Major depressive disorder as a co-morbid diagnosis in schizophrenia versus the diagnosis of schizoaffective disorder – depressed type

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ABSTRACT
The purpose of this article is to focus on the importance of depressive symptoms in patients suffering from schizophrenia, and the dilemma posed by hierarchical classification methods, which exclude co-morbid diagnoses such as Major Depressive Disorder in patients with schizophrenia. The question arises that if Major Depressive Disorder is only categorized under the diagnosis of Schizoaffective Disorder (depressed type), are we able to recognize these symptoms promptly and treat them sufficiently? The duration of the substantial period of depressed mood referred to in the DSM IV TR criteria for Schizoaffective Disorder is unspecified. We suggest that one should only allocate the latter diagnosis if the substantial period is that of one third or more of the whole duration of the illness. Identification of the optimal cutoff point can generate further hypothesis testing research and refinement of the diagnostic model. It is not only important to refine the diagnosis, but it is even more important to detect these symptoms and treat promptly and effectively. According to the latest literature, the best possible treatment for depression in schizophrenia appears to be the combination of a second-generation antipsychotic and cognitive psychotherapy.

Keywords: Major depression; Schizophrenia; Schizoaffective; Depressed

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Introduction

At present, psychiatry is in a state of flux and advances in neuroscience and genetics are soon likely to challenge many of its current theoretical underpinnings, particularly those related to the causation and definition of mental disorders. It is increasingly recognized that the validity of the diagnostic concepts enshrined in contemporary classifications of mental disorders cannot be taken for granted.[1] Indeed Goodwin and Guze[2] went so far as to assert that 'diagnosis is prognosis' and referred approvingly to P.D.Scott's observation that the 'follow up is the great exposer of truth…..' It is to the psychiatrist what the post-mortem is to the physician.

It is important to distinguish between validity and utility in considering psychiatric diagnoses. Diagnostic categories defined by their syndromes should be regarded as valid only if they have been shown to be discrete entities with natural boundaries that separate them from other disorders. Although most psychiatric diagnostic concepts have not been shown to be valid in this sense, many possess high utility by virtue of the information about outcome, treatment response and etiology that they convey and are therefore invaluable working concepts for the clinician.[1]

According to the diagnostic and statistical manual of mental disorders (DSM IV TR)[3] diagnostic criteria for schizophrenia, major depressive disorder is excluded and should rather be diagnosed under schizoaffective disorder (depressed type). Criteria for schizoaffective disorder (depressed type) state that mood symptoms must be present for a substantial portion of the total duration of the active and residual periods of the illness, but they do not specify the time period.[3] It is suggested that this period must be clearly defined so as to distinguish between

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schizoaffective disorder and the possibility of major depressive disorder as co-morbid diagnosis.

Previously the diagnosis of schizoaffective disorder was considered confusing and controversial. The different classifications (ICD-10[4] and DSMIV TR[3]) agree that schizoaffective disorder presents a combination of schizophrenia-like and affective symptoms, but differ as to the quality, number and time sequence of the symptoms.

Hierarchical assumptions at the foundation of the diagnostic system stand in the way of recognizing associated psychiatric syndromes. It is unclear if associated psychiatric syndromes are separate and distinct co-occurring or co-morbid syndromes or whether they are part of the patients' schizophrenic disorder, i.e. dimensions of schizophrenia that need further attention.[5]

Co-occurring or associated psychiatric syndromes such as depression may have been hidden from view by exclusion criteria, which prohibited their being diagnosed in the presence of schizophrenia.

Hierarchical thinking has been present in virtually all systems of psychiatric nosology and has been traced back to the tendency in medicine to give each patient only one diagnosis, an approach found in the 17th century. Bogenschutz[6] also emphasized the importance of recognizing multiple diagnoses in one patient to clarify our thinking about categories of illness and the boundaries between them as well as the relationship among these categories.

With respect to the categorical versus dimensional argument one false assumption is that the disorder is either categorical or dimensional whereas in a real sense every disorder is both. It is either present or not, but when the disorder is present patients may vary with respect to age-of-onset, severity, symptomatology, impairment, resistance to treatment and the variety of other disorder characteristics. One of the important issues in using categorical approaches pertains to the choice of a cutoff point from which the categorical classification is generated.[7] The choice for a cutoff point of the duration of depression is unclear in schizoaffective disorder and this can lead to erroneous conclusions regarding outcome and stage of illness.

