Chapter 9
Antidepressants in Schizophrenia: A Place for Them?

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Abstract Antipsychotic monotherapy is often insufficient to achieve optimal outcome in schizophrenia. One of the numerous adjunctive psychopharmacological strategies proposed to overcome this drawback is a combination of an antipsychotic with an antidepressant. Existing evidence on the efficacy of such combination is ambiguous and varies by syndrome domains and antidepressant classes and—within a class—by individual compounds. The most dependable data favor—as a group—receptor-blocking antidepressants. Of these, mirtazapine demonstrates probably the most consistent beneficial effects, in particular for negative symptoms and cognitive deficits. While current guidelines warn about possible antidepressant-provoked psychotic exacerbation, no data today support these reservations, at least in chronic schizophrenia and when a contemporaneous antipsychotic therapy continues. Moreover, one randomized controlled trial (RCT) revealed an additive antipsychotic effect of an adjunctive antidepressant (mirtazapine) and, according to a recently published large cohort study concomitant antidepressants can reduce suicide rates and overall mortality of patients with schizophrenia. It appears hence that caution regarding the add-on antidepressant use recommended by current guidelines can be soon softened. Due to scarcity of data, conservative use of antidepressants may, however, be still justifiable in acute schizophrenia. If an antipsychotic-antidepressant combination is to be prescribed, a thorough knowledge of pharmacodynamic and pharmacokinetic (especially, regarding several CYP450 liver enzymes) interactions is essential to avoid adverse effects and complications.

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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_9,

A convincing amount of evidence is emerging on some previously unknown mechanisms of action beyond the classical neurotransmitter/monoamine receptor theory—findings that may boost research and development in the nearest future. For instance, the novel body of data on the proneuroplastic effect of antidepressants may help us to understand how an add-on antidepressant can improve neurocognition in chronic schizophrenia, and how antidepressant monotherapy can prevent psychosis in high-risk groups. More large RCTs with various combinations are needed to reveal the most feasible antidepressant therapy strategies for schizophrenia.

Abbreviations

AIMS	Abnormal Involuntary Movement Scale
APA	American Psychiatric Association
BDI	Beck Depression Inventory
EPS	Extrapyramidal Symptoms
FGA	First-Generation Antipsychotic
HDRS	Hamilton Depression Rating Scale
MDD	Major Depressive Disorder
NICE	National Institute for Health and Clinical Excellence
PANSS	Positive and Negative Syndrome Scale
RCT	Randomized Controlled Trial
SAS	Simpson-Angus Scale
SGA	Second Generation Antipsychotic
SNRI	Selective Noradrenaline Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant

9.1 Background and Rationale

Schizophrenia is one of the most debilitating and difficult-to-treat psychiatric disorders, with a worldwide prevalence of about 0.7% [1]. The mainstay of acute and maintenance treatment of schizophrenia nowadays is antipsychotic medication [2]. Despite adequate treatment with antipsychotics, the optimal outcome can, however, be achieved in only 10–20% of patients, with 15–20% showing partial or complete treatment resistance [3]. In cases of insufficient response to at least two adequate trials of a First Generation Antipsychotic (FGA) or Second Generation Antipsychotic (SGA), the gold standard is clozapine monotherapy. Though efficacious in treatment-resistant schizophrenia, clozapine medication fails to invariably yield the optimal outcome [4]. Moreover, treatment with clozapine is associated with a number of adverse effects, some of them serious and potentially fatal. Thus, there still exists a call for alternative strategies.

During recent decades, a numerous adjunctive psychopharmacological treatments are emerging to improve clinical and functional outcomes in schizophrenia, including lithium, anticonvulsants, sex hormones, COX-inhibitors, glutamatergic drugs, acetylcholine esterase inhibitors, and antidepressants [5].

Antidepressants as adjuncts in schizophrenia are under extensive study and are—despite contradictory evidence regarding their efficacy—in wide clinical use [5, 6]. The existing guidelines do not yet unconditionally recommend antidepressants for treatment of negative, positive, or cognitive symptoms—neither in the acute nor in the stable phase of the disease. For example, the *Practice Guideline for the Treatment of Patients with Schizophrenia* developed by the American Psychiatric Association suggests that antidepressants "can be considered for treatment of comorbid major depression," with caution, due to a possible risk that sometimes an antidepressant may exacerbate psychosis [7]. Similarly, the NICE guideline on the treatment of schizophrenia by the British Royal College of Psychiatrists suggests limiting the augmentation of antipsychotics with antidepressants only to treatment of "comorbid or secondary psychiatric problems, such as depression and anxiety" [8].

Nevertheless, recent research data show that in actual practice clinicians tend widely to use antidepressants to overcome, in addition to co-occurring depression, posttraumatic stress disorder, anxiety, or schizoaffective disorder [6], also negative symptoms and cognitive deficits. In the Clinical Trials of Intervention Effectiveness (CATIE) study, approximately a third of the participants were receiving an antidepressant at the study baseline [9].

