CNS Spectrums (2019), **24**, 239–248.
doi:10.1017/S1092852917000554

REVIEW ARTICLE

Treating depressive episodes or symptoms in patients with schizophrenia

Geeske van Rooijen,[1] Jentien Marloes Vermeulen,[1] Henricus Gerardus Ruhé,[1,2,3]† and Lieuwe de Haan[1]†*

[1] Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[2] Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, United Kingdom
[3] Radboudumc Department of Psychiatry, Reinier Postlaan 8, 6500, HB Nijmegen

Depressive episodes or symptoms occur frequently in patients with schizophrenia and may have far-reaching consequences. Despite the high prevalence rate and clinical relevance of this comorbidity, knowledge about treatment options is still limited. The aim of this review is to provide an overview of the literature concerning treatment options for depressive episodes or symptoms in schizophrenia. Based on the current evidence, we present a stepwise treatment approach. The first step is to evaluate the current antipsychotic treatment of psychotic symptoms and consider lowering the dosage, since increased blockade of the dopamine D_2 receptors may be associated with a worse subjective sense of well-being and dysphoria. A second step is to consider switching antipsychotics, since there are indications that some antipsychotics (including sulpiride, clozapine, olanzapine, aripiprazole, quetiapine, lurasidone, or amisulpride) are slightly more effective in reducing depressive symptoms compared to other antipsychotics or placebo. In the case of a persistent depressive episode, additional therapeutic interventions are indicated. However, the evidence is indecisive regarding the treatment of choice: either starting cognitive-behavioral therapy or adding an antidepressant. A limited number of studies examined the use of antidepressants in depressed patients with schizophrenia showing modest effectiveness. Overall, additional research is needed to determine the most effective treatment approach for patients with schizophrenia and depressive episodes.

Received 5 May 2017; Accepted 24 July 2017; First published online 20 September 2017

Key words: Schizophrenia, comorbid depression, treatment, neurobiology, antipsychotics.

Clinical Implications

- Depressive symptoms occur frequently in patients with schizophrenia (with an estimated modal prevalence rate of 25%).
- Validated questionnaires (e.g., the Calgary Depression Rating Scale for Schizophrenia) are considered useful for diagnosing depressive episodes in this patient population.
- Current evidence suggests that sulpiride, clozapine, olanzapine, aripiprazole, quetiapine, lurasidone, and amisulpride have a modest beneficial effect on reduction of depressive symptoms compared to other antipsychotics.
- Physical activity is highly recommendable when patients suffer from depressive symptoms given its beneficial effects on symptom severity and the lack of adverse effects.
- Although based on only a few studies, additional treatment with antidepressants or cognitive-behavioral therapy showed modest effectiveness in depressed patients with schizophrenia.

* Address for correspondence: G. van Rooijen, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Meibergdreef 5, 1105 AZ Amsterdam, The Netherlands.
(Email: g.vanrooijen@amc.nl)
† Shared last authorship.

Introduction

Depressive symptoms are often seen in patients with schizophrenia, with an estimated modal prevalence rate of 25%.[1,2] Because of this frequently cooccurring symptomatology, there is an ongoing debate as to whether mood symptoms should not be considered as part of the symptom profile of schizophrenia.[2]

The recognition and diagnosis of depressive episodes or symptoms in patients with schizophrenia can sometimes be challenging due to its conceptual overlap with negative symptoms. Nevertheless, diagnosing depressive episodes is highly relevant since it is associated with a higher risk of suicide,[3–5] a poorer quality of life,[6] and

decreased treatment adherence.[6] Clinicians may focus on the treatment of psychotic symptoms, while patients report that depressive symptoms bother them most and have the greatest impact on their satisfaction with life.[7] The above led to the inclusion of depressive symptoms as one of the dimension scores in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM–5, §III).[8] Next to the dimension of depression, the DSM–5 incorporates seven other dimensions: hallucination, delusion, mania, disorganized speech, abnormal psychomotor behavior, negative symptoms, and impaired cognition. By offering the Clinician-Rated Dimensions of Psychosis Symptom Severity Scale, more emphasis is given on the differences in occurrence and severity of several symptom dimensions. This may facilitate administration of specific interventions.[9]

Despite the high prevalence rates of depressive symptomatology in schizophrenia, treatment studies that use reduction of depressive symptoms as the primary outcome of interest are scarce. However, some new studies that investigated the addition of antidepressants[10] to care as usual practice and the effectiveness of exercise[11] on depressive symptoms have not yet been included in recent guidelines and articles on this topic.[12–14] Therefore, the present review aims to give an overview of treatment possibilities for depressive episodes and symptoms in schizophrenia. Based on the current evidence, we will provide a stepwise approach that can be applied when treating a patient with schizophrenia and depressive episodes or symptoms.

Methods

The articles included in this review were selected after performing a literature search in PubMed (Medline). To find the most relevant studies on this topic, we combined the following search terms: "schizophreni*," "psychos*," and "depress*." The search was last performed on 14 June 2017. For this review, we restricted our search to meta-analyses, systematic reviews, and randomized controlled clinical trials that were performed over the previous 10 years. Articles were included if they investigated effectiveness on depressive episodes or symptoms as a primary or secondary outcome in patients diagnosed with schizophrenia.

Diagnosing depressive episodes in schizophrenia

In the current literature, the terms "comorbid depression," "depressive symptoms," and "depression" are often used interchangeably. For the uniformity of this review, we will use the term "depressive episode(s)" if patients were included who met the criteria for a major depressive episode (in accordance with the DSM–5 criteria) and/or a validated questionnaire was employed for diagnosing a depressive episode in patients with schizophrenia. Of note, these episodes are often recurrent. In all other cases, including subsyndromal depression, we will use "depressive symptoms."

