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REVIEW ARTICLE

Forms of antipsychotic therapy: improved individual outcomes under personalised treatment of schizophrenia focused on depression

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Abstract Depressive symptoms are common in schizophrenia and they can occur during any phase of the disorder. Early diagnosis, adequate differential diagnosis and promptly initiated interventions have been shown to reduce further deterioration of illness and to improve patients' quality of life. Common psychiatric rating scales for early detection of depressive symptoms in schizophrenia are Calgary Depression Scale for Schizophrenia and Hamilton Depression Rating Scale, but the most appropriate assessment instrument today regarding this topic is Calgary Depression Scale for Schizophrenia. Treatment of depression in schizophrenia consists of a combination of pharmacologic and psychosocial approach. Atypical antipsychotics have advantages over typical in reducing depressive symptoms in the context of schizophrenia. Most of the studies referred that clozapine, olanzapine, quetiapine and risperidone have an antidepressant spectrum of activity in patients with schizophrenia. Antidepressant augmentation of antipsychotic treatment in schizophrenic patients with depressive symptoms improves depressive symptomatology, particularly SSRI and SNRI augmentation.

Keywords Schizophrenia · Depressive symptoms · Calgary Depression Scale for Schizophrenia · Hamilton Depression Rating Scale · Atypical antipsychotics · Antidepressant augmentation

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Depressive symptoms in schizophrenia

Depressive symptomatology has been recognized as a feature of schizophrenia since Bleuler first introduced this term in 1908. He described depressive symptoms as either directly triggered by the very process of the disorder in the acute stages (i.e. as essential symptoms of schizophrenia) or as secondary symptoms of this disorder [1].

ICD-10 classification recognizes two diagnostic categories that encompass the coexistence of schizophrenia and depression: post-schizophrenic depression (F20.4) and schizoaffective disorder, depressed type (F25.1) [2]. In 1994, DSM classification defined a post-psychotic depression, which is called a post-psychotic depressive disorder of schizophrenia in DSM-IV classification [2, 3]. This is, however, a limited approach since there are other depressive conditions associated with schizophrenia that have not been covered by these diagnostic classifications [2].

Depressive symptoms in patients with schizophrenia may be observed during each phase of the disorder: the prodromal phase, the acute episode, the post-psychotic phase and the chronic phase, over the long-term course.

Depressive symptoms are frequent in the prodromal period but they are most commonly associated with the acute phase of the disease. These symptoms most frequently occur before the beginning of the treatment and in as many as half of the patients with first psychotic episode who have not started medication [4–6]. The close relationship between depressive symptoms and acute episodes supports the hypothesis that these symptoms are an inherent characteristic of schizophrenia and suggests that depressive symptoms and typical schizophrenic symptoms may result from one and the same pathophysiological process [5, 7–10].

In the course of the chronic phase of the disease, the incidence of depressive symptoms is lower and ranges from 4 to 25% [11–15].

Post-psychotic depression, according to the current DSM definition, is occurrence of symptoms during the residual phase of depression i.e. it follows after the symptoms which fulfill criterion A for schizophrenia have dissolved. Main clinical signs of post-psychotic depression are depressive affect and overall psychomotor retardation [3, 7, 16].

The majority of depressive symptoms that develop in various phases of schizophrenia fail to fulfill the criteria for major depressive episode of moderate or severe intensity. Results from one study [17] showed that in the subjects with schizophrenia the mild depression is predominant, being present in over a half of the subjects (52%); 46% of the subjects manifested moderate depression and 2% severe depression. This means that patients with schizophrenia more frequently develop depression of mild or moderate intensity. The majority of researchers have come to the same conclusion i.e. that mild and moderate depression are the commonest degrees of depression intensity in patients with schizophrenia, whereas severe depression is much less frequently reported in these patients [1, 18–22].

Data from literature show significant diversity in prevalence of depression in schizophrenic patients, ranging from 7 to 75%, depending on the definition for depression. In other words, depression may denote a description of mood, syndrome (cognitive, affective and neurovegetative symptoms) or a disorder (most commonly a major depressive disorder). The wide range of prevalence of depressive symptoms in schizophrenic patients is also due to the fact that the studies have been performed in different stages of the disease, that different methods have been applied, as well as the differences in the treatment conditions [21, 23–27]. Babinkostova and Stefanovski [17] concluded that the incidence of patients with depressive symptoms among the patients with schizophrenia was 54% i.e. out of 92 examined patients, 50 showed prominent depressive symptoms, assessed objectively using the 17-item Hamilton Rating Scale for Depression (score over 7). Johnson [8] showed that 70% from the sample of 30 subjects with schizophrenia had depressive episode in two years period and authors of another study [28] that were assessing depression in 70 patients with first schizophrenic episode (followed in 5 year period), concluded that 75% of the patients had major depressive disorder at the beginning of the schizophrenic episode. Depressive symptoms during the acute phase of the disorder are registered even before the start of the medication treatment and are present in about 50% of the unmedicated patients, but the percentage of the depressive symptoms in chronic schizophrenia (clinically stabile patients) is lower [29]. In one study only 9% of the examined patients with schizophrenia, that were clinically stabile and socially accepted, had depressive symptoms [12].

