Wahlbeck K (2006) Glutamatergic drugs for schizophrenia. Cochrane Database Syst Rev (2): CD003730. doi:10.1002/14651858.CD003730.pub2
177. de Bartolomeis A, Sarappa C, Magara S, Iasevoli F (2012) Targeting glutamate system for novel antipsychotic approaches: relevance for residual psychotic symptoms and treatment resistant schizophrenia. Eur J Pharmacol 682(1–3):1–11
178. Baulieu EE (1997) Neurosteroids: of the nervous system, by the nervous system, for the nervous system. Recent Prog Horm Res 52:1–32
179. Labrie F, Luu-The V, Bélanger A et al (2005) Is dehydroepiandrosterone a hormone? J Endocrinol 187:169–196
180. Maninger N, Wolkowitz OM, Reus VI et al (2009) Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Front Neuroendocrinol 30:65–91
181. George MS, Guidotti A, Rubinow D et al (1994) CSF neuroactive steroids in affective disorders: pregnenolone, progesterone, and DBI. Biol Psychiatry 35:775–780
182. Semeniuk T, Jhangri GS, Le Melledo JM (2001) Neuroactive steroid levels in patients with generalized anxiety disorder. J Neuropsychiatry Clin Neurosci 13:396–398
183. Heydari B, Le Melledo JM (2002) Low pregnenolone sulphate plasma concentrations in patients with generalized social phobia. Psychol Med 32:929–933
184. Ritsner M, Maayan R, Gibel A, Weizman A (2007) Differences in blood pregnenolone and dehydroepiandrosterone levels between schizophrenia patients and healthy subjects. Eur Neuropsychopharmacol 17:358–365
185. Tourney G, Erb JL (1979) Temporal variations in androgens and stress hormones in control and schizophrenic subjects. Biol Psychiatry 14:395–404
186. Oades RD, Schepker R (1994) Serum gonadal steroid hormones in young schizophrenic patients. Psychoneuroendocrinology 19:373–385
187. Strous RD, Maayan R, Lapidus R et al (2004) Increased circulatory dehydroepiandrosterone and dehydroepiandrosterone-sulphate in first-episode schizophrenia: relationship to gender, aggression and symptomatology. Schizophr Res 71:427–434
188. Goyal RO, Sagar R, Ammini AC et al (2004) Negative correlation between negative symptoms of schizophrenia and testosterone levels. Ann N Y Acad Sci 1032:291–294
189. di Michele F, Caltagirone C, Bonaviri G, Romeo E, Spalletta G (2005) Plasma dehydroepiandrosterone levels are strongly increased in schizophrenia. J Psychiatr Res 39:267–273
190. Ritsner M, Maayan R, Gibel A et al (2004) Elevation of the cortisol/dehydroepiandrosterone ratio in schizophrenia patients. Eur Neuropsychopharmacol 14:267–273
191. Ritsner M, Gibel A, Ram E et al (2006) Alterations in DHEA metabolism in schizophrenia: two-month case-control study. Eur Neuropsychopharmacol 16:137–146
192. Gallagher P, Watson S, Smith MS et al (2007) Plasma cortisol-dehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar disorder. Schizophr Res 90:258–265
193. Yilmaz N, Herken H, Cicek HK et al (2007) Increased levels of nitric oxide, cortisol and adrenomedullin in patients with chronic schizophrenia. Med Princ Pract 16:137–141
194. Ritsner MS (2008) Dehydroepiandrosterone administration in treating medical and neuropsychiatric disorders: High hopes, disappointing results, and topics for future research. In: Ritsner MS, Weizman A (eds) Neuroactive steroids in brain functions, and mental health. New perspectives for research and treatment. Springer Science + Business Media B.V., pp 337–368
195. Oberbeck R, Benschop RJ, Jacobs R et al (1998) Endocrine mechanisms of stress-induced DHEA-secretion. J Endocrinol Invest 21:148–153