The conceptual overlap of depressive symptoms with other symptoms (e.g., negative symptoms and/or extrapyramidal side effects) might provide another explanation for the broad range of prevalence rates and the clinical challenge to diagnose a depressive episode in patients with schizophrenia. To give some clinical guidance, a depressive episode is characterized by a depressed mood, while a flat or blunted affect and emptiness rather points to negative symptoms. Furthermore, feelings of hopelessness and guilt as well as suicidal thoughts are seen more frequently in the case of depressive symptomatology.[2,14] Because of these differences, it is recommended to use validated questionnaires to diagnose a depressive episode in patients with schizophrenia. For example, the Calgary Depression Rating Scale for Schizophrenia (CDSS)[15] is specifically designed to distinguish between depressive symptoms and other symptom domains (i.e., negative and or extrapyramidal side effects).[16,17] Nevertheless, a thorough clinical evaluation that integrates several important factors (i.e., time of onset, course of symptomatology, and relation between the use of medication and depressive symptomatology) remains crucial when diagnosing a depressive episode in patients with schizophrenia. Hausmann *et al.*[18] have provided a clinically useful overview on this topic.

Moreover, clinicians should be aware of several somatic disorders that can contribute to the emergence of a depressive episodes or symptoms. This can occur, among others, in endocrine disorders, malignancies, and cardiovascular diseases.[19] This is highly important, since the prevalence of cardiovascular and oncological diseases is higher in patients with schizophrenia compared to healthy controls.[20] Additionally, depressive symptoms can also occur after the use (or discontinuation) of certain medications (e.g., [lipophilic] antihypertensive agents and corticosteroids) and the use of substances (i.e., drugs, alcohol, and caffeine).[21]

Possible causes and explanations for depressive episodes in schizophrenia

In the last few decades, different studies have tried to elucidate the high prevalence rates of depressive symptomatology in patients with schizophrenia. On the one hand, there are several biological studies that tried to investigate the difference in underlying pathophysiology of patients diagnosed with schizophrenia with and without depressive symptomatology. The neurobiological studies that investigated both disorders (i.e., schizophrenia and unipolar depression) showed a large overlap

https://doi.org/10.1017/S1092852917000554 Published online by Cambridge University Press

between these two disorders with respect to potential factors contributing to the pathophysiology of both disorders. These include comparable risk factors during youth (such as childhood trauma and neglect),[22] changes in the immune–inflammatory system,[23] and structural changes in brain morphology from neuroimaging studies.[24] These observations may point to a common pathophysiology, which might explain why depressive episodes or symptoms are often seen in patients with schizophrenia, and/or that patients with schizophrenia are vulnerable for developing depressive symptoms.[23] On the other hand, several studies[13,22,25] have emphasized the effects of the different psychological factors that are believed to play an important role in the onset of depression (e.g., depression as a psychological reaction to being diagnosed with schizophrenia and the social consequences of this disease or as a reaction to psychotic relapse).

The evidence to date regarding the possible causes and explanations for depressive episodes in patients with schizophrenia is sometimes conflicting and appears highly dependent on selection of samples and sample size. It is beyond the scope of this review to discuss the pathophysiology of depressive episodes in depth. For a more comprehensive discussion on this topic, we refer the reader to a review by Upthegrove *et al.*[13] In sum, there is no evidence for a single, straightforward explanation of the high prevalence of depressive episodes in schizophrenia. In line with the plausible causal pathways of unipolar depression, current evidence points toward a multifactorial etiology, including psychosocial, neurobiological, and environmental risk factors.

The treatment of depressive episodes and symptoms in schizophrenia

Below we will first review studies focused on pharmacological treatment (antipsychotics, antidepressants in addition to antipsychotics, and other pharmacological treatments) and nonpharmacological interventions. When evidence is available, we will first discuss the effects on depressive episodes and then the effects on depressive symptoms. We will also consider the most important limitations of the current reports. Current findings are summarized in a practical stepwise approach (Figure 1). Lastly, we briefly discuss the treatment aspects of suicide, as the risk on suicide is elevated by the presence of depressive episodes or symptoms.

First phase of treatment

In the acute phase of psychosis, it is advisable to treat depressive symptoms primarily with antipsychotics only, because depressive symptoms can improve or disappear with the remission of a psychosis.[26,27] For example, when patients suffer from severe positive symptoms (such as delusions and hallucinations), these may potentially lead to social isolation and in turn cause depressive symptoms. Resolution of psychotic symptoms by D_2 antagonists might therefore lead to improvement of depressive symptoms. However, previous research also showed that an increased blockade (i.e., higher dosages or higher affinity of antipsychotic agent) of the dopamine D_2 receptors by antipsychotics is associated with worse subjective well-being and/or dysphoria.[28–30] Likewise, the induction of EPS by antipsychotics has previously been associated with "neuroleptic dysphoria."[31,32] It seems plausible that especially an unwarranted high dosage of antipsychotics is associated with these side effects and dysphoria, which might especially manifest itself after the acute-phase treatment of psychosis. Consequently, the first step of treating depressive symptoms is to adequately treat positive symptoms with antipsychotics but also to optimize the dosage of this medication and when possible lower the dosage of current D_2 antagonists. Herein, we acknowledge the complex balance of efficacy and tolerability of antipsychotic treatment in the case of depressive symptoms.

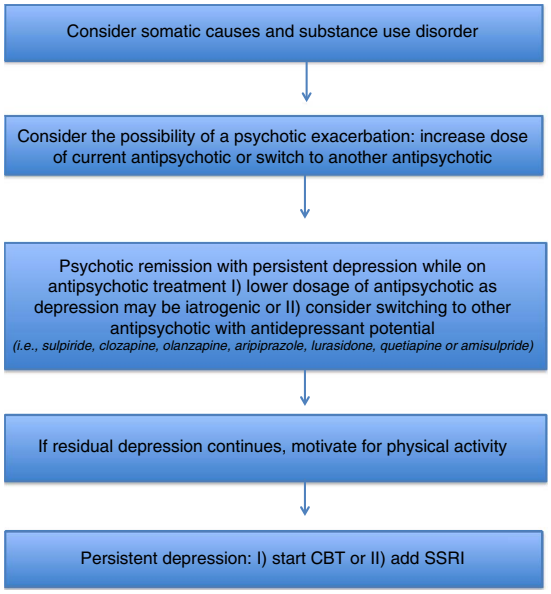

FIGURE 1. Framework for treating depression in patients with schizophrenia. Based on the framework as designed by Castle and Bosnac.[14]

Pharmacological treatment

Antipsychotics

Over the last few decades, several studies have investigated the antidepressant effect of antipsychotics. However, the number of studies investigating the effectiveness of antipsychotics for treating depressive episodes in schizophrenia specifically are limited, as shown in a Cochrane review by Furtado *et al.*[33]

https://doi.org/10.1017/S1092852917000554 Published online by Cambridge University Press

The possible effects in this Cochrane review were expressed as "weighted mean differences" (WMDs), which calculate the difference between decreases of a score on a depression rating scale by different interventions, weighted by the pooled variance of these differences.