Depression in schizophrenic patients has been shown to be associated with family history of depression, early loss of a parent, higher doses of depot antipsychotics, although no significant difference between sexes has been demonstrated [6, 16, 18, 30].

Subotnik and coworkers [31] have found that depression in schizophrenia correlates with a positive family history for depression indicating a genetic liability. Conversely, other findings on a shared genetic liability between depression and schizophrenia are questioning the concept of genetic monocausality [32]. Many researchers report on a strong genetic predisposition and accentuate that patients with schizophrenia and depressive symptoms more frequently have first-line relatives with unipolar depression [7, 19, 32, 33]. One study [17] demonstrated that in patients with schizophrenia and depressive symptoms positive history of depression is predominant (in 22%) and 20% of them have a family history of schizophrenia.

Depressive symptoms play an important role in schizophrenia as these contribute to a further worsening of already existing deficit state and further exacerbation of illness. It is important to define and clinically assess such symptoms accurately as there is now increasing evidence that they can be treated successfully [7, 18, 34, 35].

Depression in schizophrenia is associated with poor overall outcome characterized by further deficits in psychosocial functioning, increased rate of relapse, more frequent and longer duration of hospitalizations, poor response to pharmacological treatments, significant work impairment, lower activity, dissatisfaction, less employment and poorer quality of life. Cognitive impairment, poor social functioning, substance abuse, negative attributional style and suicide/suicide attempts have also been reported [13, 16, 26, 32, 36]. This further contributes to the poor prognosis of the illness. Early diagnosis, adequate differential diagnosis and promptly initiated interventions have been shown to bring down the morbidity and mortality in schizophrenic patients with depressive symptoms, to reduce further deterioration of illness and to improve patients' quality of life [7, 18, 32].

Instruments for early detection of depression in schizophrenia

One of the most encouraging developments in schizophrenia management is the focused attention on aspects of the early detection of depressive symptoms and the importance of early interventions. Structured psychiatric clinical interview is the first diagnostic procedure that should be conducted for early detection of depressive symptoms in

patients with schizophrenia. Common psychiatric rating scales for clinical evaluation of presence and prominence of depressive symptomatology in schizophrenia are Calgary Depression Scale for Schizophrenia (CDSS) and Hamilton Depression Rating Scale (HDRS). The most appropriate dimensional assessment instrument today is Calgary Depression Rating Scale for Schizophrenia, but Hamilton Depression Rating Scale, from which some modified items are also included in the CDSS, is still widely used in clinical researches regarding this field. The Calgary Depression Scale for Schizophrenia is a clinician-rated depression scale specifically developed to assess the level of depression in schizophrenia [37, 38]. It has been extensively evaluated in both relapsed and remitted patients and appears sensitive to change. The CDSS is a nine item scale, each item scored from 0 to 3. This scale was derived from the HDRS and the Present State Examination. Factor analysis showed that the CDSS is unidimensional, has high internal consistency, and significant strong correlation with scores on the HDRS, Beck and BPRS depression scales. The scale is currently available in 35 languages. Authors of one study [9] compared the psychometric properties of the Calgary Depression Rating Scale and the Hamilton Depression Rating Scale for severity assessment of depression in schizophrenia. They investigated 119 inpatients with acute schizophrenia using the CDSS, the HDRS and a global 4-point Depression Severity Scale and they concluded that although both depression scales were correlated and highly effective in separating mild, moderate and severe depression, significant advantages emerged in favor of the CDSS. Thus the CDSS should be used particularly for a sensitive detection of mild (for example subthreshold) depression at early stages or to assess schizophrenic patients with severe depression who require through follow-up assessment and specific interventions [9]. Also Calgary Depression Scale for Schizophrenia seems to have more efficiency and ability to distinguish between depression, negative and extrapyramidal symptoms [39]. Collins et al. [40] demonstrated the methodological superiority of the Calgary Depression Rating Scale in the assessment of depressive symptoms in schizophrenia over scales developed for nonschizophrenic populations such as the Hamilton Depression Rating Scale and the Present State Examination.

Depression may also occur as part of a prodromal syndrome of schizophrenia. The interview for the Retrospective Assessment of the Onset of Schizophrenia is a semi-structured interview which can help determine whether this is the case [41].

The Psychotic Depression Scale (PDS) also can be useful for early detection of depression in schizophrenia [41]. It has been shown that there is no overlap between negative or extrapyramidal and depressive symptoms assessed by the PDS in schizophrenic patients. The Psychotic Depression Scale is a 32 item scale and each item is rated from 0 to 7.

Some authors use the Beck Depression Inventory (BDI), Montgomery-Asberg Depression Rating Scale and depression subscale of the Brief Psychiatric Rating Scale (BPRS) for evaluation of severity of depressive symptoms in schizophrenic patients [27, 42–44].