9.1.1 Rationale for Antidepressant Medication in Schizophrenia

In earlier studies, use of antidepressants for (other than comorbid depression) symptoms of schizophrenia relied on the clinical overlap between some symptoms of the disease and unipolar depression. An assumption of antidepressants' stimulative effects prompted, for instance, antidepressant treatment of anhedonia and avolition [10].

In regard to biological understanding of both major depressive disorder and schizophrenia, the 1990s became the Serotonin Decade; manipulation of the serotonin system became the focus of interest. In particular, the adjunctive SSRIs were supposed to affect the primary negative symptoms and cognitive deficits by re-setting the dysfunctional serotonergic system [11, 12].

The mechanism of action of the SSRIs and the vast majority of other antidepressants is based on inhibition of transporters of serotonin or other monoamines, and thereby hindered re-uptake and enhanced availability of monoamines for neurotransmission. There exists, however, a small group of antidepressants that act via inhibition of monoamine receptors rather than of transporters. These antidepressants—trazodone, nefazodone, mianserin, and mirtazapine—share the ability to inhibit several receptors, including postsynaptic 5-HT_2 receptors. The rationale for combination of these antidepressants with antipsychotics stemmed from the theory of "atypicality"

especially popular in the late 1990s to early 2000s. According to this theory, antipsychotics inhibiting $5HT_2$ receptors more than inhibiting D_2 receptors ("atypical", or SGAs) were more effective in treating positive, negative, and cognitive symptoms, while causing fewer extrapyramidal side effects than did their conventional counterparts—D_2 blockers with negligible $5HT_2$ inhibition [13, 14]. One proposal was that combination of an inhibitor of the $5HT_2$ receptor with a "pure" D_2 blocker would result in a clinical effect resembling that of an atypical antipsychotic, with additional benefits in terms of both efficacy and tolerability [15, 16].

Preliminary evidence supporting this theory grew out of an earlier study in haloperidol-treated schizophrenia patients receiving add-on ritanserine, a pure $5HT_2$ blocker devoid of antidepressive properties; ritanserin alleviated negative symptoms [17]. After that, interest in research concerning combinations of receptor-blocking antidepressants with FGAs has gradually grown. Several studies performed during the 1990s and 2000s have provided additional evidence in support of this theory (see Sections 9.2.1–9.2.5).

Though theoretically a combination of receptor-blocking antidepressants with SGAs (which are $5HT_2$ inhibitors, too) might make little sense, this approach became popular in the 2000s due to current clinical realities—SGAs became a first-line antipsychotic medication, while the use of FGAs was rapidly fading [18]. These findings fueled the existing interest in research into the pathogenesis of schizophrenia and the role therein of serotonin receptors [14].

Some of these receptor-blocking antidepressants demonstrate—beyond their inhibition of the $5HT_2$ receptors—effects on other types of receptors, e.g. mirtazapine and mianserin that inhibit $5HT_3$ serotonin receptors, presynaptic alpha-2 noradrenaline receptors, and postsynaptic histamine receptors, and they also indirectly stimulate $5HT_{1A}$ serotonin receptors. A possible role for these receptors in the pathogenesis of some psychiatric disorders, including schizophrenia, has been the subject of intense research.

There exists a body of preclinical evidence that 5-HT_{1A} receptors, together with cholinergic and glutamatergic systems, modulate learning consolidation. For instance, 5-HT_{1A} receptor antagonists may alleviate a cognitive deficit caused by an N-Methyl-D-Aspartate glutamatergic receptor antagonist [19]. In clinical studies, treatment with the adjunctive partial 5-HT_{1A} agonists tandospirone [20] and buspirone [21] improved schizophrenia patients' cognitive performance.

Moreover, 5-HT_3 receptor antagonists demonstrated, in preclinical studies, procognitive effects [22]. In a clinical study as well, Zhang and co-authors [23] found that the 5-HT_3 blocking agent ondansetron, when added to on-going haloperidol, improved negative symptoms, general psychopathology, and cognitive functions.

Alpha-2 noradrenoreceptor blockade also seems a potentially useful mechanism to improve schizophrenia treatment. In a preclinical study by Wadenberg and co-authors [24], the alpha-2 antagonist idazoxan enhanced the efficacy of both typical (haloperidol) and atypical (olanzapine) antipsychotics and reversed haloperidol-induced catalepsy. This was replicated in another preclinical study, by Marcus and co-authors [25], when idazoxan enhanced the therapeutic effect of risperidone and

facilitated cortical dopaminergic and glutamatergic neurotransmission. Earlier, in an RCT by Litman and co-authors [26], idazoxan combined with fluphenazine produced clinical improvement comparable to that of clozapine.