Identification of an optimal cutoff point must generate a hypothesis, with subsequent research and refinement of the diagnostic model.

The impact of depression in schizophrenia

It is a fact that depression occurs in patients with schizophrenia.[8,9,10] The studies on depressive symptoms and signs in schizophrenia show a variation from between 7 and 65%, with a modal rate of 25%.[11,12] It is clear that these symptoms are of considerable clinical relevance and compromise the level of functioning of these patients, even to the extent of an increased risk of relapse and suicide.[9,10,11]

We all are familiar with the facts that schizophrenia reduces the life span of those afflicted by an average of 10 - 15 years, and suicide is the leading cause of premature death among patients with schizophrenia.[12,13,14,15] The overall lifetime risk for patients with schizophrenia is 50% for suicide attempts and they have a 9-13% lifetime risk for completed suicide.[10,11,12,13]

Depression may occur in the different phases of the disease, either during the prodromal phase, psychotic phase or post psychotic phase.

For the latter we at least have the better definition of post psychotic depression in schizophrenia in the research criteria in the DSM IV TR.[3] Kohler[16] and Jeczmien[17] discuss post psychotic depression in schizophrenia in their respective publications and highlight the significant prevalence estimated at 25%. Criteria for a major depressive episode must be met and this episode is superimposed on the residual phase of schizophrenia.

With regard to depression in the prodromal phases, recent research has increasingly focused on the early course of schizophrenia, extending from onset of symptoms to the first treatment contact. A high prevalence of depressive symptoms in the early course of schizophrenia has been established in several studies.

Hafner et al[18] did the so-called ABC schizophrenia study, a population-based, first –episode study. To study depression in the early course of schizophrenia, Hafner's study looked at symptom appearance and accumulation. For this purpose, four depressive symptoms, without overlap with negative symptoms of schizophrenia, namely depressed mood, guilt feelings, lack of self-confidence and attempted suicide were used.

Their findings showed that the prodromal phases lasted on average for 5 years and in total 81% of patients with first episode psychosis did suffer from depressed mood for at least 2 weeks before admission. On average depressive mood emerged as early as 52 months before first admission. Important reasons for investigating depression in schizophrenia involve the influence of these additional symptoms on the quality of life of these patients, as well as the introduction of the second- generation antipsychotics with their possible antidepressant effect is another important reason.[8,109]

The difficulties in diagnosing depression in schizophrenia

Whilst one includes the assessment of hopelessness, suicidality and the degree of depression as central tasks in treating affective disorders, this is not always the case for patients with schizophrenia.

Schizophrenic patients present with a myriad of disturbances in perception, cognition and communication, and depression can go unnoticed especially during the acute phase as noted by Knights and Hirsch.[19] They introduced the term "[un] revealed depression" and argued that these symptoms may be unrecognized because of florid psychotic symptoms.

It is also the legacy of Kraeplin's division of psychotic conditions into affective psychoses and dementia praecox. This contributed to the belief that schizophrenia and depression were and are distinct and non-overlapping entities. Yet again this may influence the threshold for diagnosing important depressive symptoms in patients with schizophrenia.

Distinguishing between negative symptoms and depressive symptoms can also be difficult in patients with schizophrenia.

Numerous studies have investigated the difference between depression and negative symptoms. In one study, an ethologically based comparison done by Schelde[20] , the behaviour pattern of schizophrenic patients wasshown to deviate from the depressed patients in only one specific behaviour and that is "talking to self". Their study confirmed the hypothesis that schizophrenic patients have characteristic and specific behaviours, which they called endemic behaviours: "nonsocial –talk", "stereotyped-movements", "non-blinking stare" and "laughing to self".

Previous studies also showed that schizophrenic patients demonstrated on a nonverbal ethological scale, more gaze aversion, detached facial expression, looking-down, non-specific gaze, less body contact and lack-of-social-smile. This as a group in comparison with both a control and depressed group. In the study of Scheld[20], it was observed that during the first week of hospitalization, the detailed behavioural manifestations of the depressed patients only moderately differed from manifestations seen among the schizophrenic patients and that the significant discriminating factor was the "non-social talk."