From the few included studies in this review, one study compared sulpiride versus chlorpromazine with a double-blind design (in which it was unclear whether participants were randomly assigned to the treatment conditions). Sulpiride was associated with a significant decrease in depression scores compared to patients receiving chlorpromazine ($n = 19$ and $n = 17$, respectively; $WMD = -0.70$; 95% confidence interval [$CI_{95\%}$] = [−1.2, −0.2]; $p = 0.0058$). In another included double-blind study, quetiapine yielded no significant improvement in depression scores compared with patients receiving haloperidol ($n = 94$ and $n = 86$, respectively; $WMD = -0.57$; $CI_{95\%} = [-1.4, 0.3]$). The authors of this Cochrane review concluded that there was insufficient evidence to determine whether or not newer atypical antipsychotics were more effective compared to older antipsychotics in the treatment of depressive episodes in patients with schizophrenia.

Furthermore, in contrast to the above Cochrane review, some meta-analyses pooled additional studies comparing the effectiveness of antipsychotics on *depressive symptoms* (instead of depressive episodes). Leucht *et al.*[34] investigated whether some antipsychotic drugs were more effective compared to placebo, assessing several outcome measures including depressive symptoms. This meta-analysis showed that a number of antipsychotics were significantly more effective in reducing depressive symptoms relative to placebo. Amisulpride (2 trials, $n = 261$, pooled effect size [ES] = −0.50; $CI_{95\%} = [-0.75, -0.24]$, $p = 0.0001$), olanzapine (3 trials, $n = 479$, pooled $ES = -0.28$, $CI_{95\%} = [-0.47, -0.10]$, $p = 0.0024$), ziprasidone (3 trials, $n = 404$, pooled $ES = -0.33$, $CI_{95\%} = [-0.52, -0.13]$, $p = 0.0011$), and zotepine (1 trial, $n = 79$, pooled $ES = -0.48$, $CI_{95\%} = [-0.92, -0.03]$, $p = 0.0349$) were significantly more effective than placebo. Haloperidol had a beneficial effect on depressive symptoms (2 trials, $n = 299$, pooled $ES = -0.33$, $CI_{95\%} = [-0.56, -0.11]$, $p = 0.0039$) compared to placebo. No significant differences in effect between the agents clozapine, quetiapine, risperidone, or sertindole were found.

The effectiveness of haloperidol in the treatment of depressive symptoms, with its high potency for dopamine D_2 receptor antagonism, is in apparent contradiction with research that describes the worse subjective well-being and/or dysphoria due to blockade of the D_2 receptor.[28–30] There are various explanations to explain this contradiction: for example, haloperidol might effectively treat psychotic symptoms, which in turn causes a decrease in depressive symptomatology (as outlined earlier). Based on these findings, there is no conclusive evidence to support switching when depressive symptoms initially appear and when a patient is already treated with haloperidol, but instead lowering the dose could be considered, while balancing the efficacy and tolerability of the drug as adequately as possible.

In a second meta-analysis of Leucht *et al.*,[35] nine second-generation atypical antipsychotics were compared with first-generation antipsychotics, with depressive symptoms as the measured outcome. From this study, amisulpride (9 trials, $n = 900$, pooled $ES = -0.37$, $CI_{95\%} = [-0.51, -0.24]$, $p < 0.0001$), aripiprazole (1 trial, $n = 1278$, pooled $ES = -0.12$, $CI_{95\%} = [-0.24, -0.01]$, $p = 0.040$), clozapine (6 trials, $n = 426$, pooled $ES = -0.51$, $CI_{95\%} = [-.0.87, -0.14]$, $p = 0.006$), olanzapine (12 trials, $n = 2893$, pooled $ES = -0.27$, $CI_{95\%} = [-0.35, -0.19]$, $p < 0.0001$), and quetiapine (4 trials, $n = 442$, pooled $ES = -0.23$, $CI_{95\%} = [-0.41, -0.04]$, $p = 0.016$) were more effective in treating depressive symptoms than first-generation antipsychotics. In contrast to the earlier mentioned meta-analysis of Leucht *et al.*,[34] zotepine and ziprasidone were not more effective in this analysis compared to other antipsychotic treatments. Of note, risperidone and sertindole were both found to be ineffective compared to first-generation antipsychotics in reducing the severity of depressive symptoms. The limitations of this second meta-analysis were the small effect sizes (apart from clozapine), the short follow-up of the included studies (i.e., 81% of the studies had a duration of 12 weeks), and that in most studies (95) antipsychotics were compared to haloperidol, mostly in relatively high doses (as pointed out in published comments).[36,37] Given the findings of previous research which showed that an increased blockade (i.e., higher dosages) of the dopamine D_2 receptors by antipsychotics is associated with worse subjective well-being and/or dysphoria,[28–30] and the favorable effect sizes of second-generation antipsychotics compared to first-generation antipsychotics, these results might reflect an overestimation due to high doses of the comparator drug.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial[38] also examined whether second-generation antipsychotics were more effective compared to first-generation antipsychotics in the treatment of depressive symptoms in schizophrenia patients ($n = 1{,}460$).[39] In the first phase of this double-blind study, patients were randomly assigned to perphenazine, olanzapine, quetiapine, risperidone, or ziprasidone and followed for 18 months. During these 18 months, depressive symptoms decreased in all treatment groups, and there were no significant differences between these groups. If only the patients were taken into account ($n = 448$) that had clinically relevant depressive symptoms (i.e., patients with a score of 6 or higher on the

CDSS) at baseline, mixed-model analyses showed that the patients who were treated with quetiapine had significantly lower depression scores at outcome compared to the group receiving risperidone. However, this was observed at four out of the seven measurements during follow-up, and only small differences were found between both groups.

Regarding the more recently approved antipsychotic lurasidone, this agent proved to be effective in the treatment of depressive symptoms.[40] Nasrallah *et al.*[40] pooled the results of double-blind randomized controlled trials that investigated the effect of lurasidone on depressive symptoms. Although the duration of these trials was short (6 weeks), patients treated with lurasidone showed a significant, though small, decrease in depressive symptoms compared to placebo (4 trials, $n = 898$ and $n = 432$, respectively; pooled $ES = -0.24$; $p < 0.001$).