The pathophysiology of schizophrenia appears to include neurodegeneration and altered neurogenesis [27]. Some antipsychotics may demonstrate neuroprotective and neurotrophic/neuroplastic properties [28, 29] that result in improved outcome, including enhanced neurocognition [30]. Antidepressants may also reactivate neuroplasticity [31] and thus—though, in themselves devoid of antipsychotic activity—contribute to the improved treatment outcomes in different phases of schizophrenia. This might be an underlying mechanism of encouraging results in a recent open study by Cornblatt and collaborators [32]. In that study, antidepressants prevented conversion to psychosis in subjects with prodromal schizophrenia symptoms more effectively than did SGAs.

What Is the Empirical Evidence?

9.2 Efficacy Studies: Data from RCTs[1]

In the literature, we were able to locate 31 RCTs designed to study the efficacy of antidepressants in schizophrenia treatment. None of these studies explored antidepressants as monotherapy, and all of them employed the add-on design, i.e. subjects received antidepressants added to their stable antipsychotic treatment. The vast majority of the studies were of small size, with subject populations ranging from 14 to 47 and with only two studies exceeding this number—90 patients in an add-on citalopram study by Salokangas and co-authors [33] and 53 patients in a add-on fluvoxamine study by Silver and co-authors [34]. The duration of the studies ranged from 1 to 24 weeks; most of them lasted from 6 to 8 weeks.

9.2.1 Efficacy of Antidepressants in Treatment of Negative Symptoms

Negative symptoms constitute a major clinical domain of schizophrenia. According to recent estimates, 15–20% of the patients demonstrate primary negative symptoms (alogia, avolition, blunted affect, anhedonia) [35]. These symptoms contribute to social isolation, poor level of functioning, and low quality of life. Compared to positive symptoms, negative symptoms tend to be less responsive to standard medical treatment, especially with FGAs. Introduction of SGAs in 1990s was accompanied by much enthusiasm based on a number of earlier reports indicating their better

[1] Open label trials are not the focus of this review; only a few will be mentioned and discussed.

efficacy against negative symptoms. More recent research data show, however, that they demonstrate at best modest benefits [36].

Antidepressants have undergone wide study as potential adjunctive agents for treatment of negative symptoms.

Earlier studies with TCAs yielded mainly positive results [10, 37, 38], but they had substantial methodological limitations, especially in regard to the outcome measures, which called their conclusions into question.

Later, the 1990s and early 2000s saw many studies of selective serotonin reuptake inhibitors. Quantitatively, the numbers with positive and negative results were approximately the same, but when analyzed separately, the efficacy of individual SSRIs appeared to differ. Namely, both studies with fluvoxamine were positive [34, 39], as was also the only study with paroxetine [40]. The studies with fluoxetine yielded, however, controversial results, with two earlier studies being positive [41, 42] and four later studies, negative [43–46]. All trials with adjunctive sertraline or citalopram in the treatment of negative symptoms in schizophrenia failed to demonstrate their superiority over placebo [33, 47–49], as did both trials with the selective noradrenaline reuptake inhibitor reboxetine [50, 51].

The vast majority of studies with receptor-blocking antidepressants as add-on treatment in chronic schizophrenia were positive. Of this type of drugs, mirtazapine appears to have demonstrated the most consistent findings. Four [16, 52–54] of five RCTs demonstrated the superiority of mirtazapine added to conventional or novel antipsychotics over add-on placebo, with effect size ranging from 0.28 to 1.92 (CI 95%) [55]; only one trial [56] failed to show any advantages of mirtazapine over placebo. Two RCTs with add-on trazodone [57, 58] were also positive, with the effect size ranging from 0.34 to 0.92 (CI 95%). The data for mianserin seem more controversial with one positive study [58] and two negative ones [59, 60]. It should be mentioned, however, that the latter study was small (n = 18). The size effect for mianserin ranged from 0.03 to 0.53 (CI 95%) [55]. No RCTs with nefazodone have yet appeared.

To summarize, results of the RCTs suggest that add-on antidepressant treatment may become a useful option in treatment of negative symptoms of schizophrenia. The receptor-blocking antidepressants may perhaps inspire more confidence than do antidepressants from other groups, since their effect on negative symptoms seems to be rather consistent.

9.2.2 Positive Symptoms

While not focused specifically upon psychotic symptoms, many of the adjunctive antidepressant reports also provided data on the positive symptoms of schizophrenia.

No RCTs with the transporter inhibitors nor the receptor inhibitors showed any additive antipsychotic effect of antidepressants with the exception of our own [53]. In that study, mirtazapine added to stable doses of FGAs in patients with chronic, highly symptomatic schizophrenia out-performed placebo in all outcome measures, including

the PANSS positive subscale. This result was replicated in an extension phase of that same study, in which positive symptoms improved after a switch of the placebo group to add-on mirtazapine [61]. The latter findings should be accepted with caution, however, since this extension phase had an open-label design, as did the earlier small pilot nefazodone study of Joffe et al. [62] in which positive symptoms also improved. Poyurovski and his group [63] also concluded that with mirtazapine, psychosis improved, but their claim seemed to be based on the change in total PANSS scores, whereas improvement on the PANSS-positive subscale scores was unspecified.

