REVIEW ARTICLE

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Depression in Patients with Schizophrenia

Prevalence, and Diagnostic and Treatment Considerations

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Abstract

Depression is a common comorbid syndrome in patients with schizophrenia. A review of the literature highlights the multitude of different expressions used to describe depression in this context. This fact exemplifies the diagnostic and therapeutic inconsistencies found in literature.

Former generations of psychiatrists considered that antidepressants could provoke psychotic symptoms. Although the evidence is still tentative, it appears to be current common practice for most psychiatrists, having ruled out confounding conditions such as extrapyramidal motor symptoms and negative symptoms, to prescribe antidepressant agents to patients who show depressive symptoms. There are controlled clinical trials that have demonstrated that tricyclic antidepressants are effective in the treatment of depression in patients with schizophrenia. In contrast, the newer antidepressants have yet to be tested in large scale controlled studies. Possible interactions between antipsychotics and antidepressants must be considered when these two classes of agent are prescribed.

Monotherapy with novel antipsychotics may be a treatment option, as some such as zotepine, olanzapine and risperidone have shown advantages over traditional antipsychotics in reducing depressive symptoms in patients with schizophrenia. Others have some pharmacological properties that resemble antidepressant drugs.

1. The Diagnostic Dilemma

A multitude of different expressions have been used in the evolutionary course of psychiatry to describe depressive states in patients with schizophrenia. Although increasing knowledge of the nature of depression in schizophrenia has evolved over recent decades, nosological agreement has been difficult to achieve and the different approaches to the diagnosis of negative symptoms and depression are still inconsistent. The constructs used to describe depression in schizophrenia are not well defined and their empirical basis appears to be rather weak. The list of terms used to describe such depression includes: postpsychotic depression, depressive neurotic response, pharmacogenic symptom shift, pharmacogenic depression, schizoaffective disorder, drug-induced depression, post-remissive exhaustion syndrome, depressive prodromal state, akinetic depression, drug-induced dysphoria, revealed depression, and the atypical akinesia syndrome.

Historically, many of these terms characterise the nosological school from which they originated. After the descriptive classification by Kraepelin,[1] the concept of depression in schizophrenia became largely dominated by psychoanalysis. All psychiatric symptoms were more or less considered to be reactions to a harmful psychosocial environment. 'Depressive neurotic reaction' was the term used at that time.

Successive redefinitions of schizophrenia started with Mayer-Gross[2] and continued with Schneider[3] and Berner et al.[4] who excluded depression from the core symptomatology of schizophrenia. Postpsychotic depression was, however, recognised. The concept of postpsychotic depression encompassed the post-remissive exhaustion syndrome,[5] which assumed that depression may occur as a reaction to being ill, when insight returns after the acute psychotic episode. It may be a psychological response to the awareness of illness, or a fear of relapse.

In 1970, Shanfield and co-workers[6] were the first to break with the traditional notion that depressive symptoms in schizophrenia are limited to the postpsychotic period. Despite this, postpsychotic depression was included as a diagnosis in the tenth edition of the International Classification of Diseases (ICD-10)[7] and appeared in the appendix of DSM-IV.[8] In 1981, three research groups reported studies which showed that depressive symptoms are regular features of schizophrenia, seen most frequently in the acute florid phase of the illness and gradually becoming less prevalent during remission.[9-12] The term 'revealed depression' was coined.[13]

1.1 Is Depression Drug Induced?

There is still inconsistency in the literature concerning the role antipsychotics play in the aetiology of depression. The background to this discussion is the fact that antipsychotics antagonise dopamine receptors. As dopaminergic pathways are involved in the reward system,[14-16] antipsychotics are likely to have a negative influence on reward or pleasure and result in anhedonia that may mimic depressive states.[17-21] Helmchen and Hippius[17] originally proposed the term 'syndromegenetic triad' (Syndromgenetische Trias) to describe the complexity of depressive syndromes seen in patients receiving antipsychotics. Under this heading, they included pharmacologically induced conditions, morbogenic (illness inherent) and individual factors. Galdi[22] subsequently coined the term 'neuroleptogenic' or 'pharmacogenic' depression. Most German psychiatrists favoured this concept, while most English psychiatrists did not.