A more recent meta-analysis and metaregression[41] was published regarding the effectiveness of antipsychotic augmentation, which is highly debated considering its cost and the ambiguous evidence. Considering the effectiveness for depressive symptoms, augmentation did not lead to a significant improvement in severity of depressive symptoms, although the pooled effect size was moderately large and significant at a trend level (10 trials, $n = 351$, pooled $ES = -0.69$, $CI_{95\%} = [-1.42, 0.05]$, $p = 0.066$).

In summary, since blockade of dopamine D_2 receptors is possibly associated with a worsening of subjective well-being and/or dysphoria, the first step is to lower the dosage of current antipsychotic treatment while maintaining remission from psychosis and/or to treat when depressive symptoms occur. There is not enough evidence to encourage switching among antipsychotics when depressive symptoms initially appear while a patient is treated with high-potency D_2 receptor antagonists. In that situation, it is advisable to reconsider the dosage of the drug to balance efficacy and tolerability. All first- and second-generation antipsychotics antagonize D_2 receptors to a greater degree as dosing increases. Most guidelines suggest lowering to the most effective antipsychotic dose,[12,42,43] which may improve depressive symptoms. However, if depressive symptoms persist, there are indications that a number of antipsychotics (including sulpiride, clozapine, olanzapine, aripiprazole, quetiapine, lurasidone, and amisulpride) have a slightly more favorable effect than other antipsychotics or placebo when treating depressive symptoms in patients with schizophrenia, and a switch may be warranted. Although haloperidol might also be effective, the increased effectiveness of second-generation antipsychotics compared to first-generation antipsychotics may be explained by the fact that several second-generation antipsychotics have a lower affinity for the dopamine D_2 receptor and an antagonistic action on the 5-HT_2 receptor, both of which may contribute to an antidepressant effect. Some second-generation antipsychotics may potentially partially agonize D_2, D_3, and $5HT_{1a}$, or antagonize $5HT_{2c}$, $5HT_3$, or $5HT_7$—all of which have theoretical antidepressant properties.[44–46] In this light, it is also important to mention brexpiprazole, which may have an antidepressant effect in patients with schizophrenia due to its receptor profile (including partially agonizing at the D_2 and $5HT_{1a}$ receptors and antagonizing at the $5HT_{2a}$ and noradrenaline α_{1b} and α_{2c} receptors).[47] Correll *et al.*[48] performed a meta-analysis on the effectiveness of brexpiprazole in one phase II study and two phase III studies, showing a significant reduction in a depression/anxiety factor in one phase III study compared to placebo. However, some uncertainties remain regarding depressive episodes, because most studies evaluated the effect on depressive symptoms instead of treatment of depressive episodes. Moreover, studies investigating second-generation antipsychotics were using relatively high doses of first-generation drugs, which limits comparability.[49] Most second-generation antipsychotics possess antidepressant properties at their lower doses.

Antidepressants in addition to antipsychotic medication

Efficacy and tolerability. In 2002, a Cochrane review by Whitehead *et al.*[50] was published regarding adding antidepressants to antipsychotics in the case of *depressive episodes* in patients with schizophrenia. Based on the small sample sizes and poor quality of the six randomized controlled trials (RCTs), the authors concluded that the addition of antidepressants to an antipsychotic in comparison to the addition of a placebo did not significantly reduce depression (6 trials, $n = 261$, $WMD = -2.1$, $CI_{95\%} = [-5.04, 0.84]$). No conclusions were made regarding the effectiveness of individual agents.

The earlier-mentioned Cochrane review by Furtado *et al.*,[33] which investigated the antidepressant effect of atypical antipsychotics, also included one short study that compared clozapine with other unspecified antipsychotics in combination with an antidepressant or placebo in a double-blind design. Severity of depression significantly decreased in patients treated with clozapine ($n = 18$) in comparison with the group of patients who received an antipsychotic agent in combination with mianserin ($n = 11$, $WMD = -5.53$, $CI_{95\%} = [-8.23, -2.8]$, $p < 0.0001$), as well as in comparison with patients receiving an antipsychotic agent in combination with moclobemide ($n = 14$, $WMD = -4.35$, $CI_{95\%} = [-6.7, -2.03]$, $p = 0.00024$), as well as in comparison with patients receiving an antipsychotic agent in combination with amitriptyline ($n = 12$, $WMD = -3.61$, $CI_{95\%} = [-6.58, -0.64]$, $p = 0.017$), and also compared to patients who received an antipsychotic agent in combination with placebo ($n = 15$, $WMD = -6.35$, $CI_{95\%} = [-8.6, -4.1]$, $p < 0.00001$).

https://doi.org/10.1017/S1092852917000554 Published online by Cambridge University Press

After these Cochrane reviews, some additional reviews and meta-analysis were published that further evaluated the addition of antidepressants in patients with schizophrenia on several outcomes, including *depressive symptoms* (instead of depressive episodes).[10,51–55] The most recent of these, which also included the majority of the studies, is a meta-analysis by Helfer *et al.*,[10] which included 82 RCTs ($N = 3{,}608$). By making use of wider inclusion criteria (i.e., including nonblinded clinical trials and trials that used control conditions in which no treatment was given), the authors included more studies at the expense of a lower level of study quality.

Of the 82 included studies, 42 trials used depressive symptoms as an outcome. Based on these studies, antidepressants provided a significant (though limited) decrease in depressive symptoms compared with control conditions (i.e., placebo or no active treatment, 42 trials, $n = 1849$, pooled $ES = -0.25$, $CI_{95\%} = [-0.38, -0.12]$, $p = 0.0001$). However, in stratified analyses, the studies using selective serotonin reuptake inhibitors (SSRIs) showed a nonsignificant decrease in depressive symptoms (19 trials, $n = 859$, pooled $ES = -0.19$, $CI_{95\%} = [-0.40, 0.02]$). The following individual antidepressants were significantly more effective in reducing depressive symptoms: trazodone (1 trial, $n = 60$, pooled $ES = -0.98$, $CI_{95\%} = [-1.51, -0.44]$, $p = 0.0004$); duloxetine (1 trial, $n = 40$, pooled $ES = -0.80$, $CI_{95\%} = [-1.45, -0.16]$, $p = 0.01$); sertraline (4 trials, $n = 205$, pooled $ES = -0.51$, $CI_{95\%} = [-0.91, -0.12]$, $p = 0.01$); and amitriptyline (4 trials, $n = 138$, pooled $ES = -0.34$, $CI_{95\%} = [-0.68, 0.00]$, $p = 0.05$).