196. Rasmusson AM, Vasek J, Lipschitz DS et al (2004) An increased capacity for adrenal DHEA release is associated with decreased avoidance and negative mood symptoms in women with PTSD. Neuropsychopharmacology 29:1546–1557
197. Porcu P, Rogers LS, Morrow AL, Grant KA (2006) Plasma pregnenolone levels in cynomolgus monkeys following pharmacological challenges of the hypothalamic-pituitary-adrenal axis. Pharmacol Biochem Behav 84:618–627
198. Bradlow HL, Murphy J, Byrne JJ (1999) Immunological properties of dehydroepiandrosterone, its conjugates, and metabolites. Ann N Y Acad Sci 876:91–101
199. Majewska MD (1992) Neurosteroids: endogenous bimodal modulators of the GABAa receptor. Mechanisms of action and physiological significance. Prog Neurobiol 38:379–395
200. Debonnel G, Bergeron R, de Montigny C (1996) Potentiation by dehydroepiandrosterone of the neuronal response to N-methyl-D-aspartate in the CA3 region of the rat dorsal hippocampus: an effect mediated via sigma receptors. J Endocrinol 150(suppl):33–42
201. Rupprecht R (2003) Neuroactive steroids: mechanisms of action and neuropsychopharmacological properties. Psychoneuroendocrinology 28:139–168
202. Le Melledo JM, Baker GB (2002) Neuroactive steroids and anxiety disorders. J Psychiatry Neurosci 27:161–165
203. Majewska MD, Demigören S, Spivak CE, London ED (1990) The neurosteroid dehydroepiandrosterone sulfate is an allosteric antagonist of the GABAA receptor. Brain Res 526:143–146
204. Widstrom RL, Dillon JS (2004) Adrenal androgens in human physiology. Semin Reprod Med 22:289–298, Editor in Chief, Bruce R. Carr, M.D.; Guest Editors, William E. Rainey, Ph.D. and Bruce R. Carr, M.D
205. Schumacher M, Liere P, Akwa Y et al (2008) All psychotic roads lead to increased dopamine D2 High receptors: a perspective. Clin Schizophr Relat Psychoses 1:351–355
206. Obut TA, Ovsyukova MV, Cherkasova OP (2006) Prolonged decrease in stress reactivity caused by dehydroepiandrosterone sulfate. Bull Exp Biol Med 141:571–573
207. Luppi C, Fioravanti M, Bertolini B et al (2009) Growth factors decrease in subjects with mild to moderate Alzheimer's disease (AD): potential correction with dehydroepiandrosterone -sulphate (DHEAS). Arch Gerontol Geriatr 49(Suppl 1):173–184
208. Flood J, Morley JE, Roberts E (1995) Pregnenolone sulfate enhances post-training memory processes when injected in very low doses into limbic system structures. Proc Nat Acad Sci USA 92:10806–10810
209. Valenti G, Ferrucci L, Lauretani F et al (2009) Dehydroepiandrosterone sulfate and cognitive function in the elderly: the InCHIANTI Study. J Endocrinol Invest 32:766–772
210. Reddy DS, Kaur G, Kulkarni SK (1998) Sigma (σ1) receptor mediated antidepressant-like effects of neurosteroids in the Porsolt forced swim test. Neuroreport 9:3069–3073
211. Belelli D, Lambert JJ (2005) Neurosteroids: endogenous regulators of the GABA(A) receptor. Nat Rev Neurosci 6:565–575
212. Baulieu EE, Robel P (1996) Dehydroepiandrosterone and dehydroepiandrosterone sulfate as neuroactive neurosteroids. J Endocrinol 150(Suppl):221–239
213. Friess E, Schiffelholz T, Steckler T, Steiger A (2000) Dehydroepiandrosterone—a neurosteroid. Eur J Clin Invest 30(Suppl 3):46–50
214. Nafziger AN, Bowlin SJ, Jenkins PL, Pearson TA (1998) Longitudinal changes in dehydroepiandrosterone concentrations in men and women. J Lab Clin Med 131:316–323