Specific scales have been developed to rate negative symptoms and depressive symptoms independently, namely the Negative Symptom Assessment (NSA) scale and the Calgary Depression Scale.

The NSA was developed to permit the reliable ratings of behaviours commonly associated with negative symptoms.[21] The NSA consists of 16 items with 6 anchors each. The items are prolonged time to respond to questions; the speech quantity; speech content; articulation of speech; emotion range; affect observed for reduced modulation of intensity and reduced display on demand; reduced social drive; poor rapport with interviewer; sexual interest; poor grooming; reduced sense of purpose; reduced interest; reduced daily activity and reduced expressive gestures; slowed movements.

The Calgary Depression Scale (CDS) was developed by Addington[22] et al in 1990 and is specifically developed to assess depression in schizophrenia. The CDS has 9 items with 4-point severity scale. The items include depression; hopelessness, self-depreciation; guilt feelings; pathological guilt; morning depression; early wakening; suicide and observed depression.

The "schizophrenia spectrum"

Several disorders have been found to cluster among the relatives of patients with schizophrenia, such as major depression, bipolar mood disorders which has given rise to the concept 'schizophrenia spectrum'. A number of studies illustrate this point. For example, three of the putative susceptibility loci associated with bipolar disorder (chromosome 13, 18, 22) seem also to contribute to the risk of schizophrenia.[1] Previous twin studies have supported a genetic contribution to the major categories of psychotic disorders and with the Maudsley Twin Psychosis Series study; the heritability estimates for schizophrenia, schizoaffective and mania were substantial and similar.[21]

Even earlier studies postulated about the schizophrenia spectrum, such as the study of Robin and Guze's.[23] This classic paper was written at a time when it was widely assumed that schizophrenia and manic-depressive disorders were transmitted by single or at the most two or three genes. They commented that the finding of an increased prevalence of the same disorder among close relatives of the original patients strongly indicates that one is dealing with a valid entity. It seems that the possibility of an increased prevalence of more than one disorder in the patient's 1st degree relatives had not occurred to them at that time.

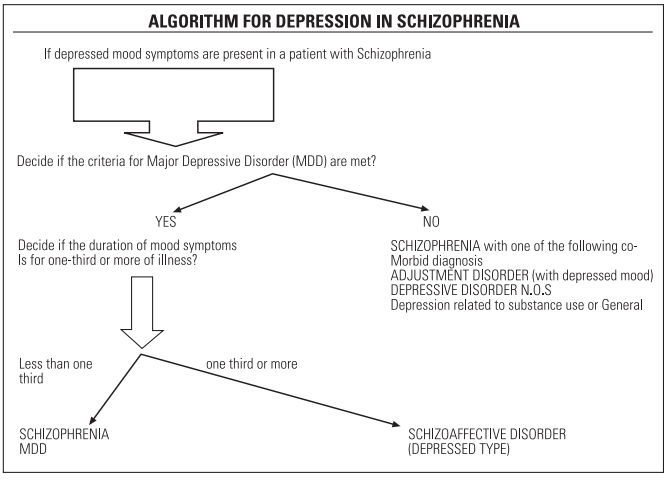
Schizoaffective disorder or a comorbid diagnosis of major depression

The question, which this article poses, is: when does one decide on a diagnosis of schizoaffective (depressed type) or when will one include depression rather as a co-morbid diagnosis on Axis I?

Bermanzohn et al[5] proposes that in the case of schizoaffective disorder the affective part (depressed mood) should exist for at least one-third of the duration of schizophrenia.

We suggest the following algorithm to decide if the patient is suffering from a schizoaffective disorder (depressed type) or a major depressive or adjustment disorder as co-morbid diagnoses. (Figure 1)

Figure 1



Management of depression in schizophrenia

Several researchers investigated the management of depression in schizophrenia and the different options will be discussed below.

John Cutting[24] gives easy approachable guidelines in managing a depressive episode. These guidelines include: ensuring that the symptoms are not the prodrome of a further psychotic episode, establishing compliance with prophylactic neuroleptic medication, (at the correct dosage), provision of psychological support, and if affective symptoms persist, adding an antidepressant.

Augmentation with antidepressants

Different opinions exist on adding an antidepressant and on deciding which antidepressant to prescribe.

Addington et al[25] in their international survey of psychiatrist's opinions on the management of depression in

schizophrenia showed that little agreement exists on the best management strategy.

