
Post-Psychotic Depression in Schizophrenia Patients

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Abstract

Depression is a frequent comorbidity in the course of schizophrenia and associated with increased mortality from suicide. Post-psychotic depression is defined as the syndrome of major depression occurring following remission of psychotic symptoms in a person with schizophrenia. Various proposed causes, differential diagnosis and issues regarding management of post-psychotic depression are discussed.

Depression in Schizophrenia: A Brief Historical Overview

Notions concerning depression in schizophrenia have been influenced by conceptual models, which have changed over time. Kahlbaum offered perhaps the earliest clinical descriptions of depression in patients with presumed schizophrenia. His series included 26 patients with similar clinical features termed catatonia, which he described as "a brain disease... in which the mental symptoms are consecutively melancholia, mania, stupor, confusion and eventually dementia" [1]. Kraepelin's Binary Model proposed a clear distinction between dementia praecox and manic-depressive illness based on the clinical

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course. Nonetheless, Kraepelin described affective disturbances that were present at the onset of dementia praecox [2]. Eugen Bleuler's views have been influential with his delineation of primary and secondary symptoms, the latter included delusions, hallucinations and depression [3]. Kasanin coined the term "schizo-affective psychosis" [4] to describe a group of patients with a blend of prominent affective and schizophrenic symptoms, however, the existence of schizoaffective disorder as a separate clinical entity has repeatedly been questioned. Mayer-Gross et al. proposed that the presence of either depression or mania in the setting of characteristic schizophrenic symptoms does not weaken the diagnosis of schizophrenia [5].

Over the last 20 years, several hypothetical models have been formed, which attempt to place schizophrenic symptoms in the context of other psychiatric symptoms and make the binary distinction between affective and schizophrenic disorders obsolete. In "The Hierarchical Schema of Symptoms" [6], disorders located in a pyramidal hierarchy exhibit symptoms not only specific to the illness, but nonspecific symptoms of disorders located on lower steps. The "Continuum Model" [7] proposed purely affective and schizophrenic disorders to be at opposite ends of a spectrum rather than mutually exclusive.

Following the introduction of antipsychotic medications in treating schizophrenia, clinical reports appeared describing a dramatic increase in the incidences of depression and suicide [8]. These reports led to the concern that depression in schizophrenia might result from antipsychotics [9]. This argument was supported by descriptions of akinetic depression related to antipsychotic medication [10-11].

According to past psychoanalytic theory, depression in particular during the post-psychotic period did not represent core symptomatology of the illness, but rather the psychological reaction as patients gain insight into their condition [12].

In early longitudinal studies, Bowers and Astrachan [13] and Roth [14] found depressive symptoms present in virtually all patients with acute exacerbation of schizophrenia, remitting with treatment of psychosis and regardless of antidepressant treatment. Subsequent studies with typical [15-17] and more recently atypical antipsychotics [18-19] have revealed improvements in both psychotic and depressive symptoms.

The lifetime prevalence for an episode of major depression in schizophrenia has been estimated to be 60%, much higher than the 8-26% risk for the general population [20]. The point prevalence ranges between 20-70%. This wide range of prevalence is likely related to variable methods of assessment, stage of illness, and patient populations. In the Epidemiological Catchment Area study, people with schizophrenia were almost 30 times more likely to experience criteria for major depression, compared to the general population [21]. Reviewing the existing longitudinal studies, it appears that depression is most common in the acute phase of illness, gradually becoming less common during remission. Depression is less common with increasing chronicity of illness, perhaps because its symptoms are gradually replaced by negative symptoms [22]. In addition, schizophrenia is associated with a high mortality as the result of suicide. The rate of suicide in schizophrenia is 20 times that of the general population [23] and while it is estimated that suicide claims the lives of 10% of sufferers [24] it is most prevalent in young males at the beginning of their illness [25]. The majority of schizophrenia patients who completed suicide were found to be depressed in the months preceding their deaths [26-28], however, other factors may contribute to suicidality [18].

Conceptualization of Post-psychotic Depression (PPD)

Depression in the period after an acute psychotic episode was first described by Mayer-Gross [29], but it was more than 40 years before there were further accounts [12-14,30]. McGlashan and Carpenter [31] described 30 patients of whom 15 experienced depressive symptoms in the period after remission of acute psychosis, when they were deemed stable for return to the community. In their definition, post-psychotic depression referred to a phasic phenomenon of depressive affect and/or a quiet, but severe, social withdrawal following remission of more florid psychotic symptoms. In their cohort, depression did not originate *de novo* in the PPD group but represented a continuation of preexisting depressive symptoms. It was unclear whether patients fulfilled diagnostic criteria for major depression. While 60% of patients in the PPD group were treated with antipsychotics, only 27% were treated in the non-PPD group. This raised the possibility regarding medication being instrumental in the experience of depression, however, it is likely that PPD group was more symptomatic and in need of medication treatment. Both groups did not differ in their depression ratings at time of admission and one year follow up. The described range of incidence of PPD ranges from most or all patients [32] to the estimate by McGlashan and Carpenter [31] that PPD occurs in 25% of all psychotic episodes. Some authors have questioned the existence of PPD [33-34], but this remains a minority position. Green et al. [35] followed 27 recent onset schizophrenia and schizoaffective disorder patients over a mean duration of 3 years and found that depressive relapse, as measured by the BPRS but not syndromatic criteria, occurred at a higher than expected frequency during the early psychotic period. However, there was no clear evidence for a syndrome of PPD.