215. Orentreich N, Brind JL, Vogelman JH et al (2002) Long-term longitudinal measurements of plasma dehydro-epiandrosterone sulfate in normal men. J Clin Endocrinol Metab 75:1002–1004
216. Melcangi RC, Panzica G, Garcia-Segura LM (2011) Neuroactive steroids: focus on human brain. Neuroscience 191:1–5
217. Marx CE, Keefe RS, Buchanan RW et al (2009) Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. Neuropsychopharmacology 34(8):1885–1903
218. Ritsner MS, Gibel A, Shleifer T et al (2010) Pregnenolone and dehydroepiandrosterone as an adjunctive treatment in schizophrenia and schizoaffective disorder: an 8-week, double-blind, randomized, controlled, 2-center, parallel-group trial. J Clin Psychiatry 71:1351–1362

219. Strous RD, Maayan R, Lapidus R et al (2003) Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia. Arch Gen Psychiatry 60:133–141
220. Strous RD, Stryjer R, Maayan R et al (2007) Analysis of clinical symptomatology, extrapyramidal symptoms and neurocognitive dysfunction following dehydroepiandrosterone (DHEA) administration in olanzapine treated schizophrenia patients: a randomized, double-blind placebo controlled trial. Psychoneuroendocrinology 32:96–105
221. Strous RD, Gibel A, Maayan R, Weizman A, Ritsner MS (2008) Hormonal response to dehydroepiandrosterone administration in schizophrenia: findings from a randomized, double-blind, placebo-controlled, crossover study. J Clin Psychopharmacol 28:456–459
222. Nachshoni T, Ebert T, Abramovitch Y et al (2005) Improvement of extrapyramidal symptoms following dehydroepiandrosterone (DHEA) administration in antipsychotic treated schizophrenia patients: a randomized, double-blind placebo controlled trial. Schizophr Res 79:251–256
223. Ritsner MS, Gibel A, Ratner Y et al (2006) Improvement of sustained attention and visual and movement skills, but not clinical symptoms, after dehydroepiandrosterone augmentation in schizophrenia: a randomized, double-blind, placebo-controlled, crossover trial. J Clin Psychopharmacol 26:495–499
224. Ritsner MS, Strous RD (2010) Neurocognitive deficits in schizophrenia are associated with alterations in blood levels of neurosteroids: a multiple regression analysis of findings from a double-blind, randomized, placebo-controlled, crossover trial with DHEA. J Psychiatr Res 44:75–80
225. Ritsner MS (2010) Pregnenolone, dehydroepiandrosterone, and schizophrenia: alterations and clinical trials. CNS Neurosci Ther 16(1):32–44
226. Mortimer AM (2007) Relationship between estrogen and schizophrenia. Expert Rev Neurother 7(1):45–55
227. Kulkarni J, de Castella A, Fitzgerald PB (2008) Estrogen in severe mental illness: a potential new treatment approach. Arch Gen Psychiatry 65:955–960
228. Kulkarni J, Hayes E, Gavrilidis E (2012) Hormones and schizophrenia. Curr Opin Psychiatry 25(2):89–95
229. Bryant DN, Dorsa DM (2010) Roles of estrogen receptors alpha and beta in sexually dimorphic neuroprotection against glutamate toxicity. Neuroscience 170:1261–1269
230. Arevalo MA, Santos-Galindo M, Bellini MJ et al (2010) Actions of estrogens on glial cells: implications for neuroprotection. Biochim Biophys Acta 1800:1106–1112
231. Arevalo MA, Santos-Galindo M, Lagunas N et al (2011) Selective estrogen receptor modulators as brain therapeutic agents. J Mol Endocrinol 46:R1–R9
232. Liu M, Kelley MH, Herson PS, Hurn PD (2010) Neuroprotection of sex steroids. Minerva Endocrinol 35:127–143