Hirsch et al.[23] stated that depressive symptoms are less common in severely ill inpatients with chronic schizophrenia than would be predicted if these symptoms were manifestations of negative symptoms or drug-induced parkinsonism. Their study failed to support the view that long term depot antipsychotic medication plays an important role in the genesis of depression. This idea was supported by findings from Johnson[9]. In a sample of patients with chronic schizophrenia, depression was more common in those patients receiving higher doses of depot antipsychotics than in those receiving lower doses.[10] Johnson[10] stated that a

significant part of depression is not drug related, but that antipsychotics could play a role in the aetiology of depression.

Barnes et al.[24] found depressed mood in 13% of a group of 194 inpatients with chronic schizophrenia. Patients were assessed for depression using Present State Examination ratings. Those with a rating of 1 (moderate) or 2 (severe) for depressed mood were matched for age, duration of illness and gender with patients scoring 0 (controls). There were no significant differences in terms of negative symptoms, parkinsonism, tardive dyskinesia, anticholinergic medication or current dose of antipsychotic drug between the controls and those patients with depression. This suggested that depression was not related to drug treatment, nor was it a direct manifestation or misinterpretation of negative symptoms. Siris,[25] in a review on depression and schizophrenia, concluded that it is improbable that antipsychotics are a cause of depression in patients with schizophrenia, as the data are not conclusive. However, antipsychotics might be a factor in some individual cases of depression.

The possible contribution of drugs to mood disorders in schizophrenia is further complicated by the existence of a syndrome resembling depressive illness which occurs in association with drug-induced parkinsonism.[26] Antipsychotics may generate parkinsonian symptoms such as bradykinesia and loss of spontaneity with emotional withdrawal that can mimic depression. The symptoms of this so called 'akinetic depression', a term coined by Van Putten and May,[26] should respond to anticholinergic drugs.

2. Clinical Relevance of Depressed Mood in Schizophrenia

Bleuler[27] and many other psychiatrists believed that the advent of depression during the course of schizophrenia is a good prognostic sign. Subsequent empirical research seemed to support this view.[28-30] However, more recent studies found that depression is associated with an increased rate of relapse,[31] longer duration of hospitalisation,[32,33] poor response to pharmacological treatments,[34] chronicity, poor social functioning,[35] and suicide.[36,37]

The onset of depression often signals impending relapse. Herz[38] found that depressive symptoms were frequently noticed by patients and their families just before rehospitalisation. Similarly, in a 2-year prospective study, Mandel et al.[31] found that relapse occurred in 64% of patients with schizophrenia who developed depression compared with 19% of those who were depression-free.

Depression also predisposes patients with schizophrenia to suicide. Suicide in schizophrenia occurs at a rate 20 times that of the general population; approximately 1 of every 10 patients with schizophrenia commits suicide.[39] The majority of these patients are depressed at the time of suicide. Roy[36] found that over 50% of patients with schizophrenia who killed themselves had experienced a past episode of depression and were depressed according to DSM-III[40] criteria at their last episode of contact. These findings were confirmed by Radomsky et al.[41]

3. Prevalence of Depression in Schizophrenia

The prevalence of depressive symptoms in schizophrenia depends on whether depression is assessed during the acute or the chronic phase of schizophrenia. Reported prevalence has varied from a low of 7%[42] to a high of 65%.[9,10] Gross and Huber,[43] in a study in Bonn, Germany, described depressive symptoms at any time during the course of the illness in 12% of patients with schizophrenia who initially showed only symptoms of schizophrenia. The data from a prospective 4.5- and 7.5-year follow-up study by Sands and Harrow[44] demonstrated depression in 30 to 40% of patients. A subgroup even experienced repeated depressive episodes. In strictly diagnosed patients with schizophrenia, Martin and colleagues[45] reported a lifetime prevalence of 65% for a DSM-III–diagnosed major depressive episode.