It is important to note that adding tricyclic antidepressant medication to a patient who has psychotic symptoms, may actually retard resolution of positive symptoms.[26] In contrast, Siris et al[8] found Imipramine was of significant benefit for management of depression.

A few studies showed that adding an antidepressant to their management was not beneficial. Whitehead et al[27] conducted an extensive review of all studies comparing antidepressant medication or placebo treatment for patients with depression in schizophrenia. The results showed there is no convincing evidence to support or refute the use of antidepressants in treating depression in schizophrenia.

They stated that the literature was overall of poor quality, and only a small number of trials made useful contributions. Though their results provide some evidence to indicate that antidepressants may be beneficial for people with depression and schizophrenia, the results, at best, are likely to overestimate the treatment effect, and, at worst, could merely reflect selective reporting of statistically significant results and publication bias.

The Selective Serotonin Reuptake Inhibitors and other antidepressants

Serotonin selective reuptake inhibitors (SSRIs) and other anti depressants have been investigated in a few trials. Specifically sertraline, citalopram and fluoxetine, reboxetine and mirtazapine.[28]

Addington et al[28] conducted a randomized, double blind prospective placebo controlled study with sertraline on patients with schizophrenia in remission and current major depression. They could not find any significant difference in symptoms between the groups.

Another study done by Thakore et al[29] showed that the addition of sertraline resulted in global improvement, with a significant reduction in positive and negative symptom scores and no increase in undesirable neuroleptic side-effects. Sertraline may act by indirectly reducing dopaminergic activity. Sertraline was found by Kirli et al[30] to be more advantageous than imipramine in terms of rapid onset of action; frequency, severity and duration of side effects, and relapse risk of schizophrenia.

A trial with reboxetine add- on therapy to haloperidol failed to demonstrate any significant difference between the placebo and reboxetine groups on any of the outcome measures.[31]

Zoccali et al[32] conducted a double blind, placebo controlled, augmentation study of mirtazapine in patients treated with clozapine and showed improvement in negative symptoms. The authors suggested that this combination might act synergistically by increasing dopamine in the medial prefrontal cortex.

The effect of fluoxetine on the plasma concentrations of clozapine and its major metabolites was studied in 10 schizophrenic patients with residual negative symptoms. Patients stabilized on clozapine therapy (200-450 mg/day) received additional fluoxetine (20 mg/day) for eight consecutive weeks. During fluoxetine administration, mean plasma concentrations of clozapine, norclozapine and clozapine N-oxide increased significantly by 58%, 36% and 38%, respectively. There was no difference in negative symptomatology, as measured by the scale for assessment of negative symptoms, and the drug combination was generally well tolerated. The concomitant elevation in plasma levels of clozapine and its major metabolites suggests that fluoxetine inhibits the metabolism of clozapine by affecting pathways other than N-demethylation and N-oxidation. Close monitoring of clinical response and, possibly, plasma clozapine levels is recommended whenever fluoxetine is given to patients stabilized on clozapine therapy.[33]

Taylor et al[34] predicted that citalopram would not elevate plasma clozapine levels when the two drugs were co-administered because it does not inhibit the relevant enzyme systems. In this preliminary study of five patients given citalopram and clozapine there was no overall change in mean clozapine levels. Based on this limited evidence, citalopram might be the antidepressant of choice in patients taking clozapine.

Patients in both groups of the study by Kasckow et al[35] improved on positive and negative symptoms, but the citalopram group had significantly greater improvement in HAM-D and Clinical Global Impression Scale scores than the control group. There were no major side effects.

Forskolin is a unique activator of adenylate cyclase that bypasses membrane receptors and directly raised levels of the second messenger cyclic AMP. Depressed patients and schizophrenic patients with negative symptoms have been reported to have reduced cyclic AMP levels. In the first study[36] of forskolin in psychiatry, intra venous forskolin was administered in a 75-minute infusion to four depressed and five schizophrenic patients. All four depressed patients showed a transient mood elevation or stimulation, as did two of the five schizophrenic patients.

Augmentation with mood stabilizers

Mood stabilizers such as lithium and valproate have also received attention. Bender et al[37] undertook a retrospective audit of patients on clozapine and lithium and found it was especially effective with affective symptoms and aggression. Basan et al[38] conducted a systematic review of randomized trials with valproate as an adjunct to antipsychotics and found it was beneficial for these patients.