233. Riecher-Rossler A, Kulkarni J (2011) Estrogens and gonadal function in schizophrenia and related psychoses. Curr Top Behav Neurosci 8:155–171
234. Taylor GT, Maloney S, Dearborn J, Weiss J (2009) Hormones in the mentally disturbed brain: steroids and peptides in the development and treatment of psychopathology. Cent Nerv Syst Agents Med Chem 9:331–360
235. Hughes ZA, Liu F, Marquis K et al (2009) Estrogen receptor neurobiology and its potential for translation into broad spectrum therapeutics for CNS disorders. Curr Mol Pharmacol 2:215–236
236. Kulkarni J, Riedel A, de Castella AR, Fitzgerald PB, Rolfe TJ, Taffe J, Burger H (2002) A clinical trial of adjunctive oestrogen treatment in women with schizophrenia. Arch Womens Ment Health 5(3):99–104
237. Akhondzadeh S, Nejatisafa AA, Amini H et al (2003) Adjunctive estrogen treatment in women with chronic schizophrenia: a double-blind, randomized, and placebo-controlled trial. Prog Neuropsychopharmacol Biol Psychiatry 27(6):1007–1012
238. Chua WL, Santiago AD, Kulkarni J, et al (2005) Estrogen for schizophrenia. Cochrane Database Syst Rev (4):CD004719
239. Kulkarni J, de Castella A, Headey B et al (2011) Estrogens and men with schizophrenia: is there a case for adjunctive therapy? Schizophr Res 125(2–3):278–283

240. Heringa M (2003) Review on raloxifene: profile of a selective estrogen receptor modulator. Int J Clin Pharmacol Ther 41(8):331–345
241. Kulkarni J, Gurvich C, Lee SJ et al (2010) Piloting the effective therapeutic dose of adjunctive selective estrogen receptor modulator treatment in postmenopausal women with schizophrenia. Psychoneuroendocrinology 35(8):1142–1147
242. Usall J, Huerta-Ramos E, Iniesta R et al (2011) Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry 72(11):1552–1557
243. Ko YH, Lew YM, Jung SW, Joe SH, Lee CH, Jung HG, Lee MS (2008) Short-term testosterone augmentation in male schizophrenics: a randomized, double-blind, placebo-controlled trial. J Clin Psychopharmacol 28(4):375–383
244. Wagner E, Luo T, Drager UC (2002) Retinoic acid synthesis in the postnatal mouse brain marks distinct developmental stages and functional systems. Cereb Cortex 12:1244–1253
245. Balmer JE, Blomhoff R (2002) Gene expression regulation by retinoic acid. J Lipid Res 43:1773–1808
246. Goodman AB (1998) Three independent lines of evidence suggest retinoids as causal to schizophrenia. Proc Natl Acad Sci USA 95:7240–7244
247. Palha JA, Goodman AB (2006) Thyroid hormones and retinoids: a possible link between genes and environment in schizophrenia. Brain Res Rev 51:61–71
248. Luthi-Carter R, Strand A, Peters NL et al (2000) Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. Hum Mol Genet 9:1259–1271
249. Wan C, Shi Y, Zhao X, Tang et al (2009) Positive association between ALDH1A2 and schizophrenia in the Chinese population. Prog Neuro-Psychopharmacol Biol Psychiatry 3(8):1491–1495
250. Bailey SJ, McCaffery PJ (2009) Retinoic acid signalling in neuropsychiatric disease: possible markers and treatment agents. In: Ritsner MS (ed) The Handbook of neuropsychiatric biomarkers, endophenotypes and genes, vol III. Springer, Netherlands, pp 171–189
251. Samad TA, Krezel W, Chambon P, Borrelli E (1997) Regulation of dopaminergic pathways by retinoids: activation of the D2 receptor promoter by members of the retinoic acid receptor-retinoid X receptor family. Proc Natl Acad Sci USA 94(26):14349–14354
252. Krezel W, Ghyselinck N, Samad TA et al (1998) Impaired locomotion and dopamine signaling in retinoid receptor mutant mice. Science 279(5352):863–867