Kim et al. [45] assessed the following four depression scales for their diagnostic validity as measures of depressive disorder in schizophrenia: the Calgary Depression Scale for Schizophrenia (CDSS), the Beck Depression Inventory (BDI), the Hamilton Rating Scale for Depression (HAM-D), and the depression subscale of the PANSS (PANSS-D). Their results suggested that the CDSS may provide the best assessment for depression in patients with schizophrenia. Hausmann and Fleischhacer [46] also recommend the Calgary Depression Scale in schizophrenic patients with depressive symptoms and also Hillside Akathisia Scale to help establish the right diagnosis.

The Positive and Negative Syndrome Scale (PANSS), the Simpson-Angus Rating Scale (SARS), Barnes Akathisia Scale, Abnormal Involuntary Movement Scale (AIMS) and the Rating Scale for Extrapyramidal symptoms (ESRS) are used to differentiate depression from the negative and extrapyramidal symptom-related depressive phenomena in schizophrenia [1, 43, 45].

Differential diagnosis of depression in schizophrenia

There are a number of important differential diagnoses of depressive symptoms in schizophrenia. A major challenge in the clinical assessment of schizophrenia is the differentiation among depressive features, negative symptoms and neuroleptic side effects [47]. Differential diagnoses to consider also include schizoaffective disorder and organic conditions [16]. Depression may also be an understandable psychological reaction to schizophrenia. When all of these possibilities have been excluded, there is evidence that depression is perhaps most often an integral part of the schizophrenic process itself [5, 7, 8]. It is essential to differentiate between depressive symptoms and previous mentioned conditions and to manage them accordingly, in order to reduce the risk of further morbidity and mortality [18, 29].

A key issue in the differential diagnosis of depressive symptoms in patients with schizophrenia is disentangling the contribution of *negative symptoms*. Based on DSM-IV classification, negative symptoms of schizophrenia include affective flattening, alogia, avolition and anhedonia [41]. There is thus a great overlap between symptoms of

depression and negative symptoms of schizophrenia [48]. Diminished interest, pleasure, energy, or motivation along with psychomotor retardation and impaired ability to concentrate are relevant overlapping features. Prominent subjectively low mood, suggesting depression, and prominent blunting of affect, suggesting negative symptoms, are the two features which are most helpful in differentiating the two syndromes. Other symptoms that help to establish the diagnosis of depression include some of the main psychological features that occur in primary depressive illness, such as hopelessness, helplessness, worthlessness, guilt, anxiety and suicidal thinking. In schizophrenia, the biological features of the depressive syndrome, such as insomnia and retardation, are not always present—and if they are present, they can be more difficult to disentangle from negative symptoms and can be an intrinsic part of the illness separate from any superimposed depressive syndrome [7, 16, 32, 49].

Schizoaffective disorder has to be differentiated from schizophrenia. In DSM-IV schizoaffective disorder refers to patients in whom a full affective syndrome coincides with the florid psychotic syndrome but who also have substantial periods of psychosis in the absence of an affective syndrome [16, 32, 41].

Dopamine blockade by a neuroleptic drug could theoretically lead to anhedonia and perhaps, depression. Indeed, a state of *dysphoria* is commonly described by neuroleptic-treated patients.

Neuroleptic-induced *akinesia* is extrapyramidal side effect of neuroleptic treatment involving impaired ability to initiate and sustain motor behavior. Patients with this form of akinesia may or may not have the classical parkinsonian feature of decreased accessory motor movements. They act "as if their starter motor is broken," and they consequently appear to lack spontaneity. Akinesia may even protect against suicidal behavior, but not against suicidal thinking [16, 32].

Akathisia is another extrapyramidal side effect of neuroleptic treatment that can easily be confounded with depression. Patients with akathisia behave "as if their starter motor won't stop" and often experience this state as substantially dysphoric. Akathisia has been associated with both suicidal ideation and, perhaps as a consequence of a general tendency toward motor action, suicidal behavior [16, 32].

A number of *medical/organic factors* can present as depression in patients with schizophrenia. These include cardiovascular disorders, pulmonary infections, autoimmune diseases, anemia, cancer, metabolic, neurological and endocrine disorders. Various pharmaceuticals used in medical treatment such as β blockers, other antihypertensive agents, sedative hypnotics, antineoplastics, barbiturates, nonsteroidal anti-inflammatory drugs, sulfonamides, and indomethacin can cause depression as a side effect. Depression can also accompany the discontinuation of other prescribed medications such as corticosteroids and psychostimulants. Used or abused substances such as alcohol, cannabis, cocaine, or narcotics can contribute to depression either on the basis of acute use, chronic use, or discontinuation [16, 32].

Reactions to disappointments, a sense of loss or powerlessness, or awareness of psychotic symptoms or psychological deficits can certainly present as or contribute to depression, especially when depression follows closely after a stressful event or exacerbation of schizophrenia. Such reactions can be acute and chronic. An acute reaction to disappointment or stress is suggested by the parallel history of a recent compatible event. Chronic reactions to disappointment or stress have also been termed the demoralization syndrome. Differentiating such a syndrome from depression is not always easy. It is characterized by hopelessness and helplessness, with a lack of confidence and feelings of incompetence. Adjunctive psychotherapy, e.g. psychoeducational family therapy or cognitive behavioral therapy is the mainstay of helping patients to cope with demoralization syndromes [7, 16, 32].