This broad range of incidence and prevalence rates indicates that different investigators may have investigated different syndromes in different

patients using different methods. Clinical features of the negative syndrome of schizophrenia encompass poverty of thought and speech, blunted affect, decreased motor activity, apathy and avolition, and diminished interpersonal interaction. It was shown that 'blue mood' and depressed cognition are not related to the negative syndrome.[46] Because of overlapping features, in terms of cognitive impairment, some authors have attempted to design a reliable tool to separate depressive from negative items. The high prevalence of subjective awareness of schizophrenic deficits motivated Liddle and Barnes[47] to develop the Subjective Experience of Deficits in Schizophrenia (SED) scale. They tried to delineate the nature of schizophrenia in order to help patients cope with the disease. They concluded that anhedonia and a lack of drive and energy were correlated with depression in the assessed group of patients with chronic schizophrenia, and suggested a phenomenological similarity between depression in schizophrenia and depressive illness.

Newcomer et al.[48] used existing tools, namely the Brief Psychiatric Rating Scale (BPRS) depression subscale and the Hamilton Rating Scale for Depression (HAM-D), and concluded that depressive symptoms as well as positive and negative items can be reliably measured with these instruments. In 1990, Addington et al.[49] presented a new tool, the Calgary Depression Scale for Schizophrenia (CDS), based on items selected from the HAM-D and the Present State Examination. In subsequent papers the authors demonstrated the specificity of the scale in comparison with the HAM-D in terms of separating depression, negative symptoms and extrapyramidal symptoms (EPS).[50,51] The reliability of the scale across both acute and chronic schizophrenia was also shown.[52] This finding was confirmed by a subsequent paper[53] in which the HAM-D and the depression subscale of the Positive and Negative Syndrome Scale (PANSS-D) were compared with the CDS. Results revealed that, although all 3 measures of depression were significantly correlated, the CDS is the most suitable measure of depression in schizophrenia.

In a more recent paper, Kibel et al.[46] recognised the overlap between depressive illness and negative features in schizophrenia, but concluded that negative items as well as depressive and positive symptoms may be reliably measured and separated.

Although further efforts have been made, the differentiation between depression and certain components of the negative syndrome and akinesia remains a clinical challenge.

4. Use of Antidepressants in Schizophrenia

4.1 Efficacy

European psychiatrists have tended to shy away from using antidepressants to treat depressive symptoms in schizophrenia because it was believed that these could exacerbate psychotic symptoms. This belief was based on early clinical experiences with tricyclic antidepressants (TCAs) for depressive symptoms in patients with schizophrenia who were not receiving antipsychotics. Heinrich[54] reported an exacerbation of paranoid hallucinatory symptoms after treatment with a first generation monoamine oxidase inhibitor. Comparable observations were made by others.[55-58] Prussoff and coworkers,[59] as well as Kramer and colleagues,[60] reported increased psychotic symptomatology or retarded resolution of psychosis associated with the addition of tricyclic antidepressants in patients with schizophrenia. Waehrens and Gerlach[61] and Johnson[10] could not find any benefit from the addition of a tricyclic antidepressant to ongoing antipsychotic treatment.

These findings are a contrast to later work which demonstrated more favourable results from the use of antidepressants in this patient population. Some reports[62-67] have reported a possible benefit from use of the combination of different antidepressants and antipsychotics. These authors, however, did not differentiate clearly between affective disorder and what would today be considered to be schizoaffective disorder. Furthermore, many of the reports were of nonblind, noncontrolled studies which used antidepressant dosages which currently would

be considered to be too low. Studies discussed later in this section that had more positive results in general utilised higher doses of antidepressants.[68-78]

As many aspects of this article reflect the historical evolution of the diagnosis and therapy of depression in schizophrenia, we thought it would be useful to give a small overview of the outcome of studies where an antidepressant was added to a patient's antipsychotic medication. The first studies had negative results. Later studies had more favourable outcomes and more recent studies had positive results.