253. Citver AS, Shields AM, Ciaccia LM et al (2002) Indirect modulation of dopamine D2 receptors as potential pharmacotherapy for schizophrenia: III. Retinoids. J Clin Pharm Ther 27(3):161–168
254. Sharma RP (2005) Schizophrenia, epigenetics and ligand-activated nuclear receptors: a framework for chromatin therapeutics. Schizophr Res 72:79–90
255. Boehm MF, Zhang L, Badea BA et al (1994) Synthesis and structure-activity relationships of novel retinoid X receptor-selective retinoids. J Med Chem 37:2930–2941
256. Lerner V, Miodownik C, Gibel A, Kovalyonok E, Shleifer T, Goodman AB, Ritsner MS (2008) Bexarotene as add-on to antipsychotic treatment in schizophrenia patients: a pilot open-label trial. Clin Neuropharmacol 31:25–33
257. Muller N, Schwarz M (2006) Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission. Neurotox Res 10(2):131–148
258. Muller C, Hennebert O, Morfin R (2006) The native anti-glucocorticoid paradigm. The J Steroid Biochem Mol Biol 100:95–105
259. Richard MD, Brahm NC (2012) Schizophrenia and the immune system: pathophysiology, prevention, and treatment. Am J Health Syst Pharm 69(9):757–766
260. Müller N (2010) COX-2 inhibitors as antidepressants and antipsychotics: clinical evidence. Curr Opin Investig Drugs 11(1):31–42
261. Muller N, Riedel M, Scheppach C et al (2002) Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. Am J Psychiatry 159:1029–1034
262. Müller NE, Riedel M, Dehning S et al (2004) Is the therapeutic effect of celecoxib in schizophrenia depending from duration of disease? Neuropsychopharmacology 29(Suppl 1):S176

263. Rapaport MH, Delrahim KK, Bresee CJ et al (2005) Celecoxib augmentation of continuously ill patients with schizophrenia. Biol Psychiatry 57(12):1594–1596
264. Akhondzadeh S, Tabatabaee M, Amini H et al (2007) Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. Schizophr Res 90(1–3):179–185
265. Muller N, Krause D, Dehning S et al (2010) Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. Schizophr Res 121(1–3):118–124
266. Laan W, Grobbee DE, Selten JP et al (2010) Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 71:520–527
267. Patel SS, Attard A, Jacobsen P, Shergill S (2010) Acetylcholinesterase inhibitors (AChEI's) for the treatment of visual hallucinations in schizophrenia: a review of the literature. BMC Psychiatry 10:69
268. Birks J, Harvey RJ (2006) Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev (1):CD001190
269. Singh J, Kour K, Jayaram MB (2012) Acetylcholinesterase inhibitors for schizophrenia. Cochrane Database Syst Rev 2012 Jan 18;1:CD007967
270. Ago Y, Koda K, Takuma K, Matsuda T (2011) Pharmacological aspects of the acetylcholinesterase inhibitor galantamine. J Pharmacol Sci 116(1):6–17
271. Keefe RS, Malhotra AK, Meltzer HY et al (2008) Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: significant placebo/practice effects in a 12-week, randomized, double-blind, placebo-controlled trial. Neuropsychopharmacology 33(6):1217–1228
272. Lee SW, Lee JG, Lee BJ, Kim YH (2007) A 12-week, double-blind, placebo-controlled trial of galantamine adjunctive treatment to conventional antipsychotics for the cognitive impairments in chronic schizophrenia. Int Clin Psychopharmacol 22(2):63–68
273. Lindenmayer JP, Khan A (2011) Galantamine augmentation of long-acting injectable risperidone for cognitive impairments in chronic schizophrenia. Schizophr Res 125(2–3):267–277