Though evidence as to the efficacy of adjunctive antidepressants for the positive symptoms of schizophrenia remains scarce, it should be emphasized that antidepressant treatment does not appear to cause any additional risk of the worsening of psychosis, provided that patients' parallel antipsychotic medication continues. Interestingly, in the study by Poyurovski and co-authors [45], patients experiencing their acute first-episode schizophrenia who received fluoxetine 20 mg/day added to a stable dose of 10 mg olanzapine demonstrated less improvement in positive and disorganized symptoms than did those who received add-on placebo. However, the patients in the fluoxetine group also demonstrated a certain degree of improvement of their positive symptoms.

Thus, although evidence is still insufficient to allow recommendation of any of the existing antidepressants to enhance the antipsychotic effects of the FGAs and SGAs, the use of add-on antidepressants seems to be safe at least in chronic schizophrenia (see also 2.3). As mentioned, the APA Guidelines suggest special caution in using antidepressants in patients with schizophrenia—a recommendation that may no longer be justified in light of the current evidence.

9.2.3 Efficacy of Antidepressants in Treatment of Depression in Schizophrenia

Depressive symptoms are common in schizophrenia (in particular, in its acute phase [64]), with an estimated overall prevalence of 50% [65]. Comorbid depression significantly elevates the risk for suicide and negatively influences patients' quality of life and level of functioning [66, 67]. Moreover, at chronic stages of schizophrenia, depression is associated with a higher risk for relapse [68].

Evidence regarding the possible role of various psychopharmacological agents in treating depression in schizophrenia is still far from convincing. FGAs may even worsen depressive symptoms [69], but some SGAs demonstrate antidepressive properties both in mood disorders and in schizophrenia [70–73]. Nevertheless, a considerable proportion of SGA-treated patients with schizophrenia suffer from depressive symptoms, as well.

The efficacy of a combination of an antipsychotic with an antidepressant for depressive symptoms has been a subject to extensive exploration. Noticeably, most of the existing body of evidence relies on patients with chronic schizophrenia and on trials not designed specifically for depression.

In regard to the TCAs, the only available RCT, the one by Siris et al. [74], revealed the superior efficacy of imipramine over placebo in the treatment of depressive symptoms in chronic schizophrenia.

For the SSRIs, of four RCTs carried out with add-on fluoxetine, only one [41] reported positive results (improvement in HDRS scores in favor of fluoxetine), whereas the later studies by Buchanan et al. [43], Arango et al. [44] and Bustillo et al. [46] failed to replicate this finding. In an RCT with another SSRI, sertraline added to different FGAs or to risperidone, HDRS- and BDI-measured depressive symptoms improved with clinical significance [48], while a study by Jockers-Scherubl et al. [40] of chronic patients treated with FGAs or SGAs revealed no superiority of paroxetine over placebo. Adjunctive citalopram led to an improvement in subsyndromal (≤8 on the HDRS) depressive symptoms as compared to adjunctive placebo in another RCT [75]. Two RCTs with a selective noradrenaline reuptake inhibitor reboxetine produced contradictory results. First, Schutz and Berk [50] found no additional antidepressant efficacy from reboxetine added to stable treatment with haloperidol. In a later RCT by Poyurovski et al. [51], reboxetine significantly improved depressive symptoms in olanzapine-treated patients with chronic schizophrenia.

Of receptor-blocking antidepressants, mianserin does not seem to be efficacious in the treatment of depressive symptoms in schizophrenia. In two published RCTs [59, 60], it failed to outperform placebo in FGA-treated subjects with chronic schizophrenia. Mirtazapine failed to improve depressive symptoms when added to haloperidol [16], clozapine [52], or various SGAs [56]. However, in a recent study by Terevnikov et al. [76], mirtazapine added to stable, relatively low doses of some FGAs in patients with chronic schizophrenia demonstrated a clear-cut superiority over placebo in the treatment of depressive symptoms (a decrease of 52% on the Calgary Depression Scale). This effect was independent of the desired effects of mirtazapine on other clinical domains.

Thus, an increasing body of evidence suggests that antidepressants may be beneficial for depressed patients with chronic schizophrenia. This evidence (although with some degree of controversy) comprises sertraline, fluoxetine, reboxetine, and mirtazapine. It should be noted that due to the small sample sizes of the majority of the studies, these results cannot be considered definite. Moreover, these studies were primarily designed to study the efficacy of antidepressants for negative or cognitive, but not for depressive symptoms of schizophrenia—another factor that limits the interpretation.

Another important question to be resolved is whether antidepressants should be used (or precluded) in the acute or chronic stage of schizophrenia. All the studies reviewed in this section involved populations with duration of illness exceeding 10 years, meaning that in chronic schizophrenia there is no reason to avoid adjunctive antidepressants.