A comparison of 30 schizophrenia patients with PPD and 30 patients without PPD [36] in India revealed that PPD patients, amongst other social characteristics, experienced a more severe course of illness more florid psychotic and depressive symptoms and higher number of hospitalizations. Huppert et al. [37] examined 63 patients with schizophrenia or schizoaffective disorder, who were stabilized after an acute psychotic episode, and found that depression and anxiety, rather than positive and negative symptoms, were most correlated with impairment in quality of life. In this study as well, no decision was made whether patients fulfilled syndromatic criteria for depression.

Criteria for PPD

According to DSM-IV [38], major depression and schizophrenia cannot be diagnosed concurrently. DSM-IV Appendix B describes Post-psychotic Depressive Disorder as the presence of depressive symptoms, which meet criteria for major depression, during the residual phase of schizophrenia. Such depression may occur at any time during the residual phase but most commonly following an acute psychotic episode. The residual phase, which commonly follows the acute psychotic episode may be chronic or lead to complete remission and is characterized by the presence of negative symptoms or attenuated positive symptoms.

Although it is commonly perceived that PPD follows remission of acute psychosis, the current definition allows for diagnosis of PPD, which can occur as prodromal to a psychotic episode. While depressive symptoms are commonly prodromal to reemergence of psychosis, they lack specificity and predictive value [39]. To distinguish PPD from prominent negative symptoms such as apathy, anhedonia and asociality, the criterion of depressed mood, rather than loss of interest should be met. Since PPD is not part of the regular DSM-IV nomenclature, people who exhibit this syndrome should receive the diagnoses of schizophrenia and depressive disorder not otherwise specified.

Differential Diagnosis

Acute Psychosis

Depression is common in the setting of acute psychosis, particularly in first episode schizophrenia patients. However, DSM-IV stipulates that depressive symptoms in the setting of acute psychosis, regardless of severity, and depressive symptoms outside acute psychosis, not fulfilling criteria for major depression or adjustment disorder are considered as part of the illness of schizophrenia and do not warrant separate classification. Koreen et al. [17] described 70 first episode schizophrenia patients (39 men, 31 women) who were followed over a five year period. During the acute episode, over half of patients experienced depressive symptoms, as characterized by a score of ≥ 15 on the HDRS [40] and an additional 22% fulfilled criteria consistent with major depression. Depression was not related to extrapyramidal side effects, did not emerge with remission of psychosis, but diminished with improvement in psychotic symptoms. In this longitudinal study only very few patients experienced symptoms consistent with PPD. In a similar long term study, Wassink et al. [41] reported that of 54 men and 16 women hospitalized with recent onset schizophrenia, more than half of patients experienced depressive symptoms and a third adjusted criteria for major depression.

Major Depression

Close longitudinal follow up is necessary for accurate diagnosis of PPD. In particular it is important to ascertain that the person has met prior criteria for schizophrenia without prominent mood symptoms and that the diagnosis of PPD is not mistakenly given to a person who has experienced a major depressive episode with psychotic features, which have cleared since.

Adjustment Disorder

People with schizophrenia are more prone to experience difficulties in achieving and maintaining goals related to psychosocial functioning, such as interpersonal relationships, school and work. Such stresses may produce anxious and sad mood consistent with adjustment disorder.

Negative Symptoms

Negative and depressive symptoms, in particular vegetative symptoms, share considerable overlap and are easily confused. McGlashan [42] addressed the possible coexistence of negative and depressive symptoms and distinguished between affective poverty - aphantasia - and PPD. Aphantasia is described as a state of psychic blankness, characterized by reports of feeling empty, motivational inertia and interpersonal isolation which commonly occurs in patients with chronic schizophrenia and which we now regard as marked negative symptoms. Studies within the last 15 years found little or no association between depressive and negative features [43-45] or found an association between negative and vegetative features of depression [46-48]. Vegetative symptoms of depression consist of somatic and nonspecific behavioral disturbances, such as anergia, anhedonia, insomnia and lack of appetite, and can be found in many psychiatric disorders.