274. Ribeiz SR, Bassitt DP, Arrais JA et al (2010) Cholinesterase inhibitors as adjunctive therapy in patients with schizophrenia and schizoaffective disorder: a review and meta-analysis of the literature. CNS Drugs 24(4):303–317
275. Lara DR, Souza DO (2000) Schizophrenia: a purinergic hypothesis. Med Hypotheses 54(2):157–166
276. Buie LW, Oertel MD, Cala SO (2006) Allopurinol as adjuvant therapy in poorly responsive or treatment refractory schizophrenia. Ann Pharmacother 40(12):2200–2204
277. Dickerson FB, Stallings CR, Origoni AE et al (2009) A double-blind trial of adjunctive allopurinol for schizophrenia. Schizophr Res 109(1–3):66–69
278. Weiser M, Gershon AA, Rubinstein K, et al. (2012) A randomized controlled trial of allopurinol vs. placebo added on to antipsychotics in patients with schizophrenia or schizoaffective disorder. Schizophr Res 2012 Apr 4. [Epub ahead of print] PubMed PMID: 22483162
279. Goldberg TE, Bigelow LB, Weinberger DR et al (1991) Cognitive and behavioral effects of the coadministration of dextroamphetamine and haloperidol in schizophrenia. Am J Psychiatry 148:78–84
280. Barch DM, Carter CS (2005) Amphetamine improves cognitive function in medicated individuals with schizophrenia and in healthy volunteers. Schizophr Res 77:43–58
281. Pietrzak RH, Snyder PJ, Maruff P (2010) Use of an acute challenge with d-amphetamine to model cognitive improvement in chronic schizophrenia. Hum Psychopharmacol 25:353–358
282. Minzenberg MJ, Carter CS (2008) Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology 33(7):1477–1502
283. Kumar R (2008) Approved and investigational uses of modafinil: an evidence-based review. Drugs 68(13):1803–1839

284. Saavedra-Velez C, Yusim A, Anbarasan D, Lindenmayer JP (2009) Modafinil as an adjunctive treatment of sedation, negative symptoms, and cognition in schizophrenia: a critical review. J Clin Psychiatry 70(1):104–112
285. Rosenthal MH, Bryant SL (2004) Benefits of adjunct modafinil in an open-label, pilot study in patients with schizophrenia. Clin Neuropharmacol 27:38–43
286. Farrow TF, Hunter MD, Haque R, Spence SA (2006) Modafinil and unconstrained motor activity in schizophrenia: double-blind crossover placebo-controlled trial. Br J Psychiatry 189:461–462
287. Pierre JM, Peloian JH, Wirshing DA et al (2007) A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia. J Clin Psychiatry 68(5):705–710
288. Freudenreich O, Henderson DC, Macklin EA et al (2009) Modafinil for clozapine-treated schizophrenia patients: a double-blind, placebo-controlled pilot trial. J Clin Psychiatry 70(12):1674–1680
289. Sevy S, Rosenthal MH, Alvir J et al (2005) Double-blind, placebo-controlled study of modafinil for fatigue and cognition in schizophrenia patients treated with psychotropic medications. J Clin Psychiatry 66(7):839–843
290. Kane JM, D'Souza DC, Patkar AA et al (2010) Armodafinil as adjunctive therapy in adults with cognitive deficits associated with schizophrenia: a 4-week, double-blind, placebo-controlled study. J Clin Psychiatry 71(11):1475–1481
291. Bobo WV, Woodward ND, Sim MY et al (2011) The effect of adjunctive armodafinil on cognitive performance and psychopathology in antipsychotic-treated patients with schizophrenia/schizoaffective disorder: a randomized, double-blind, placebo-controlled trial. Schizophr Res 130(1–3):106–113
292. Scoriels L, Barnett JH, Soma PK et al (2012) Effects of modafinil on cognitive functions in first episode psychosis. Psychopharmacology (Berl) 220(2):249–258