In earlier times, the term *postpsychotic depression* was used to describe a dysphoric state that immediately followed a psychotic episode. DSM-IV now suggests that the term "postpsychotic depression" be used to describe depression that occurs at any time after a psychotic episode in schizophrenia, even after a prolonged interval [16, 32].

The appearance of a depression-like state as a *prodrome* of a new psychotic episode is a short-lived phenomenon, often lasting only a couple days to a couple weeks, before being superseded by more prominent and definitive psychotic symptoms [16, 32].

Treatment of depression in schizophrenia

The assessment and treatment of depressive symptoms in schizophrenia remains clinically challenging. The therapeutic goal is significantly to reduce the excess morbidity and mortality associated with depressive symptoms and to improve individual patients' quality of life [27]. A rational approach to treating depression in schizophrenia flows from considering the differential diagnosis [16]. The first steps are to exclude cases of schizoaffective disorder and to treat them appropriately, to treat any medical conditions that are present and to consider the possibility of substance misuse as a contributing factor. Any evidence that antipsychotic medication is producing akinesia should lead to a reduction in dosage and/or the introduction of anticholinergic medication. Akathisia, with its concomitant feeling of dysphoria, should always be considered in patients describing subjec-

tive mood disturbance. The akathisia/dysphoria syndrome, if present, requires active management. Use of an anticholinergic drug is generally effective. Other options include β-adrenoceptor antagonists (e.g. propranolol), a benzodiazapine or a change in antipsychotic drug. If the above factors have been addressed and the clinician is sure that negative symptoms are not being mistaken for depressive symptoms, then the treatment options are largely dictated by the stage of the illness. During acute episodes, depressive symptoms should not be treated separately from other symptoms and are likely to resolve as the episode resolves. In the majority of cases increased antipsychotic medication, increased psychosocial support and, if necessary, hospitalization, will successfully treat depression as well as positive symptoms. Moller HJ [50] in his comprehensive review reported that besides the potential risk of inducing depressive symptoms, the first generation antipsychotics seem to have a certain antidepressive effect, in the sense that depressive symptoms secondary to positive symptoms can be alleviated with the reduction of positive symptoms. The second generation antipsychotics seem to have no risk to induce depressive symptoms, appear to have better antidepressive effect and therefore represent a better option for the treatment of depressive symptoms in schizophrenic patients. There is accumulating evidence that the new atypical antipsychotics are more efficacious in treating the depression associated with an acute episode [51]. Olanzapine, for example, is superior to haloperidol in this regard [42, 52, 53]. Other atypicals, such as risperidone, ziprasidone and zotepine, may also have a mood-elevating effect. The atypicals may prove to be useful for the depression that emerges during the chronic phase of the illness. Clozapine has been shown to reduce hopelessness, depression and suicidality in patients with chronic schizophrenia [54–59]. Clinicians should consider switching patients to an atypical antipsychotic if they are not taking one already [16]. In addition, dose optimization needs to be targeted towards depressive as well as positive and negative psychotic symptoms [16, 41, 60]. Administration of antidepressants in combination with antipsychotics seems to be a meaningful option to treat depressive symptoms in schizophrenia. Data collected show that treatment with antidepressants in addition to antipsychotic treatment is only of limited benefit [25, 61]. This might especially be the case in combining antidepressants with second generation antipsychotics. The risk of inducing positive symptoms by antidepressants has to be considered [50]. Despite this there is a good case for the prescription of an antidepressant when the patient has persistent depressive symptoms and is not in a phase of acute illness [60]. Recent studies have shown that antidepressants are prescribed by clinicians to 30% of inpatients and 43% of outpatients of all ages with schizophrenia and depressive symptoms [62]. SSRIs when compared with the triciclics appear to be the treatment of choice considering the side effects and efficacy [16, 18]. One needs to start with a low dose and then cautiously titrate upward to reduce depressive symptoms. If remission is not achieved after adequate treatment duration (8–12 weeks) or with an adequate dose (similar to that used for major depression without schizophrenia), switching to another agent or adding augmenting therapy is recommended.

Whitehead and coworkers [63] in their systematic review of antidepressants for the treatment of depression in patients with schizophrenia concluded that the meta-analysis of the 5 suitable trials found that using antidepressants was beneficial and there was no evidence that antidepressant treatment led to a deterioration on psychotic symptoms in the trials. On the other hand, Zisook et al. [24] in their research paper compared the patients who were taking antidepressant medications to those who were not, on the 17-item Hamilton depression scale total score and on the percentage of subjects classified as minimally, mildly and moderately to severely depressed and they found no difference between groups on any of these measures. Also they stated that correlation between severity of depression and daily neuroleptic dose was low, negative and nonsignificant.

Siris [64] reported that long-term maintenance treatment with antidepressants would be beneficial for patients who responded favorably to the initial treatment. He stated that besides the fact that some patients were resistant and even refractory to pharmacological treatment, it would be also probable that therapists found it difficult to administer high doses of antidepressants to these patients, because of the fear of recidivation of psychotic symptoms which lead to the use of subtherapeutical doses of antidepressants making it difficult to cute this syndrome and to a subsequent chronification of the condition.