A Medline search was performed to identify relevant work in the field. Trials or reports that were judged to contribute significantly to the content of this manuscript were distilled from this search. A copy of the search is available upon request.

Kennedy and Miller[79] assessed 137 hospitalised patients with schizophrenia who were receiving an amitriptyline-perphenazine regimen and reported a remission rate of 86%. Rada and Donlon[80] observed that the addition of low doses of TCAs quickly alleviated depressive symptoms during the reintegrating phase of the schizophrenic episode in patients who had symptoms that had not responded to phenothiazine alone. Other authors found similar good results when combining tricyclic antidepressants with antipsychotics.[81-85] Hogarty and coworkers,[85] in a more recent study, found that tricyclic antidepressant agents improved chronic nonphasic depression in contrast with the acute episodic forms.

Several reviews have also concluded that combination antidepressant and antipsychotic treatment is effective for depression in non-acutely ill patients with schizophrenia. Plasky[86] and Siris[25] concluded that studies conducted in the 1970s and 1980s addressing the question of combining an antidepressant with an antipsychotic drug, while producing mixed results, were generally favourable. Levinson and colleagues,[87] in another overview article, arrived at the same conclusion.

Depressive symptoms along with a positive family history of affective disorder and previous depressive episodes have been identified as being positive prognostic signs for the efficacy of adjunctive lithium in patients with chronic schizophrenia.[88] Although this therapeutic approach awaits replication, it seems that the combination of an antipsychotic and lithium is a valuable option in patients with postpsychotic depression who have symptoms that have failed to respond to other treatment trials. There are only very few studies which show a benefit of lithium in the maintenance phase of treatment, and predictors of a favourable response are states of excitement rather than depressive symptoms.[25]

There is an almost complete lack of controlled studies of the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) or newer compounds in treating depression in patients with schizophrenia.[89]

Despite conflicting evidence, it appears to be common practice nowadays to combine antidepressants and antipsychotic medication after a careful evaluation of the nature of the depressive syndrome. More controlled studies will be necessary to determine the effects of the newer antidepressants.

4.2 Pharmacokinetic Interactions

Pharmacokinetic interactions have been reported between SSRIs and antipsychotics TCAs and antipsychotics.

Interactions between TCAs and antipsychotics can result in elevated blood concentrations of either the antipsychotic or the antidepressant.[90] This is due to competition between these substances for specific cytochrome P450 metabolic pathways (see table I). Because of the limited therapeutic range of TCAs, the risk of adverse effects is increased when the combination causes increases in TCA concentrations.

Interactions have been reported with the use of amitriptyline, imipramine and nortriptyline with chlorpromazine. These drugs were associated with increases in plasma concentrations of the antipsychotic by 30 to 50%.[91,92] Phenothiazines, and perhaps haloperidol, can decrease urinary excretion of nortriptyline and imipramine by as much as 50%,

with concomitant increases of plasma TCA concentrations ranging from 30%[93] to 100%.[94,95]

The coadministration of SSRIs and classical antipsychotics can result in interactions. Interactions between SSRIs and newer antipsychotics have uncertain clinical significance. Concentrations of clozapine and norclozapine were significantly higher (20 to 60%) in patients concomitantly treated with an SSRI[96] than in those receiving clozapine monotherapy.[97,98] Caution is therefore required when combining clozapine with SSRIs, especially fluoxetine and fluvoxamine. Because some adverse effects of clozapine such as electroencephalogram aberrations[99], sexual dysfunction[100] and toxic confusion[101] are dose and/or plasma-concentration related, such interactions may result in treatment complications.