293. Scoriels L, Barnett JH, Murray GK et al (2011) Effects of modafinil on emotional processing in first episode psychosis. Biol Psychiatry 69(5):457–464
294. Cheine M, Ahone J, Wahlbeck K (2003) Beta-blocker supplementation of standard drug treatment for schizophrenia (Cochrane Review). Cochrane Database Syst Rev (3):CD000234
295. Caspi N, Modai I, Barak P, Waisbourd A, Zbarsky H, Hirschmann S, Ritsner M (2001) Pindolol augmentation in aggressive schizophrenic patients: a double-blind crossover randomized study. Int Clin Psychopharmacol 16(2):111–115
296. Pur BK, Richardson AJ, Horrobin DF et al (2000) Eicosapentaenoic acid treatment in schizophrenia associated with symptom remission, normalization of blood fatty acids, reduced neuronal membrane phospholipid turnover and structural brain changes. Int J Clin Pract 54:57–63
297. Peet M, Horrobin DF (2002) EE Multi Centre Study Group. A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. J Psychiatr Res 36:7–18
298. Joy CB, Mumby-Croft R, Joy LA (2006) Polyunsaturated fatty acid supplementation for schizophrenia. Cochrane Database Syst Rev (3):CD001257
299. Juneja LR (1999) Suntheanine and its relaxation effect in humans. Trends Food Sci Tech 10:199–204
300. Kimura K, Ozeki M, Juneja LR, Ohira H (2007) L-Theanine reduces psychological and physiological stress responses. Biol Psychol 74(1):39–45
301. Ritsner MS, Miodownik C, Ratner Y et al (2011) L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8-week, randomized, double-blind, placebo-controlled, 2-center study. J Clin Psychiatry 72(1):34–42
302. Miodownik C, Maayan R, Ratner Y, Lerner V, Pintov L, Mar M, Weizman A, Ritsner MS (2011) Serum levels of brain-derived neurotrophic factor and cortisol to sulfate of dehydroepiandrosterone molar ratio associated with clinical response to L-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients. Clin Neuropharmacol 34(4):155–160

303. Cantoni GL (1953) S-adenosylmethionine: a new intermediate formed enzymatically from L-methionine and adenosine-triphosphate. J Biol Chem 204:403–416
304. Surtees R, Leonard J, Austin S (1991) Association of demyelination with deficiency of cerebrospinal-fluid S-adenosylmethionine in inborn errors of methyl-transfer pathway. Lancet 338:1550–1554
305. Strous RD, Ritsner MS, Adler S et al (2009) Improvement of aggressive behavior and quality of life impairment following S-adenosyl-methionine (SAM-e) augmentation in schizophrenia. Eur Neuropsychopharmacol 19(1):14–22
306. Monti JM (2010) Serotonin 5-HT(2A) receptor antagonists in the treatment of insomnia: present status and future prospects. Drugs Today (Barc) 46(3):183–193
307. Werkman TR, McCreary AC, Kruse CG, Wadman WJ (2011) NK3 receptors mediate an increase in firing rate of midbrain dopamine neurons of the rat and the guinea pig. Synapse 65(8):814–826. doi:10.1002/syn.20908
308. Kirilly E, Gonda X, Bagdy G (2012) CB(1) receptor antagonists: new discoveries leading to new perspectives. Acta Physiol (Oxf) 205(1):41–60
309. López-Muñoz F, Álamo C (2011) Neurobiological background for the development of new drugs in schizophrenia. Clin Neuropharmacol 34(3):111–126
310. Correll CU. Adjunctive therapy for schizophrenia: current and emerging directions. From Medscape Education Psychiatry & Mental Health. Available at http://www.medscape.org/viewarticle/738924. Accessed February 25, 2012