Table 1 presents the main results from the conducted studies for antidepressant augmentation in schizophrenic patients with depressive symptoms. Results from the several studies showed that citalopram augmentation of antipsychotic treatment in patients with schizophrenia and depressive symptoms improves depressive symptomatology [65–67]. Authors of several studies evaluated addition of venlafaxine to antipsychotic treatment in schizophrenic patients with depression and they concluded that the dual mechanism of this drug may contribute to a more complete antidepressant response than the single mechanism of selective serotonin reuptake inhibitor medication [68, 69].

Psychosocial therapies in combination with pharmacotherapy are very important additional treatments needed for this patient population in order to alleviate residual symptoms and to improve social functioning and quality of life [16, 41]. Cognitive therapy also has been shown to

Table 1 Antidepressant augmentation in schizophrenia with depressive symptoms

Study	Year	Study design	Type of antidepressant	Main results
Kasckow et al.	2010	Randomized, placebo-controlled	Citalopram	Improvement in depressive symptoms, negative symptoms, social functioning and quality of life with citalopram
Zisook et al.	2009	Double-blind, randomized, placebo-controlled	Citalopram	Significantly more effective than placebo in improving depressive symptoms
Ciobanu et al.	2008	Randomized, prospective	Venlafaxin, fluvoxamine, mirtazapine	Improvement in depressive symptoms with all antidepressants, quicker response with venlafaxine
Mazeh et al.	2004	Open-label study	Venlafaxine	Improvement in depressive symptoms
Addington et al.	2002	Randomized, double-blind, prospective, placebo-controlled	Sertraline	Limited benefit of added sertraline
Kasckow et al.	2001	Open-label study	Citalopram	Significant improvement in HAMD scores
Mullholand et al.	1997	Double-blind, placebo-controlled	Sertraline	No significant benefit of added sertraline (limited benefit)

be effective, although its role in the treatment of depressive symptoms in particular has not been studied [7, 35, 41, 70].

Antipsychotics and depression in schizophrenia

Several different concepts have been employed to explain the role of antipsychotics in schizophrenic patients with depression. It has been suggested that antipsychotics cause a so called "pharmacogenic depression" by a direct action on the dopaminergic system affecting the pleasure and reward pathways [32, 71, 72]. Akinesia and other extrapyramidal adverse effects of antipsychotics, excluding tremor, accompanied by depressed mood or dysphoria may also mask depression. The so called "akinetic depression" accounts for 10–15% of depressive symptoms and it includes a reduced level of activity as well as anhedonia, responding to anticholinergic medication. Certain authors suggest that iatrogenic depression associated with the extrapyramidal adverse reactions of the antipsychotic treatment is less common nowadays than it used to be in the past [18, 73, 74].

Although certain observations support the hypothesis of a "pharmacogenic depression", suggesting that antipsychotics are responsible for several cases of depression in schizophrenia, the evidence against it carries more weight [75, 76]. Depression may also occur in patients with schizophrenia who do not receive antipsychotics, and when antipsychotics are discontinued, the proportion of patients who need antidepressants is increased. Several studies have demonstrated that there are no differences between depressed and non-depressed patients with schizophrenia in terms of the dose of the antipsychotic that they received [7, 24, 27].

There are several reasons to suspect that schizophrenia treated with atypical antipsychotics may prove to be a different condition than schizophrenia treated with conventional neuroleptics from the point of view of depression. Atypical antipsychotic agents have a greatly reduced extrapyramidal side effect profile. Since akinesia and akathisia figure prominently in the differential diagnosis of depression in schizophrenia, this issue could be responsible for a different expression of depression in schizophrenia. Since atypical agents seem to rely much less exclusively on dopaminergic blockade for their therapeutic activity, they might circumvent the mechanism of neuroleptic-induced dysphoria that could contribute to the depression syndrome. Atypical antipsychotics have frequently been reported to be superior to standard neuroleptics in the treatment of negative symptoms, which can sometimes appear similar to depression and it is possible that atypical antipsychotic agents have direct antidepressant activity on their own. Combinations of any or all of these effects could potentially be responsible for more favorable depression profiles in patients treated with atypical antipsychotics versus conventional neuroleptics [16, 23, 28, 48].

The broad array of affinities for receptor sites attributable to the novel atypical antipsychotic agents (including a wide array of 5-hydroxytryptamine [5-HT], dopamine [other than D2], and muscarinic sites as well as α1-noradrenergic and histamine-1 receptor sites) suggest a variety of potential mechanisms through which atypical antipsychotics might exercise antidepressant effects and that their antipsychotic and antidepressive effects are mostly based on different pharmacological mechanisms [16, 77].

The dopamine deficit in cortical prefrontal areas was a unifying hypothesis to explain both some symptoms of depression and negative symptoms of schizophrenia.

Studies in animal confirm this view and show that the association of an atypical antipsychotic drug and an SSRI (olanzapine plus fluoxetine) increases synergistically the release of dopamine in prefrontal areas [48].