In an additional analysis, the authors found no indication of increased efficacy of antidepressants in patients with "*pronounced depressive symptoms*" compared to patients with lesser severity ($p = 0.38$). However, in contrast to the overall nonsignificant effects of SSRIs against depressive symptoms, SSRIs were beneficial in schizophrenia patients with depressive episodes (7 trials, $n = 422$, pooled $ES = -0.48$, $CI_{95\%} = [-0.84, -0.11]$, $p = 0.01$). These additional analyses suggest that antidepressants in general, and SSRIs more specifically, are beneficial when patients meet the criteria for a depressive episode. Future high-quality studies are required to validate these results.

Additionally, *tolerability* is a relevant outcome when adding antidepressants for the treatment of depressive episodes. This is of high importance since patients diagnosed with schizophrenia are, in general, already being treated with antipsychotics prone to side effects. Patients treated with additional antidepressants had significantly more complaints of abdominal pain, constipation, dizziness, and dry mouth, which are common adverse effects of antidepressants. However, psychotic exacerbations were not more frequently observed in the group treated with antidepressants.

Interactions due to combined antipsychotic–antidepressant treatment. Most pharmacokinetic interactions between antipsychotics and antidepressants are the result of competitive binding with different cytochrome P450 (CYP) enzymes.[56] These interactions result in changing plasma levels of drugs (increase or decrease depending on inhibition or induction of specific CYP enzymes). Some new antidepressants act as inhibitors of different CYP enzymes, where most antipsychotic drugs do not have these inhibiting effects but are indeed metabolized (i.e., substrates) by these enzymes.[56] Due to the inhibitory effect of the antidepressants, the elimination of antipsychotic drugs might be diminished, resulting in higher plasma levels of antipsychotic drugs. A constantly updated overview of the strength of the inhibitory effects of different antidepressants can been found in "drug Interaction tables" (available at http://medicine.iupui.edu/clinpharm/ddis/main-table).[57]

Since there are SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs) (e.g., sertraline, (es)citalopram, and duloxetine) with mild to moderate inhibitory effects of CYP enzymes, it may be recommended to use one of these drugs, especially if monitoring of the serum levels of antipsychotics is not available. Moreover, it is advisable to use therapeutic drug monitoring (TDM) of the antipsychotic. These blood levels can be done before and during the process of adding an antidepressant and might clarify the intraindividual interactional effects. However, TDM results might be difficult to interpret, especially since large intraindividual differences have been described.[56] Whenever there is too little evidence for the application of TDM (e.g., for aripiprazole and quetiapine) and/or where TDM is not available,[58] as a third option correction factors could be applied. Correction factors give an indication if and how a dosage of a substrate (i.e., those drugs that are metabolized by CYP enzymes) should be reduced in the case of adding an antidepressant to antipsychotic medication (for an extensive overview of correction factors when combining specific combinations of antidepressant and antipsychotics, we refer to the review by Spina and Leon).[56]

Additionally, pharmacodynamic interactions (at the level of binding to receptors) are also important. These effects, in contrast to the pharmacokinetic interactions, are not a result of changes in plasma levels and may result in improved or reduced effectiveness, but at the same time with more or less adverse drugs reactions. However, the possible occurring effects when combining antidepressants and antipsychotics are poorly investigated, although these interactions are more likely to occur with mirtazapine and bupropion.[56] Prolonged QTc interval, with torsades de pointes as a rare but possibly lethal outcome, is described when SSRIs and second-generation antipsychotics are combined. Additive risk factors include a "family history of sudden death; personal history of

https://doi.org/10.1017/S1092852917000554 Published online by Cambridge University Press

syncope, arrhythmias or heart conditions; hypokalemia, hypomagnesaemia and co-prescription of other medications that increase QTc."[56] If the aforementioned situations are applicable, an electrocardiogram is recommended.[56]

Other pharmacological treatments

Two Cochrane reviews[59,60] investigated the effect of the addition of lithium or valproate, respectively, on depressive symptoms in patients with schizophrenia, but neither treatment showed a significant improvement in depressive symptoms. With respect to lithium, to the best of our knowledge, there are no studies to date that have investigated the effect of addition of lithium in combination with both antipsychotics and antidepressants. This indeed could be a plausible strategy, considering the effects of addition of lithium in the case of nonresponse to antidepressants in patients with unipolar depression.[19]

In summary, there is evidence that the use of antidepressants to treat depressive symptoms and depressive episodes may be of help to some degree in patients with schizophrenia. However, interactions between antidepressants and antipsychotics should be taken into account. There is not enough evidence to indicate which antidepressant is preferred as an additive to antipsychotic medication; however, the best available evidence supports the use of SSRIs. Within the group of SSRIs, no advice can be given regarding the effectiveness of individual agents; nonetheless, agents with mild to moderate inhibitory effects on CYP enzymes might be preferable to reduce pharmacokinetic interactions.

Nonpharmacological interventions

A recent systematic review and meta-analysis by Dauwan *et al.*[11] examined the effect of exercise in patients with schizophrenia on several outcome measures, including depressive symptoms. They compared exercise to both a passive and an active control condition (the "active" control group included, e.g., patients with schizophrenia who played table soccer or followed occupational therapy, whereas the "passive" condition comprised patients with schizophrenia who were on a waiting list). There were seven trials included ($N = 296$) that examined the effect on depressive symptoms, and these found that exercise reduced depressive symptoms in patients with schizophrenia compared to control conditions (pooled $ES = -0.71$, $p < 0.001$). Qualitative assessment showed that patients had to perform physical activity for at least 30 minutes, three times weekly, at a considerable intensity, for at least three months. The positive effects of exercise are extremely important, especially in patients with schizophrenia who are mostly treated with antipsychotics for a longer period of time, but antipsychotics are particularly known for their harmful side effects, including weight gain, diabetes mellitus, and dyslipidaemia.[61]