The role of antidepressants in the acute phase of disease is less clear. An early precaution of antidepressants' ability to trigger psychotic exacerbation [77] was not based on evidence, nor has such evidence emerged later on. In the abovementioned trial by Poyurovsky and co-authors [45] fluoxetine added to olanzapine did not

prevent, though it delayed improvement of psychotic symptoms. Mirtazapine seems to improve psychotic symptoms when added to FGAs [53, 61]. To summarize, though the evidence is too sparse to be convincing, adjunctive antidepressants may be safer in the acute phase of schizophrenia than previously proposed. Nevertheless, not enough data exist on their benefits either, making a conservative attitude toward such co-administration still valid.

9.2.4 Efficacy of Antidepressants in Treatment of EPS

The theoretical assumption that add-on antidepressants may be effective against antipsychotic-induced EPS relies on the theory of dopamine deficiency in the basal ganglia. This theory states that pharmacological agents increasing available dopamine in this area may alleviate EPS symptoms. One possible mechanism may be their $5HT_2$ receptor antagonism—a property shared by SGAs and several receptor-blocking antidepressants.

Several studies tested this theory in the late 1990s and 2000s. Hayashi et al. [58] revealed a positive effect of trazodone on FGA-induced tardive dyskinesia. In contrast, both mianserin studies [58, 60] failed to demonstrate its superiority over placebo in treatment of EPS. Wynchank and Berk [78] found nefazodone to improve haloperidol-induced EPS measured by the SAS, but not to affect symptoms of akatisia or tardive dyskinesia. Results of several trials with mirtazapine were conflicting. Two studies found no improvement in haloperidol-induced [16] or risperidone-induced [54] EPS, while in another study [53], SAS-measured EPS improved in the mirtazapine-, but not in the placebo group (the difference in between-group comparisons was, however, not statistically significant).

There exists no theoretical basis for the possible efficacy of the transporter inhibitors in treatment of antipsychotic-induced EPS. Moreover, SSRIs may even cause EPS in patients with Major Depressive Disorder (MDD). Nevertheless, the influence of SSRIs and SNRIs on EPS was a secondary variable in a number of studies (see 2.1, 2.2 and 2.3.). Perhaps not surprisingly, all these studies yielded negative results.

Thus, some evidence suggests the plausible efficacy of the receptor-blocking antidepressants (except mianserin) in treatment of antipsychotic-induced EPS, but this evidence is rather limited and applies only to FGA-induced EPS.

9.2.5 Efficacy of Antidepressants in Treatment of Cognitive Symptoms of Schizophrenia

Cognitive impairment is one of the core components of schizophrenia [79]. Continuously growing evidence indicates that cognitive dysfunction is an even more important determinant of outcome in schizophrenia than are positive or negative

symptoms [80]. What still remains unclear is whether remediation of cognitive deficits in patients with schizophrenia may be achievable, and whether interventions targeting specifically cognitive symptoms may be beneficial [81]; if these are true, this would make the search for new, efficacious cognitive enhancement strategies meaningful. These strategies may include both psychosocial and pharmacological interventions [82]. The several groups of compounds identified to have a plausible cognitive-enhancing effect include alpha-7 nicotinic receptor agonists, M_1-muscarinic receptor agonists, dopaminergic agents, sympatomimetics, acetylcholinesterase inhibitors, glutamatergic agents, $5HT_{1A}$ receptor agonists, $5HT_{2A}$ receptor antagonists, and $\alpha 2$ adrenergic receptor antagonists [83].

The latter two mechanisms of action are shared by some receptor-blocking antidepressants. Of these, mianserin and mirtazapine served as potential cognitive enhancers in several trials. First, Poyurovski and co-authors [60] found that low-dose mianserin added to several FGAs in patients with chronic schizophrenia improved memory and learning, but not executive function as measured by the Wisconsin Card Sorting Test. In a 6-week RCT by Stenberg and co-authors [84], mirtazapine (n = 19 vs. placebo, n = 18) added to stable doses of various FGAs in patients with chronic schizophrenia significantly improved visuospatial functions as well as general mental speed and attentional control. Of note, a prolonged exposure to mirtazapine for an additional 6 weeks under open-label conditions led to further improvement in several neurocognitive parameters, as did a shift from placebo to open label mirtazapine in the control group [85]. In 2011, Cho and collaborators [86] published another RCT in which mirtazapine combined with risperidone improved not only negative symptoms, but also vocabulary and immediate memory in 21 patients with schizophrenia. And DelleChaie [87] found mirtazapine to improve some cognitive functions in clozapine-treated patients, but this study also relied on an open-label design and thus should not be overvalued.

Other classes of antidepressants have received negligible attention from researchers as potential cognitive enhancers in schizophrenia. Friedman and co-authors [49] found no statistically significant differences between effects of an adjunctive SSRI citalopram and placebo on any cognitive measures, indicating probably that increased availability of serotonin in the brain is by itself insufficient for treating cognitive impairment in schizophrenia.