With the appearance of the latest antidepressants, the clinician may choose antidepressants with low liability for interaction at the cytochrome P450 level. Venlafaxine and mirtazapine were shown to have a lower risk of clinically significant interactions than the 'older' SSRIs.[102] The cytochrome P450 enzyme 3A4 metabolises 4 of the newer antipsychotics including clozapine, quetiapine, zotepine and ziprasidone. For these antipsychotics the clinical implication is that concomitant administration with cytochrome P450 3A4 inhibitors may require dosage reduction.[103]

5. Antipsychotics with 'Built In' Antidepressant Properties

Some of the newer antipsychotics such as zotepine[104-106] and ziprasidone[107,108] are noradrenaline (norepinephrine) and/or serotonin reuptake inhibitors, i.e. they have pharmacological properties similar to those of effective antidepressants. Open studies with zotepine have suggested efficacy against delusional depression.[109] In a double-blind 28-day trial involving 139 patients with an acute exacerbation of schizophrenia or schizoaffective disorder,[110] ziprasidone 120 mg/day was significantly more effective than placebo in improving BPRS total, BPRS anxiety-depression cluster and BPRS anergia factor scores.

Table I. Interactions of newer antidepressants and antipsychotics involving cytochrome P450 (CYP)–mediated metabolism. The parentheses indicate low interaction potential at the relevant CYP isoenzymes

Antidepressants	Antipsychotics						Comments
	risperidone	clozapine	olanzapine	quetiapine	ziprasidone	zotepine	
Fluvoxamine	(2D6)	(2D6) 1A2 (3A4)	(2D6) 1A2	(3A4)	(3A4)	(2D6) (3A4)	Strong inhibitor
Fluoxetine	2D6	2D6 (3A4)	2D6	(3A4)	(3A4)	2D6 (3A4)	Strong inhibitor
Norfluoxetine		(3A4)		(3A4)	(3A4)	(3A4)	Weak inhibitor
Sertraline	2D6	2D6 (3A4)	2D6	(3A4)	(3A4)	2D6 (3A4)	Strong inhibitor at high doses only
Paroxetine	2D6	2D6	2D6			2D6	Strong inhibitor
Citalopram	2D6	2D6 1A2	2D6 1A2			2D6	Weak inhibitor
Nefazodone	(2D6)	(2D6) (1A2) (3A4)	(2D6) (1A2)	(3A4)	(3A4)	(2D6) (3A4)	Weak inhibitor
Reboxetine	(2D6)	(2D6) 3A4	(2D6)	3A4	3A4	(2D6) 3A4	Weak inhibitor
Venlafaxine	(2D6)	(2D6) (1A2)	(2D6) (1A2)			(2D6)	Weak inhibitor
Mirtazapine	(2D6)	(2D6) (1A2) (3A4)	(2D6) (1A2)	(3A4)	(3A4)	(2D6) (3A4)	Weak inhibitor

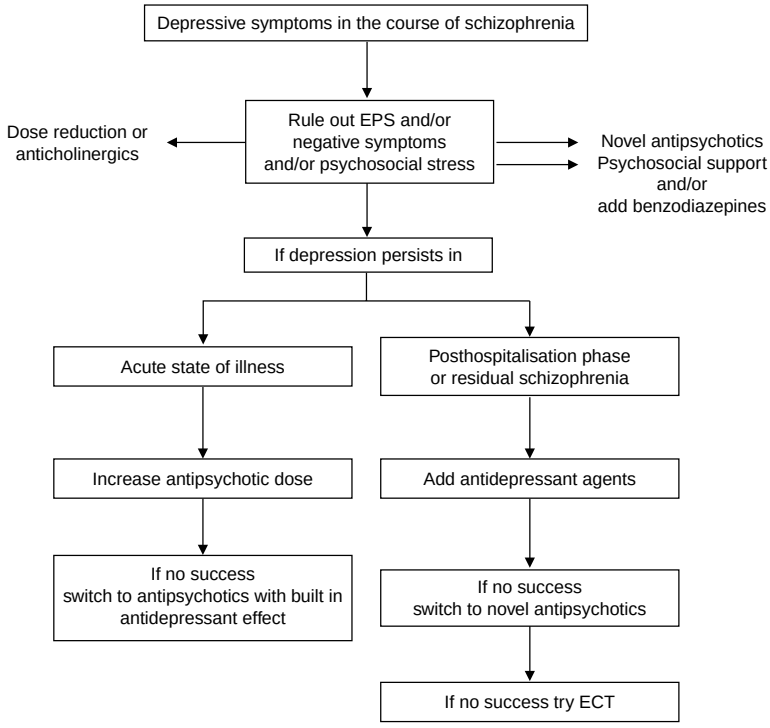

Fig. 1. Algorithm for the proposed management of depression in patients with schizophrenia. **ECT** = electroconvulsive therapy.