Regarding cognitive-behavioral therapy (CBT), most studies focus on the effectiveness of CBT on psychotic symptoms, and no studies investigated the effectiveness of this intervention on depressive symptoms as a primary outcome.[13] Nevertheless, the National Institute for Clinical Excellence (NICE, 2014)[12] described a small to moderate positive effect ($ES = -0.30$) for reduction of depressive symptoms in comparison with standard treatments[62] or other psychosocial treatments.[63] Given the beneficial effects of CBT in patients with unipolar depression, CBT is an interesting intervention to further investigate in patients with schizophrenia and a depressive episode.[19]

Other therapeutic interventions, which are frequently used in the treatment of unipolar depressive disorder[19] (e.g., electroconvulsive therapy [ECT] and repetitive transcranial magnetic stimulation [rTMS]) have also been investigated in schizophrenia. A Cochrane review[64] investigated the effectiveness of ECT in patients ($n = 30$) with schizophrenia and showed that there is no evidence that ECT is effective in the treatment of depressive symptoms, which is at least remarkable considering the success rates of ECT in the treatment of resistant unipolar depression. Another Cochrane review by Dougall *et al.*[65] examined the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in patients with schizophrenia on various outcomes, including depressive symptoms. These studies, which evaluated the effectiveness of rTMS on depressive symptoms (5 trials, total sample sizes ranging between 22–43), suggested some beneficial effects. These findings are in need of further replication since the included studies were of limited quality and small in size. Thus, there is currently no evidence available to support the use of ECT and insufficient evidence to fully support rTMS for the treatment of depressive symptoms in patients with schizophrenia.

Suicide

Suicide is an important cause of death in patients diagnosed with schizophrenia, being responsible for approximately 5% of mortality in these patients.[66,67] An in-depth review regarding the treatment and management of suicidality in patients with schizophrenia is beyond the scope of our review (e.g., see Harvey and Espaillat[66]). However, previous (and current) depressive episodes constitute an important risk factor for suicide and suicide attempts in patients with schizophrenia.[3–5,66] An earlier meta-analysis on this topic showed that previous depressive episodes are associated with (completed) suicide in patients with schizophrenia (odds ratio $[OR] = 3.03$, $CI_{95\%} = [2.06, 4.46]$). Here, we think it is important to

https://doi.org/10.1017/S1092852917000554 Published online by Cambridge University Press

mention that treatment with clozapine diminishes suicidality in patients with schizophrenia, as proved by the International Suicide Prevention Trial (InterSePT).[68] This was further established in a meta-analysis[69] based on five studies that compared clozapine to other agents. This meta-analysis showed a 2.9-fold reduction in completed suicides in patients treated with clozapine compared to other agents (pooled risk ratio = 2.9 favoring clozapine, $CI_{95\%} = [1.5, 5.7]$, $p = 0.002$).[69]

Discussion

In the present review, we aimed to provide an overview of the current evidence regarding treatment of depressive episodes and symptoms in patients diagnosed with schizophrenia. Depressive symptoms are often seen in patients with schizophrenia; however, prevalence rates vary widely.[1,2] There is a strong urgency to diagnose and treat depressive episodes, since they are associated with serious consequences. Regarding the treatment of depressive episodes and symptoms, we provided a practical stepwise approach when facing patients with schizophrenia and a depressive episode (Figure 1). In general, more research concerning the effectiveness of therapeutic interventions for depressive episodes in patients with schizophrenia is needed.[13] The overall interpretation of the results of the treatment studies is complicated by the use of different questionnaires, which were not always validated for diagnosing depressive episodes or assessing the severity of depressive symptoms in patients with schizophrenia. Additionally, the follow-up of these studies was often short, and there was considerable variation in the populations studied.

The recommendations of our review need to be considered in the light of the following limitations. First, it should be noted that this review cannot be considered a systematic review, though we aimed to provide a comprehensive overview of the most important studies on this topic. Second, differences between countries regarding the registration and availability of specific antipsychotic agents may reduce the choices described. However, we aimed to give an overview despite these differences. Consequently, we summarized the available international evidence, which should be combined with the availability and registration of antipsychotics per country.

Conclusions

Based on the current evidence, it is advisable to treat depressive episodes and symptoms in the acute phase of psychosis primarily with antipsychotics only, because depressive symptoms can also improve or disappear with the remission of a psychosis. If depressive symptoms persist (or develop later), it must be determined whether the depressive symptoms are the result of a too powerful and persistent dopamine D_2 receptor blockade. If so, decreasing the dosage of antipsychotics or switching to an antipsychotic with a weaker affinity for dopamine D_2 receptors (or a partial agonist) or those with other potential antidepressant properties may be appropriate. Current evidence suggests that sulpiride, clozapine, olanzapine, aripiprazole, quetiapine, lurasidone, and amisulpride have a modest beneficial effect on depressive symptoms in patients with schizophrenia compared with other antipsychotics. Physical activity is recommended when depressive symptoms are present, given its beneficial effects and the favorable balance between efficacy and side effects. If the depressive symptoms persist, and especially if there is a depressive episode diagnosed, a next step is recommended. Based on current evidence, it is difficult to advise whether to start CBT or add an antidepressant (e.g., SSRIs). When antidepressants are chosen, the possibility of pharmacological interactions reducing the antipsychotic effects and/or increasing side effects must be considered.

Disclosures

Drs. van Rooijen, Vermeulen, de Haan, and Ruhé hereby declare that they have no conflicts of interest to disclose.