Based on the theory that the noradrenergic system mediates cognitive dysfunction in schizophrenia patients, Poyurovsky and co-authors [88] investigated the efficacy of a Noradrenaline Reuptake Inhibitor reboxetine added to olanzapine on cognitive symptoms—also with disappointing results.

9.3 Effectiveness Studies

Only a handful of effectiveness studies (e.g., “real world” studies, in contrast to efficacy studies using an artificial “purified” scientific design, i.e., the RCT) concern adjuvant antidepressants in schizophrenia. A large study recently performed by

Tiihonen and co-authors [89] investigated relationships between polypharmacy and mortality rates in a complete nationwide cohort of 2,588 Finnish patients hospitalized for the first time with a diagnosis of schizophrenia between January 2000 and December 2007. They found that adjunctive antidepressant treatment was associated with diminished mortality from all causes (HR 0.57; 95% CI 0.28–1.16) including that from suicide (HR 0.15; 95% CI 0.03–0.77).

In a recent prospective study, Längle and co-authors [90] investigated the effects of psychotropic polypharmacy, including antidepressants, benzodiazepines, and mood stabilizers, on clinical outcomes and quality of life in 374 patients with schizophrenia and schizoaffective disorder treated with SGAs. Patients were assessed with the PANSS, the Global Assessment of Functioning, the Lancashire Quality of Life Profile, SAS, and AIMS during 24 months' follow-up. In that study, combinations of SGAs with antidepressants were associated with PANSS-measured clinical outcomes similar to those from antipsychotic monotherapy alone. Patients treated with an SGA-antidepressant combination demonstrated, however, a significantly larger improvement in EPS than with all other treatments, including monotherapy with SGAs. Notably, in that study population the mean baseline PANSS scores were low, ranging from 49.8 to 57.7, making it thus unclear whether these results can be extrapolated to more severely ill patients.

Glick and co-authors [91] investigated the clinical effect of tapering of an antidepressant treatment in a group of 22 stabilized patients with schizophrenia during their 3–12 months of follow-up. The outcome measure was the Clinical Global Impression-Improvement Scale (CGI-I). Tapering of an antidepressant led to worsening of a patient's mental condition in only one case, while in 18 cases no change was evident, and in three cases the patients' condition improved. This led the authors to conclude that tapering the adjunctive antidepressant treatment does not change outcome and that clinicians should attempt to withdraw from their adjunctive medications those stabilized chronic patients already on adequate antipsychotic therapy.

To conclude, it appears that in real-life clinical settings no reason exists for concern about the general safety of antidepressants among schizophrenic patients. Moreover, in this patient group, antidepressants seem to reduce mortality and prevent suicide; hence, the threshold for their use should be lowered.

9.4 Safety and Tolerability of Antidepressants in Schizophrenia

9.4.1 Adverse Effects

The main classes of antidepressants are characterized by typical adverse effects which affect their tolerability and, in some cases, limit their use in clinical practice. Exacerbation of psychosis as a complication of antidepressant treatment in schizophrenia has been discussed above (see 2.3) and seems not to be an issue of

concern, at least in antipsychotic-treated patients with chronic schizophrenia. Detailed description and analysis of the general adverse effect profile for each group of antidepressants is beyond the scope of this chapter and will be mentioned only in brief. The most common adverse effects of any antidepressants in general differ by class and compound and include (although are not limited by) anticholinergic and cardiotoxic effects and sometimes sedation for TCAs; gastrointestinal and sexual adverse effects for SSRIs; nausea, dizziness, headache, insomnia, and perspiration for SNRIs and reboxetine; sedation and weight gain for most receptor-blocking antidepressants; possible hepatotoxicity for nefazodone and agomelatine; and tyramine crisis for monoamineoxidase inhibitors [92, 93]. The "second generation" antidepressants such as SSRIs, SNRIs, receptor-blocking antidepressants, and some other newer agents, are in general safer and better tolerated than are the older drugs, i.e. TCAs and monoaminooxidase-inhibitors [94, 95]. The safety and tolerability of antidepressants in schizophrenia have not inspired a separate area of pharmacological research. However, data from the efficacy studies suggest that antidepressant-induced adverse effects in patients with schizophrenia do not differ from those in patients with MDD. Nevertheless, polytherapeutic combinations of antidepressants and antipsychotics may lead to increased risk for adverse effects due to drug interactions.

9.4.2 Drug Interactions

Drug interactions can be classified as either pharmacokinetic (when a drug interferes with absorption, distribution, metabolism, or excretion of other drugs) or pharmacodynamic (when they target the same organs or neurotransmitter pathways) [96].

9.4.2.1 Pharmacokinetic Interactions

Pharmacokinetic drug interactions between antidepressants and antipsychotics are associated mainly with the CYP 450 oxidases—a family of liver enzymes that play a key role in the biotransformation of both classes of drugs [97]. Some psychotropics may inhibit certain enzymes, often causing an unpredictable, drastic, or even toxic increase in blood concentrations of medications metabolized by these same enzymes (substrates) [98]. Conversely, some other drugs (inductors) noticeably whip up the activity of a CYP enzyme which can "eat away" correspondent substrates. Finally, two or more substrates of the same CYP enzyme prescribed concomitantly compete for this enzyme with a resultant moderate increase in their concentrations.