Tollefson et al.[111] published a depression-specific subanalysis (n = 1996) of one of the previous prospective blinded trials of olanzapine versus haloperidol. They found that both compounds were associated with mood improvement, but only olanzapine showed a significant direct effect on the Montgomery-Åsberg Depression Rating Scale in patients with a predetermined level of depression at the outset of their acute schizophrenic/ schizoaffective episode.

Peuskens and co-workers[112] analysed the effects of risperidone on anxious/depressive symptoms by pooling data from 6 double-blind comparative trials of risperidone and haloperidol in a total of 1254 patients with chronic schizophrenia. Patients in the risperidone group had a significantly greater improvement in depression scores than patients receiving haloperidol or placebo. In addition, Keck and collaborators[113] reported risperidone to be useful for patients with a schizoaffective disorder, especially of the depressive subtype, and for patients with bipolar disorder, when used in addition to mood stabilisers. In a recent paper, Keck and colleagues[114] reviewed the latest literature regarding the efficacy of clozapine, risperidone, olanzapine, quetiapine and ziprasidone in the treatment of depression, hostility and suicidality in patients with schizophrenia. They found that these agents may have therapeutic effects on depression and hostility and that clozapine and olanzapine may reduce suicidality in these patients.

6. Conclusions and Recommendations

The occurrence of depressive symptoms in patients with schizophrenia must always result in increased observation and support. Depressive symptoms

occurring during acute psychotic decompensation are hard to identify and distinct diagnosis may often only be made by a longitudinal overview. Antidepressants do not seem to be indicated for depressive states in acutely ill patients with schizophrenia, since such symptoms tend to disappear with antipsychotic treatment in parallel with the florid psychotic symptoms. In fact, antidepressants may even retard the resolution of psychosis.

It is important to relate depressive symptoms in patients with schizophrenia to the course of the illness and the patient's response to a change in treatment. Several strategies can help the clinician to diagnose medication-induced adverse effects. If the patient shows EPS, such as reduction of arm swing, stiffness and/or cogwheeling, the clinician should consider a dose reduction of the antipsychotic and/or consider the administration of anticholinergics (see fig. 1). If the symptoms improve after such a change in treatment, the diagnosis is most likely EPS. Indeed, some clinicians use an anticholinergic challenge to rule out EPS before making a diagnosis of depression. If the depressive symptoms persist, an increase in the dosage of antipsychotic can be tried. If the patient improves, depression is more likely to be part of the primary process of schizophrenia.

The clinician must also be aware of the patient's psychosocial background. If depression is triggered by stressful events or unfavourable psychosocial circumstances, patients are likely to benefit from psychosocial support programmes, and a change or adjustment of the antipsychotic drug may not be necessary. Adding benzodiazepines may help the patient to cope with concurrent anxiety symptoms (see fig. 1).

Symptoms common to depression, EPS and negative symptoms include anhedonia withdrawal, blunted effect, retardation and a lack of drive and energy. The clinical symptom that is most likely to separate these conditions is probably 'blue mood' (feeling of sadness) which is normally present in depression. Somatic symptoms of depression, such as sleep disturbances, early morning awakening, may also be helpful in establishing the diagnosis of depression.

After having ruled out all of the confounding conditions mentioned above, add-on treatment with an antidepressant is generally advocated, although the evidence for this approach is still tentative. Should the depressive syndrome persist, a change in the antipsychotic management is warranted. Changing from traditional antipsychotics to a novel antipsychotic is advisable (see fig. 1).

Understanding the diagnosis and management of mood disorder in patients with schizophrenia is vital to be able to reduce the suffering and suicide risk caused by this very common comorbid state.

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