REFERENCES:

1. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. *Schizophr Bull*. 2009; **35**(2): 383–402.
2. Siris SG. Depression in schizophrenia: perspective in the era of "atypical" antipsychotic agents. *Am J Psychiatry*. 2000; **157**(9): 1379–1389.
3. Karvonen K, Sammela HL, Rahikkala H, *et al*. Sex, timing, and depression among suicide victims with schizophrenia. *Compr Psychiatry*. 2007; **48**(4): 319–322.
4. Schwartz RC, Cohen BN. Psychosocial correlates of suicidal intent among patients with schizophrenia. *Compr Psychiatry*. 2001; **42**(2): 118–123.
5. Hawton K, Sutton L, Haw C, Sinclair J, Deeks JJ. Schizophrenia and suicide: systematic review of risk factors. *Br J Psychiatry*. 2005; **187**: 9–20.
6. Conley RR, Ascher-Svanum H, Zhu B, Faries DE, Kinon BJ. The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. *Schizophr Res*. 2007; **90**(1–3): 186–197.
7. Fervaha G, Agid O, Takeuchi H, Foussias G, Remington G. Clinical determinants of life satisfaction in chronic schizophrenia: data from the CATIE study. *Schizophr Res*. 2013; **151**(1–3): 203–208.
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, CA: American Psychiatric Association; 2013.
9. Heckers S, Barch DM, Bustillo J, *et al*. Structure of the psychotic disorders classification in DSM–5. *Schizophr Res*. 2013; **150**(1): 11–14.
10. Helfer B, Samara MT, Huhn M, *et al*. Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a

https://doi.org/10.1017/S1092852917000554 Published online by Cambridge University Press

systematic review and meta-analysis. *Am J Psychiatry*. 2016; **173**(9): 876–886.
11. Dauwan M, Begemann MJ, Heringa SM, Sommer IE. Exercise improves clinical symptoms, quality of life, global functioning, and depression in schizophrenia: a systematic review and meta-analysis. *Schizophr Bull*. 2016; **42**(3): 588–599.
12. The National Institute for Health and Care Excellence (NICE). *Psychosis and Schizophrenia in Adults*. London: NICE; 2014. https://www.nice.org.uk/guidance/cg178/evidence/full-guideline-490503565. Accessed August 15, 2016.
13. Upthegrove R, Marwaha S, Birchwood M. Depression and schizophrenia: cause, consequence or trans-diagnostic issue? *Schizophr Bull*. 2017; **43**(2): 240–244.
14. Castle D, Bosnac P. Depression and schizophrenia. *Adv Psychiatr Treat*. 2012; **18**: 280–288; http://apt.rcpsych.org/content/aptrcpsych/18/4/280.full.pdf. Accessed August 15, 2017.
15. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. *Schizophr Res*. 1990; **3**(4): 247–251.
16. Goldman RG, Tandon R, Liberzon I, Greden JF. Measurement of depression and negative symptoms in schizophrenia. *Psychopathology*. 1992; **25**(1): 49–56.
17. Lako IM, Bruggeman R, Knegtering H, *et al*. A systematic review of instruments to measure depressive symptoms in patients with schizophrenia. *J Affect Disord*. 2012; **140**(1): 38–47.
18. Hausmann A, Fleischhacker WW. Differential diagnosis of depressed mood in patients with schizophrenia: a diagnostic algorithm based on a review. *Acta Psychiatr Scand*. 2002; **106**(2): 83–96.
19. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*, 3rd ed. Arlington, VA: American Psychiatric Association; 2010.
20. Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. *JAMA Psychiatry*. 2015; **72**(12): 1172–1181.
21. Baker A, Bucci S, Lewin TJ, Richmond R, Carr VJ. Comparisons between psychosis samples with different patterns of substance use recruited for clinical and epidemiological studies. *Psychiatry Res*. 2005; **134**(3): 241–250.
22. Birchwood M, Iqbal Z, Upthegrove R. Psychological pathways to depression in schizophrenia: studies in acute psychosis, post psychotic depression and auditory hallucinations. *Eur Arch Psychiatry Clin Neurosci*. 2005; **255**(3): 202–212.
23. Anderson G, Maes M, Berk M. Schizophrenia is primed for an increased expression of depression through activation of immuno-inflammatory, oxidative and nitrosative stress, and tryptophan catabolite pathways. *Prog Neuropsychopharmacology Biol Psychiatry*. 2013; **42**: 101–114.
24. Meisenzahl EM, Seifert D, Bottlender R, *et al*. Differences in hippocampal volume between major depression and schizophrenia: a comparative neuroimaging study. *Eur Arch Psychiatry Clin Neurosci*. 2010; **260**(2): 127–137.
25. Birchwood M. Pathways to emotional dysfunction in first-episode psychosis. *Br J Psychiatry*. 2003; **182**: 373–375.
26. Tapp A, Kilzieh N, Wood AE, Raskind M, Tandon R. Depression in patients with schizophrenia during an acute psychotic episode. *Compr Psychiatry*. 2001; **42**(4): 314–318.
27. Tandon R, Goldman RS, Goodson J, Greden JF. Mutability and relationship between positive and negative symptoms during neuroleptic treatment in schizophrenia. *Biol Psychiatry*. 1990; **27**(12): 1323–1326.
28. de Haan L, van Bruggen M, Lavalaye J, Booij J, Dingemans PM, Linszen D. Subjective experience and D_2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. *Am J Psychiatry*. 2003; **160**(2): 303–309.
29. de Haan L, Lavalaye J, Linszen D, Dingemans PM, Booij J. Subjective experience and striatal dopamine D_2 receptor occupancy in patients with schizophrenia stabilized by olanzapine or risperidone. *Am J Psychiatry*. 2000; **157**(6): 1019–1020.
30. Mizrahi R, Rusjan P, Agid O, *et al*. Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D_2 receptors: a PET study in schizophrenia. *Am J Psychiatry*. 2007; **164**(4): 630–637.
31. Tandon R. Antipsychotics in the treatment of schizophrenia: an overview. *J Clin Psychiatry*. 2011; **72**(Suppl 1): 4–8.
32. Voruganti L, Awad AG. Neuroleptic dysphoria: towards a new synthesis. *Psychopharmacology (Berl)*. 2004; **171**(2): 121–132.
33. Furtado V, Srihari V, Kumar A. Atypical antipsychotics for people with both schizophrenia and depression. *Cochrane Database Syst Rev*. 2008;1): CD005377. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171386/. Accessed August 15, 2017.
34. Leucht S, Arbter D, Engel RR, Kissling W, Davis JM. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Mol Psychiatry*. 2009; **14**(4): 429–447.
35. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009; **373**(9657): 31–41.
36. Gotzsche P. Are new drugs for schizophrenia better than old ones? *Lancet*. 2009; **373**(9671): 1248; author reply 1249–1250.
37. Johnsen E. Review: second generation antipsychotics are a heterogeneous drug class. *Evid Based Ment Heal*. 2009; **12**(3): 90.
38. Lieberman JA, Stroup TS, McEvoy JP, *et al*. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005; **353**(12): 1209–1223.
39. Addington DE, Mohamed S, Rosenheck RA, *et al*. Impact of second-generation antipsychotics and perphenazine on depressive symptoms in a randomized trial of treatment for chronic schizophrenia. *J Clin Psychiatry*. 2011; **72**(1): 75–80.
40. Nasrallah HA, Cucchiaro JB, Mao Y, Pikalov AA, Loebel AD. Lurasidone for the treatment of depressive symptoms in schizophrenia: analysis of 4 pooled, 6-week, placebo-controlled studies. *CNS Spectr*. 2015; **20**(2): 140–147.
41. Galling B, Roldán A, Hagi K, *et al*. Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. *World Psychiatry*. 2017; **16**(1): 77–89.
42. Falkai P, Wobrock T, Lieberman J, *et al*. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry*. 2005; **6**(3): 132–191.
43. Werkgroep Richtlijn Schizofrenie. *Multidisciplinaire Richtlijn Schizofrenie*. Utrecht: Nederlandse Vereniging voor Psychiatrie; 2012.
44. Nikiforuk A. Targeting the serotonin 5-HT_7 receptor in the search for treatments for CNS disorders: rationale and progress to date. *CNS Drugs*. 2015; **29**(4): 265–275.
45. Bétry C, Etiévant A, Oosterhof C, Ebert B, Sanchez C, Haddjeri N. Role of 5-HT_3 receptors in the antidepressant response. *Pharmaceuticals*. 2011; **4**(4): 603–629.
46. Meltzer HY, Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. *Curr Opin Pharmacol*. 2011; **11**(1): 59–67.
47. Garnock-Jones KP. Brexpiprazole: a review in schizophrenia. *CNS Drugs*. 2016; **30**(4): 335–342.
48. Correll CU, Skuban A, Hobart M, *et al*. Efficacy of brexpiprazole in patients with acute schizophrenia: review of three randomized, double-blind, placebo-controlled studies. *Schizophr Res*. 2016; **174**(1–3): 82–92.