Three of the CYP 450 enzymes are responsible for the main metabolic pathways of antipsychotics and antidepressants (and thus of their potential pharmacokinetic interactions): CYP1A2, CYP2D6, and CYP3A4.

The role of these enzymes must be kept in mind when combining antidepressants and antipsychotics, especially if any of them (most often, an antidepressant but in some cases, an antipsychotic [99]) is an inhibitor of a CYP enzyme.

Since current knowledge relies mostly on in vitro studies [98], and reports on clinically significant interactions are scarce, some authors [100] conclude that the risks of antipsychotic-antidepressant pharmacokinetic interactions are theoretically rather than clinically relevant. Conversely, some others [101] suggest that such interactions, especially those with SSRIs, must become a matter of serious concern; they postulate that, for instance, fluoxetine and fluvoxamine should be used in combinations "cautiously," if at all.

For safety's sake, the authors of this chapter recommend a modestly conservative approach, meaning caution when using combinations with well-established major interactions such as fluvoxamine-clozapine, fluoxetine-perphenazine, or paroxetine-risperidone. Nevertheless, at best clinically significant interactions may even be used by skilled clinicians on purpose. For instance, Lu and co-authors [102] co-administered fluvoxamine and clozapine, and this enabled a decrease in dosage of the latter, with consequent monetary savings. Likewise, Albers and co-workers [103] achieved a reduction in olanzapine dosage by co-administration of a nontherapeutic dose of fluvoxamine.

9.4.2.2 Pharmacodynamic Interactions

Risk for clinically relevant and potentially dangerous pharmacodynamic interactions with antipsychotics is substantially higher for the TCAs and monoamineoxidase inhibitors than for the "second-generation" antidepressants. The most common mechanism of the interaction is augmentation of the same neurotransmitter pathway [104]. Another possible mechanism is competition at receptor sites and a direct effect on an organ/system's physiological functioning. Mechanisms of some interactions remain at least in part unclear.

The most common pharmacodynamic interactions between antipsychotics and antidepressants are:

1. Anticholinergic effects:

Both TCAs (especially amitriptyline, doxepine and imipramine) and numerous antipsychotics (especially clozapine, chlorpromazine, flupentixol, fluphenazine, and zuclopentixol) are blockers of muscarine receptors. Co-administration of these drugs may lead to worsening of anticholinergic adverse effects such as constipation, dry mouth, blurred vision, and cognitive impairment.

2. Sedation:

Although sedation in antidepressants and antipsychotics may be mediated via differing neurotransmitter mechanisms (H_1-receptor blockade in TCAs and some receptor-blocking antidepressants, melatonin receptor blockade in agomelatine, dopamine receptor blockade in antipsychotics), co-administration of two drugs with pronounced sedative effects may lead to excessive sedation. The agents providing the most pronounced sedation among antipsychotics are chlorpromazine, clozapine,

levomepromazine, olanzapine, promazine, and zotepin, and among antidepressants are amitriptyline, doxepine, trimipramine, mianserin, mirtazapine, trazodone, and agomelatine [105].

3. Weight-gain and untoward metabolic effects (dyslipidemia, impaired glucose tolerance):
   Among antipsychotics, clozapine, olanzapine, and chlorpromazine are associated with an increased risk for weight-gain [106]. Clozapine and olanzapine also share a propensity to induce a number of other untoward metabolic side-effects [107]. These features may be exaggerated in concomitant use of TCAs, mianserin, trazodone (weight-gain), and mirtazapine—notorious metabolic offenders among antidepressants.
4. Extrapyramidal symptoms:
   In animal studies, combination of haloperidol with fluoxetine, paroxetine, or clomipramine can lead to worsening of haloperidol-induced extrapyramidal adverse effects, whereas combination with mirtazapine has led to alleviation of EPS [108]. Several case reports suggest a plausible role for TCAs and SSRIs in augmentation of antipsychotic-induced EPS [109]. What remains unclear is whether the mechanism of this interaction is pharmacodynamic or pharmacokinetic. It should be kept in mind that TCAs and SSRIs may in themselves produce akatisia and some other EPS in antipsychotic-naive patients [110].
5. Cardiac effects:
   The TCAs have established arrythmogenic effects, whose principal mechanism is cardiac sodium channel blockade [111]. Some antipsychotics, too, are arrhythmogenic, especially at high doses [112]. A prolongation of the QT-interval often observed on the ECG of patients using TCAs may lead to Torsades de Pointes—a dangerous and potentially fatal condition. The TCAs should thus be combined with caution with haloperidol, thioridazine, olanzapine, ziprazidone, or sertindole [113]—antipsychotics that also tend to lengthen the QT interval.
   TCAs cause tachycardia, most likely due to their anticholinergic properties [104]. Reboxetine may also cause increased heart rate, presumably because of its noradrenergic mechanism [114]. Combinations of TCAs and reboxetine with antipsychotics sharing the same adverse effect (regardless of its mechanism), for example, clozapine and low-potency FGAs, may potentiate tachycardia, although clinical evidence regarding this interaction is lacking.
6. Vascular effects:
   Hypotension due to alpha-1 receptor blockage is a common adverse effect of both TCAs and numerous antipsychotics—chlorpromazine, levomepromazine, thioridazine, trifluoperazine, clozapine, risperidone, zotepine, and sertindol [115].
7. Proconvulsive effect:
   TCAs, especially maprotiline and clomipramine [116] and bupropion [117], can lower the seizure threshold, as do chlorpromazine, clozapine, and zotepine [118]. The seizure risk is dose-dependent [116].