Medication Effects

Following the introduction of antipsychotic medications in treating schizophrenia, clinical reports appeared describing a dramatic increase in the incidences of depression and suicide [8]. Experience with the antihypertensive agent reserpine, also used to treat schizophrenia and known to cause depression in some patients, led to the concern that depression might result from pharmacotherapy in schizophrenia and introduction of the term "pharmacogenic depression" [9,49]. In 1975, Rifkin reported on a small group of young male patients who experienced akinetic depression, characterized by apathy and sad mood, while being treated with high potency antipsychotics. These results were replicated in a larger sample by Van Putten and May [11] who reported that in two thirds of patients depressed mood improved with anticholinergic medication. Akathisia, another side effect of, in particular high potency, antipsychotic medications has been linked with dysphoria [11,50] and suicidality [51-52]. Subsequent studies on patients treated with typical antipsychotics [14-17] have refuted a strong association with depressed mood. Even more consistently, recent studies with atypical antipsychotics have shown to improve depressed mood and suicidality in schizophrenia patients to an extent superior to typical antipsychotics [19]. Atypical antipsychotics may exert discrete antidepressant effects since, in addition to dopamine, they influence neurotransmitters such as serotonin, norepinephrine, GABA and glutamate.

Medical Illness

It has been estimated that nearly 50% of patients with schizophrenia have a comorbid medical condition, but many of these illnesses are misdiagnosed or undiagnosed [53]. A fragmented health care system, lack of access to care and inability of patients to appreciate or describe physical symptoms contribute to the lack of attention to medical problems in patients with schizophrenia. Even basic assessments, including physical examination, blood chemistry and hematology tests can detect underlying physical illness in over three fourths of patients [54]. Medical conditions associated with depressed mood are mostly systemic and include hypothyroidism, renal failure, cancer and chronic infectious processes such as TB, HIV and tertiary syphilis, which has made a recent resurgence. At times the treatment for unrelated medical illnesses can produce or potentiate depressed mood, examples are antihypertensive beta and alpha blocking agents and antiepileptics, in particular phenobarbital.

Substance Abuse

Drug abuse disorders occur in schizophrenic patients at a higher frequency than the general population [55] and are commonly associated with disturbances in mood. It has been estimated that up to 50% of people with schizophrenia abuse drugs or alcohol [55,56]. In many parts of the Western world cocaine, particularly the free base form "crack" is favored by patients with schizophrenia, followed by marijuana and alcohol to a lesser extent, which in our experience may be quite different from patients with other mental illnesses, for example bipolar disorder. The reason for this preference is unclear, perhaps it is the properties of cocaine, which produce a transient increase in goal oriented behavior and mood. It has been hypothesized that functional abnormalities in the hippocampal formation and frontal cortex, as occur in schizophrenia, may facilitate positive reinforcing effects of drugs and reduce inhibitory control over drug-seeking behavior [57]. After repeated use many drugs, but especially cocaine, are known to often produce a syndrome of pronounced dysphoria, which can last an extended period of time. Even commonly used and socially accepted drugs, such as nicotine and caffeine, have been shown to produce depression like states during withdrawal periods. This may have an effect in inpatient settings, which commonly endorse smoke and caffeine free policies.

Treatment

Medication

In general, antidepressant medications have not been shown to be beneficial in the treatment of depressive symptoms during acute psychosis in both schizophrenia and schizoaffective disorder [58-61]. Similarly, results on treatment of depression in stable schizophrenia patients are sparse and limited to trials with older generation antidepressants. Siris reported on the use of imipramine in 33 patients with schizophrenia or schizoaffective disorder and PPD [62] who mostly fulfilled criteria for major depression and found improvement in depression over a 6 week period, when compared to placebo. More recently, Siris et al. [63] reported on a larger group of 72 patients with schizophrenia or schizoaffective disorder, who also experienced post-psychotic depressive symptoms. The majority of patients experienced symptoms consistent with PPD. Patients were treated with fluphenazine and a 6week double-blind trial of imipramine or placebo. Patients treated with imipramine experienced greater improvement in depressive symptoms without worsening of psychotic symptoms. Surprisingly, there have been no placebo controlled trials reporting on the efficacy of newer generation selective serotonin or mixed reuptake inhibitors.

Psychotherapy

As described above, efforts to ameliorate symptoms in the person with schizophrenia have mainly been in the realm of antipsychotic medications. Although medication intervention has been shown to be the essential component for effective treatment, it is limited by medication compliance and beneficial versus side effects. Supportive therapy and psychosocial intervention, such as family education, social skills training, and cognitive rehabilitation (skills-training in attention, memory, etc) have been described as useful additions to the medication treatments [64-65].