Harrow and coworkers [74] observed that depression in schizophrenia correlated with first generation antipsychotic treatment and suggested that depression is associated with anhedonia and mesolimbic dopaminergic dysfunction, which may be potentiated by dopaminergic blockade induced by typical antipsychotics. Although depressive symptoms are described in neuroleptic-naive schizophrenic patients having a first episode, patients receiving conventional antipsychotic drugs may have higher rates [41, 42]. By contrast second-generation antipsychotics may have some efficacy for depressive symptoms over improvement in positive and negative symptoms, perhaps due to their direct antidepressant effects [55, 77]. On the other hand, as reported by Freudenreich et al. [23] there was no difference in depressive symptoms between the different classes of antipsychotics used (typical, atypical antipsychotics and a clozapine group). Also this study found that HAMD scores did not vary between the group receiving antidepressant therapy (22% of the examinees) and the rest of the sample, nor did PANSS scores. Authors of this study stated that treatment with second-generation antipsychotics did not confer benefit compared to first-generation antipsychotics with regard to depressive symptoms. Also they concluded that mood stabilizers were associated with less depression. Similar to this, Mauri and coworkers [27] in their article refer to comparison of first and second generation antipsychotics did not found that atypical antipsychotics as a class are more effective on the depression dimension during the course of schizophrenia than typical ones. Their results showed that none of the drugs seemed to have a real depressogenic effect. They did not confirm correlation between the severity of the depressive symptoms and the doses of the antipsychotics. They referred that all of the typical and atypical antipsychotics alone improved depressive symptoms, but the improvement was statistically significant in cases of fluphenazine decanoate, haloperidol, olanzapine, risperidone and l-sulpiride, which partially conflicts with some published data concerning the depressogenic effect of classical neuroleptics ("pharmacogenic depression"), especially fluphenazine decanoate and haloperidol.

Aguilar et al. [54] in their article stated that second-generation antipsychotic agents appear to have a better potential for preventing suicide in schizophrenia. The strongest and perhaps unique evidence has been shown for clozapine, which seems to have a clinically relevant advantage over both first- and second-generation antipsychotics for reducing suicidality. Suggestion that suicidality may be reduced in schizophrenic patients receiving clozapine is also confirmed by other authors [55–59].

Table 2 presents the main results from the studies that evaluated effects of the different types of antipsychotics on depression in schizophrenic patients. The strongest evidence for the benefit of atypical antipsychotics in the treatment of concurrent depressive symptoms in schizophrenic patients comes from trials of olanzapine and ziprasidone. First randomized double-blind study regarding efficacy and tolerability of atypical antipsychotics in the treatment of patients with schizophrenia and depressive symptoms, compared olanzapine with ziprasidone therapy in these patients. Their results showed that for up to 8 weeks patients treated with olanzapine or ziprasidone had significant improvements on Calgary Depression Scale for Schizophrenia, but treatment group differences were not statistically significant. Over 24 weeks, olanzapine treated patients showed significantly greater improvements in depressive symptoms and GAF scores [43]. In a comparison of olanzapine and ziprasidone for the 6-week treatment of patients with acute schizophrenia or schizoaffective disorder, both antipsychotics were efficacious in improving positive, negative and depressive symptoms without significant treatment differences, suggesting that ziprasidone was as efficacious as olanzapine in improving the Calgary Depression Scale for Schizophrenia score [78]. Another study that compared olanzapine and ziprasidone in patients with schizophrenia demonstrated significantly greater improvement in olanzapine-treated patients on positive, negative and depressive symptoms at the 28-week study, suggesting that treatment response may differentiate over longer treatment durations [79]. In a systematic review and meta-analysis, Leucht et al. [80] reported that olanzapine was found to have superior efficacy compared to aripiprazole, quetiapine, risperidone and ziprasidone. In addition, clozapine had superior efficacy compared to zotepine and risperidone when clozapine doses at 400 mg a day were used.

Tollefson et al. [42] in their double-blind, controlled clinical trial compared the use of olanzapine with that of haloperidol for up to 52 weeks of treatment in patients with schizophrenia, schizoaffective and schizophreniform disorder and they referred that the use of olanzapine was statistically significant superior to that of haloperidol in the early improvement of depressive signs and symptoms evaluated with the Montgomery-Asberg Depression Rating Scale and there was no dose difference based on the depressive signs and symptoms. Similar results presented other studies that evaluated the efficacy of olanzapine compared to risperidone and haloperidol in the treatment of schizophrenia-related depressive symptoms [52, 53].