49. Rosenheck RA. Effectiveness versus efficacy of second-generation antipsychotics: haloperidol without anticholinergics as a comparator. *Psychiatr Serv*. 2005; **56**(1): 85–92.
50. Whitehead C, Moss S, Cardno A, Lewis G, Furtada V. Antidepressants for people with both schizophrenia and depression. *Cochrane Database Syst Rev*. 2002;(2): CD002305. doi: 10.1002/14651858.CD002305.
51. Terevnikov V, Joffe G, Stenberg JH. Randomized controlled trials of add-on antidepressants in schizophrenia. *Int J Neuropsychopharmacol*. 2015; **18**(9): 1–14.
52. Mao YM, Zhang MD. Augmentation with antidepressants in schizophrenia treatment: Benefit or risk. *Neuropsychiatr Dis Treat*. 2015; **11**: 701–713; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4370910/. Accessed August 15, 2017.
53. Kishi T, Hirota T, Iwata N. Add-on fluvoxamine treatment for schizophrenia: an updated meta-analysis of randomized controlled trials. *Eur Arch Psychiatry Clin Neurosci*. 2013; **263**(8): 633–641.
54. Kishi T, Iwata N. Meta-analysis of noradrenergic and specific serotonergic antidepressant use in schizophrenia. *Int J Neuropsychopharmacol*. 2014; **17**(2): 343–354.
55. van Dijk HG, Dapper EA, Vinkers CH. SSRIs en depressieve klachten bij schizofrenie: een systematische review [SSRIs and depressive symptoms in schizophrenia: a systematic review] [in Dutch]. *Ned Tijdschr Psychiatr*. 2017; **59**(1): 40–46.
56. Spina E, de Leon J. Clinically relevant interactions between newer antidepressants and second-generation antipsychotics. *Expert Opin Drug Metab Toxicol*. 2014; **10**(5): 721–746.
57. Flockhart DA. *Drug Interactions: Cytochrome P450 Drug Interaction Table*. Bloomington: Indiana University School of Medicine; 2007. http://medicine.iupui.edu/clinpharm/ddis/clinical-table. Accessed April 25, 2017.
58. Hiemke C, Baumann P, Bergemann N, *et al*. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry*. 2011; **44**(6): 195–235.
59. Leucht S, Helfer B, Dold M, Kissling W, McGrath JJ. Lithium for schizophrenia (Review). *Cochrane Database Syst Rev*. 2015;10): CD003834. doi: 10.1002/14651858.CD003834.pub3.
60. Wang Y, Xia J, Helfer B, Li C, Leucht S. Valproate for schizophrenia. *Cochrane Database Syst Rev*. 2016;(11): CD004028. doi: 10.1002/14651858.CD004028.pub4.d.
61. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2012; **8**(2): 114–126.
62. Wykes T, Steel C, Everitt B, Tarrier N. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. *Schizophr Bull*. 2008; **34**(3): 523–537.
63. Jones C, Hacker D, Cormac I, Meaden A, Irving CB. Cognitive behaviour therapy versus other psychosocial treatments for schizophrenia. *Cochrane Database Syst Rev*. 2012; **4**(4): CD008712. doi: 10.1002/14651858.CD008712.pub2.
64. Tharyan P, Adams C. Electroconvulsive therapy for schizophrenia. *Cochrane Database Syst Rev*. 2005;(2): CD000076. doi: 10.1002/14651858.CD000076.pub2.
65. Dougall N, Maayan N, Soares-Weiser K, McDermott L, McIntosh A. Transcranial magnetic stimulation for schizophrenia. *Cochrane Database Syst Rev*. 2015;(8): CD006081. doi: 10.1002/14651858.CD006081.pub2.
66. Harvey PD, Espaillat S.. Suicide in schizophrenia. In Koslow SH, Ruiz P, Nemeroff CB, eds. *A Concise Guide to Understanding Suicide Epidemiology: Pathophysiology and Prevention*, 1st ed.. Cambridge: Cambridge University Press; 2014: 406.
67. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry*. 2005; **62**(3): 247–253.
68. Meltzer HY, Alphs L, Green AI, *et al*. Clozapine treatment for suicidality in schizophrenia. *Arch Gen Psychiatry*. 2003; **60**(1): 82–91.
69. Hennen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. *Schizophr Res*. 2005; **73**(2–3): 139–145.