Despite the current recommendations to use only monotherapy with antipsychotics in the treatment of schizophrenia [7], in clinical practice, polytherapy and polypharmacy are common. Many patients receive one or more other drugs in addition to their

antipsychotic-antidepressant combination [5]. Hence, the whole spectrum of concomitant medications must be taken into account in choosing an adjunctive antidepressant. This requires prudent decisions based on the existing broad but still insufficient knowledge of the pharmacodynamics and pharmacokinetics of a wide range of psychotropics. If a combination of drugs with a potential for pharmacodynamic interactions is necessary, careful monitoring is to be strongly recommended, and discontinuation or a shift to another antidepressant should be an option in case of significant adverse effects or insufficient clinical response.

9.5 Summary and Further Directions

Despite the proven effectiveness of antipsychotics in treatment of schizophrenia, there exist a substantial number of patients with only a sub-optimal clinical outcome. This is especially true for negative symptoms and cognitive deficits, but often also positive symptoms. Insufficiently treated depressive symptoms contribute to poor outcome and increased suicide rates.

To date, evidence in favor of antidepressant augmentation of both FGAs and SGAs for negative symptoms is fairly convincing, being probably the most consistent for receptor-blocking antidepressants, especially mianserin and mirtazapine. For SSRIs as a group the data are equivocal.

Antidepressants seemingly fail to improve positive symptoms of schizophrenia (with the possible exception of mirtazapine), but in contrast to widely accepted opinion, nor do they appear to worsen psychosis—at least in chronic schizophrenia and when combined with antipsychotic medication. Moreover, they may reduce rates of suicide and overall mortality in patients with schizophrenia. The current level of caution in the use of add-on antidepressants in schizophrenia therefore needs reappraisal.

With some degree of uncertainty, several antidepressants such as sertraline, fluoxetine, reboxetine, and mirtazapine can be recommended for the treatment of depressive symptoms in schizophrenia. This recommendation, however, applies mostly to patients in the chronic stage of the disease, whereas for depressive symptoms in acute episodes, antipsychotic therapy may suffice. The same uncertainty exists regarding antidepressants as agents alleviating antipsychotic-induced EPS. The receptor-blocking antidepressants are seemingly worth trying in patients treated with the FGAs. Conversely, the SSRIs may even provoke EPS and should be avoided in patients predisposed to neurological adverse effects of antipsychotics.

Some antidepressants, especially mirtazapine (and possibly mianserin), may be of interest as potential neurocognitive enhancers, but more evidence is required. When co-administering an antidepressant and an antipsychotic, a clinician should consider possible drug pharmacokinetic (especially for some SSRIs with a propensity to inhibit CYP 450 enzymes) and pharmacodynamic (especially for TCAs) interactions. Preference should usually go to the most pharmacokinetically and pharmacodynamically neutral agents.

In general, evidence regarding the efficacy and effectiveness of add-on therapy with antidepressants supports their use in schizophrenia, but further well-designed,

randomized, controlled trials are necessary, ones of larger size in differing subpopulations of patients with schizophrenia; more naturalistic effectiveness trials are needed, too. Possible areas of interest are, for example, the comparative efficacy of various antidepressants in treatment of negative and depressive symptoms of schizophrenia, as well as head-to-head comparison of an add-on antidepressant with plausible additive antipsychotic potential (such as mirtazapine), combined with FGAs or SGAs vs. clozapine in treatment-resistant schizophrenia. Add-on antidepressants, especially the receptor-blocking ones, may be promising neurocognitive enhancers, but large, methodologically sound research in this field is vital. A capability of antidepressant monotherapy to preclude or postpone onset of schizophrenia in high-risk groups is another promising field of research.

Aknowledgements The authors thank Jan-Henry Stenberg, PM, for providing the most up-to-date information on the cognitive impairment in schizophrenia and its treatment.

The authors are also indebted to Kari Raaska, MD, PhD, for comprehensive consultations in the field of pharmacokinetics.

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