Most studies referred that olanzapine, risperidone or ziprasidone may have an antidepressant spectrum of activity in patients with schizophrenia [16, 43, 56, 78–80]. One trial [44] presented data suggesting that risperidone

Table 2 Effects of antipsychotics on depression in schizophrenia

Study	Year	Study design	Type of antipsychotic medication	Main results
Kinon et al.	2006	Randomized, double-blind	Olanzapine vs. ziprasidone	Olanzapine showed significantly greater improvement in depressive symptoms
Breier et al.	2005	Randomized, controlled, double-blind	Olanzapine vs. ziprasidone	Significatntly greater improvement in olanzapine-treated patients on depressive, positive and negative symptoms
Mergui et al.	2005	Case study	Quetiapine	Quetiapine-associated depression in schizophrenic patients
Simpson et al.	2004	Randomized, controlled, double-blind	Ziprasidone vs. olanzapine	Both antipsychotics were efficacious in improving depressive, positive and negative symptoms
Emsly et al.	2003	Randomized, controlled	Quetiapine vs. haloperidol	Quetiapine showed greater reduction in depressive scores
Tollefson et al.	1999	Double-blind, randomized	Olanzapine vs. risperidone	Olanzapine was superior to risperidone in alleviating depression
Tollefson et al.	1998	Randomized, controlled, double-blind	Olanzapine vs. haloperidol	Olanzapine was associated with a significantly higher improvement of depressive symptoms
Ceskova et al.	1993	Double-blind, randomized	Risperidone vs. haloperidol	Risperidone was inferior to haloperidol in terms of BPRS depression factor improvement

may be inferior to haloperidol in terms of BPRS anxiety/depression factor improvement. One research study [53] suggested that olanzapine was superior to risperidone in alleviating depression.

It is noteworthy that quetiapine has been found to have an antidepressant effect. In one study patients suffering from schizophrenia derived greater reduction in depressive scores in comparison to haloperidol [81]. In another study quetiapine was found to improve symptoms of depression, over the course of long term use [82]. Contrary to this the authors of one case report [47] presented a quetiapine-associated depression in schizophrenic patients. It is the first description of depression associated with quetiapine treatment and their authors suggested that atypical antipsychotics may be a cause of depression, but further data based on controlled studies are required before one can draw definitive conclusions.

In a recent review by Furtado et al. [83] the authors included randomized clinical trials of atypical antipsychotic drugs used for the treatment of patients with a diagnosis of both schizophrenia and depression. One trial found no significant differences between quetiapine and haloperidol for the outcome of less than 50% reduction in PANSS score [81]. In a second trial, sulpiride was compared to chlorpromazine; the group treated with sulpiride had more reductions in depressive symptoms based on scores of the Comprehensive Psychopathologic Rating Scale [84]. In a third trial, Jasovic [58] used Hamilton Depression Rating Scale scores to compare clozapine to any other antipsychotic plus an antidepressant; use of clozapine lead to greater reductions in Hamilton symptoms.

Authors of this review article conducted a cross-sectional study which involved 92 patients with schizophrenic disorder, 50 of whom with prominent depressive symptoms (total score >7 on the 17-item Hamilton Rating Scale for Depression) with the aim of evaluation of the effect of the different type of antipsychotic treatment administered on the depression intensity in schizophrenic patients. The group was created by randomization of inpatients and outpatients of both sex who were treated at the University Clinic of Psychiatry within a period of 6 months. For the purposes of the study, the test group was subsequently subdivided in several subgroups according to the type of used antipsychotic therapy (oral/depot; typical/atypical; olanzapine/risperidone/clozapine). 60% of the examinees were taking oral antipsychotics and 40% of them were administered depot antipsychotic treatment (long-acting atypical antipsychotic).

According to the treatment with different classes of oral antipsychotics (typical/atypical), the results indicated that 20% of the oral antipsychotic group were taking typical antipsychotics (haloperidol), whereas 80% of these subjects received atypical oral antipsychotic medications. From the atypical oral antipsychotic subgroup 37.5% were taking olanzapine, same percentage were on risperidone and 25% were on clozapine.

The results obtained from this study suggested that subjects who received depot antipsychotics had less severe depression in comparison to the subjects who received oral antipsychotics, although this difference, when tested using the t-test for independent samples, was not statistically

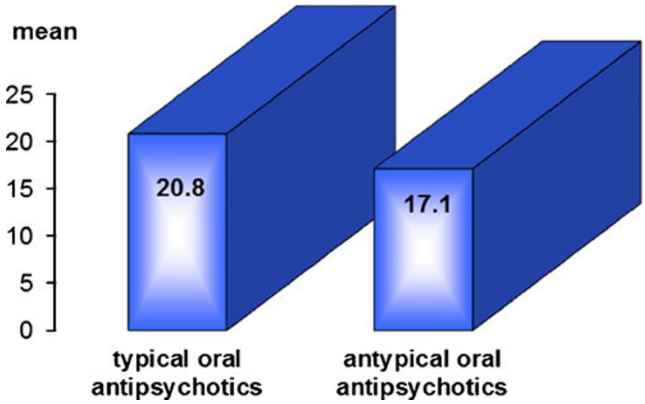

Fig. 1 Total score on HAMD - typical vs. atypical oral antipsychotics

significant. Contrary to this, some earlier studies in this direction showed a positive relationship between the intensity of depression and a higher dose of depot antipsychotics in patients with schizophrenia [6, 7, 18, 30].

Further results of this study showed that subjects treated with depot antipsychotics had statistically significant lower depression intensity in comparison to the subjects treated with typical oral antipsychotics.

Figure 1 presents the difference in depression intensity between the subgroup with typical oral antipsychotics and the subgroup with atypical oral antipsychotics.