Both lithium and valproate have an additional important benefit in neurodegenerative diseases. They both upregulate brain concentrations of cytoreactive proteins, which exhibit neurotrophic effects, including regeneration of CNS axons.[39]

Antipsychotic medication

Another option is that of treating these symptoms with optimal antipsychotic medication. Tapp et al[40] showed improvement in depressive symptoms after 4 weeks on antipsychotic medication for a sample of patients who were initially antipsychotic free. Their improvement corresponded with the improvement in both positive and negative symptoms.

Amisulpride is a second-generation antipsychotic, a

substituted benzamide. It appears to be an effective agent in treating the positive and negative symptoms of schizophrenia. The recommended doses are between 400 mg/day and 800 mg/day. Amisulpride demonstrates a good global safety profile, particularly when compared with first-generation antipsychotics, such as haloperidol. There are interesting studies that point towards amisulpride's antidepressant effect in dysthymia speculating on possible roles in affective psychoses and chronic fatigue syndrome.[41]

Pani and gessa[42] imply the proposed mechanism of action of substituted benzamides is a selective modulation of the dopaminergic system in the mesocorticolimbic area. This is important for cognitive processing of internal and external cues, related to survival. The selective antagonism of dopamine D2-D3 receptors has been evoked to explain, in small to moderate doses (ie 50-100 mg day(-1)), the antidepressant effect and, in moderate to medium doses (100-400 mg day(-1)), the reported efficacy on negative symptoms of schizophrenia. Thus, substituted benzamides could represent the first class of atypical antipsychotics successfully employed for both depressive states and schizophrenia. Interestingly, recent evidence in the literature suggests that depressive episodes belonging to the bipolar spectrum are among "alternative indications" of other atypical antipsychotics such as olanzapine and risperidone.

Clozapine is especially linked with studies showing decreased numbers of suicide.[43] Olanzapine was shown to be superior to haloperidol for depression and this effect was independent of the reduction of psychotic symptoms.[44] Olanzapine was also shown to be more effective in the acute resolution of depression cluster symptoms in comparison with risperidone.[45]

Risperidone was shown to be more effective than haloperidol for affective symptoms in patients with schizophrenia.[46]

Studies showed no difference between treatment with amisulpiride or risperidone as measured by PANSS and the Bech Rafaelsen Melancholia Scale.[47] This study also looked at the effect of these antipsychotic medications on the quality of life of these patients. Tollefson, Andersen and Tran[45] concluded that concurrent depressive symptoms are treatment responsive and during treatment with second-generation antipsychotics there was an association with improvement in quality of life. Positive quality of life advantages were seen with olanzapine and risperdione, but the effects on the PANSS mood item were more robustly influenced by olanzapine.

It is evident that the treatment of depression in schizophrenia is a complicated matter. Evidence does lean to the second-generation antipsychotic treatment for the best responses. The basis for this effectiveness resides in the activity of these agents at multiple neurotransmitter receptor sites, including adrenergic, dopaminergic and serotonergic receptors.

Additional cognitive therapy as treatment modality

Patients with schizophrenia and depression have similar cognitive styles to those patients with only depression. This supports the potential role for cognitive therapy, particularly for paranoid patients. The negative attributional style present in these groups of patients has been suggested as a psychological correlate with depression according to Abramson's reformulated learned-helplessness model.[48] This entails the tendency to attribute negative or bad events to internal, stable and global causes. Efficacious short-term group therapy may fill the gap between quality of care and the ideal economic allocation of mental health care services for people with chronic mental illnesses, for instance Interactive-Behavioural-Training –a group psychotherapy model that actively combines cognitive behavioral and group process techniques.

Conclusion

It is the authors' opinion that depression is a very important 'entity' in patients with schizophrenia.The aim of this article was to remind and focus clinicians treating patients with schizophrenia on this very important symptom-profile. The question posed is whether this 'entity' should not receive more recognition and appear as a co-morbid diagnosis in patients with schizophrenia (with depressive symptoms), fulfilling the criteria for major depressive disorder, providing these symptoms last for less than one-third of the illness.

Early diagnosis and prompt treatment of these symptoms should improve quality of life. According to current literature it seems that the combination of a second-generation antipsychotic and cognitive therapy may be the treatment of choice.

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