Psychosocial Interventions

Psychosocial interventions utilize activity-oriented interventions rather than psychotherapy. Therapeutic approaches heavily rely on interpersonal relationships, involving social skills training, vocational rehabilitation, and, to a lesser extent, supportive psychotherapy. Communications with patients should be simple, clear, and coherent, and may involve family members. Goals of psychosocial interventions are to reduce overstimulating and stressful situations or life events and in turn decrease psychotic relapse and hospitalizations. Decreasing stressful situations and life events will not only help stabilize delusions and hallucinations, but may also decrease frustration anxiety and resultant depression.

Supportive Psychotherapy

The term supportive psychotherapy has been accepted for many years, although without a widely accepted definition [66]. In supportive psychotherapy, the therapist takes on active role offering support and recommendations about how to cope with symptoms and life circumstances, rather than exploring and directly decreasing symptoms of the illness. Recent studies have shown a general benefit from treatment modalities including supportive psychotherapy, but failed to elucidate specific effects [67-68].

Cognitive Therapy

Cognitive therapy is based on the premise that thoughts exert influence on a person's emotions and behavior. Identifying and correcting cognitive distortions can lead to improvement in a person emotional state and behavior. To date, cognitive therapy [69-73] has proven to be useful in the treatment of depressive, anxiety and addictive disorders. Clinical and investigational efforts in England and Canada have applied these techniques ameliorating delusions and hallucinations. Unlike supportive therapy, which is not time limited, CBT represents a structured and time limited approach, typically consisting of 20 sessions over 6-9 months. Patients learn to view delusions and hallucinations as symptoms, that are part of their psychiatric disorder, rather than as frightening and believable entities. In an effort to allow questioning of these beliefs, false, delusions are reevaluated with reference to alternative possible explanations, including their psychological meaning. Although CBT has not been specifically applied to treat depressive symptoms in schizophrenia, lessening of hallucinations and delusions, which are known to be associated with depression, will in turn decrease anxiety, frustration and depressive symptoms. Additional goals of cognitive therapy for people with psychosis include reduction of disability secondary to symptoms, acceptance of illness and participation in prevention of relapse. Over the past 10 years there have been fewer than a dozen of studies [74-80] on the benefit of cognitive therapy in schizophrenia. Most, but not all studies have shown a beneficial effect of CBT on improvement of positive and negative symptoms beyond the period of active treatment. Two studies compared more immediate and delayed effects of CBT to supportive therapy and routine care in patient groups with recent onset of schizophrenia. They found time limited courses of CBT to exert superior and lasting effects on positive, and negative symptoms, and clinical outcome at one month [76] and up to 2 years later [75]. A single study [81] included symptoms of depression as a secondary outcome measure with the main emphasis on reduction of psychotic symptoms. In this study, CBT compared to befriending, which incorporates aspects of supportive psychotherapy, produced a significant and lasting reduction of depressive symptoms over a period of nine months. However, since most CBT studies have focused on amelioration of delusions and hallucinations, there remains insufficient evidence of efficacy for amelioration of depressed mood in schizophrenia. More studies need to be done to determine whether CBT actually has any specific effect other than the benefits due to increased quality of therapeutic contact [82].

Practical steps to consider, once depression in the post-psychotic period has been established, include decrease of antipsychotic medication to lessen the probability of depressive symptoms induced by antipsychotic medication, addition of anticholinergic medication to treat possible akinetic depression, addition of a newer generation

antidepressant medication such as selective serotonin or serotonin-norepinephrine reuptake inhibitors, and, lastly, switch to an atypical antipsychotic medication. Psychotherapy, in particular cognitive-behavioral therapy which has recently been found beneficial in improving, not only residual [83], but also depressive [81] symptoms in schizophrenia. In addition, the possibility of undiagnosed medical illness and substance abuse needs to be considered.

Conclusion

PPD represents a syndrome of depressed mood, which meets criteria for major depression, in the setting of residual schizophrenia. This syndrome and its possible causes received considerable attention 20-30 years ago, however in the past 10 years, there have been only a few publications that have investigated this syndrome. In two patient series [17,35], PPD was found to be rare. Chintalapudi et al. [36] found PPD patients to differ on account of increased severity of illness during the psychotic phase. Except in these recent studies, PPD was generally not defined by the presence of major depression, as stipulated by DSM-IV. Reviewing the body of literature it appears that PPD in the period following acute psychosis may represent continuation of depression from the acute stage, whereas PPD after a period of relative stability may herald the reemergence of psychosis. Perhaps the change of standard of care from typical to atypical antipsychotics as first line medications in the treatment of acute schizophrenia is responsible for the lessened attention on PPD, as atypical antipsychotics are superior in the treatment of depressive symptoms. However, as depression in schizophrenia is associated with greatly increased mortality from suicide, early detection and management of PPD is clearly important. Treatment of depression in schizophrenia include optimal treatment of psychosis, preferably with an atypical antipsychotic, continued evaluation regarding akinetic depression or akathisia, cognitive-behavioral psychotherapy and evaluation for undetected medical problems or substance abuse.

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