The tested difference in depression intensity between the subgroups treated with different types of oral atypical antipsychotics in this study showed that the subjects treated with clozapine had statistically significant lower depression intensity in comparison to the subjects treated with risperidone (Fig. 2) and also they had lower depression intensity in comparison to the subjects treated with olanzapine, but statistically not significant. The patients treated with olanzapine had lower depression intensity in comparison to those treated with risperidone, but statistically not significant.

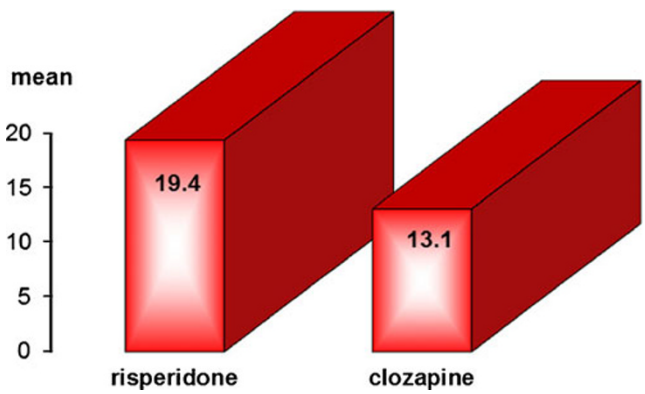

Fig. 2 Total score on HAMD - risperidone/clozapine

Conclusions and outlook

Depressive symptoms are common in patients with schizophrenia and they can occur during any phase of the disorder. They are associated with a variety of undesirable outcomes and are a significant cause of higher rates of morbidity and mortality in these patients. Early diagnosis, adequate differential diagnosis and promptly initiated interventions have been shown to bring down the morbidity and mortality in schizophrenic patients with depressive symptoms, to reduce further deterioration of illness and to improve patients' quality of life. Structured psychiatric clinical interview is the first diagnostic procedure that should be conducted for early detection of depressive symptoms in patients with schizophrenia. Common psychiatric rating scales for clinical evaluation of presence and prominence of depressive symptomatology in schizophrenia are Calgary Depression Scale for Schizophrenia (CDSS) and Hamilton Depression Rating Scale (HDRS). The most appropriate dimensional assessment instrument today is Calgary Depression Rating Scale for Schizophrenia, but Hamilton Depression Rating Scale, from which some modified items are also included in the CDSS, is still widely used in clinical researches regarding this field. The Calgary Depression Scale for Schizophrenia is a clinician-rated depression scale specifically developed to assess the level of depression in schizophrenia. The CDSS showed higher sensitivity in detecting mild and severe depression. The results can help clinicians to initiate psychosocial interventions and medications. The Psychotic Depression Scale (PDS) also can be useful for early detection of depression in schizophrenia. It has been shown that there is no overlap between negative or extrapyramidal and depressive symptoms assessed by the PDS in schizophrenic patients. The Positive and Negative Syndrome Scale (PANSS), the Simpson-Angus Rating Scale (SARS), Barnes Akathisia Scale, Abnormal Involuntary Movement Scale (AIMS) and the Rating Scale for Extrapyramidal symptoms (ESRS) are used to differentiate depression from the negative and extrapyramidal symptom-related depressive phenomena in schizophrenia.

An appropriate treatment approach to depression in schizophrenia begins with a consideration of the differential diagnostic possibilities. Depressive symptoms should be adequately differentiated from negative symptoms, schizoaffective disorder, neuroleptic induced side effects, reactions to disappointments and a number of medical/organic factors. Treatment of depressive symptoms in schizophrenia is accomplished through a combination of pharmacologic and psychosocial approach. Atypical antipsychotics have advantages over typical in reducing depressive symptoms in the context of schizophrenia. They do not induce depressive symptoms, which is known side effect of

traditional neuroleptics. Their antidepressive potential is presumably related to their pharmacological mechanisms, which differ from those of traditional neuroleptics. The benefits of atypical antipsychotics might be of relevance also for reducing the risk of suicidality. From a pharmacologic perspective, the treatment of depressive symptoms in patients with schizophrenia requires antipsychotics and antidepressants. A lot of studies referred that clozapine, olanzapine, quetiapine and risperidone have an antidepressant spectrum of activity in patients with schizophrenia. Clozapine has been shown to reduce suicidality in schizophrenic patients with depression. Most of the studies showed that antidepressant augmentation of antipsychotic treatment in patients with schizophrenia and depressive symptoms improves depressive symptomatology, especially SSRI and SNRI augmentation. Implementing psychosocial interventions in combination with pharmacotherapy is also an important part of patients' treatment plan.

We can conclude that in patients with schizophrenia early detection of depressive symptoms can be obtain conducting structured psychiatric clinical interview and using the appropriate assessment instruments regarding this topic in everyday psychiatric clinical practice. In schizophrenic patients with depressive symptoms preferable pharmacological treatment include use of atypical antipsychotics and antidepressants augmentation, particularly SSRI and SNRI. Pharmacological treatment in these patients should be combined with psychosocial interventions. Early diagnosis and promptly initiated interventions have been shown to reduce further deterioration of illness and to improve patients' quality of life.

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