Post-Psychotic Depression in Schizophrenia

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Abstract

Although a depressive state is known to occur following the resolution of an acute psychotic episode, little research has investigated its etiology, course, prognosis and treatment. Very often the depression is mistaken for an extrapyramidal-like syndrome – the secondary effect of antipsychotic medication – as a sense of inevitability assails both the patient and therapist. Post-psychotic depression, far from being an obscure and undefined clinical picture, has the characteristics of a clear-cut syndrome. Nevertheless, it was only recently referred to as a distinct entity in psychiatric classification systems. As a result, different researchers used varying criteria for the definition of the phenomenon, and the data collected in the different studies are therefore difficult to compare. We present a critical review of the data published to date, with emphasis on the importance of early recognition and treatment of post-psychotic depression.

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Depressive complaints are a well-known complication of a psychotic episode [1]. Patients usually experience a strong sense of anhedonia (apathy and lack of interest in everything) and depressed mood. They also complain of insomnia and lack of or diminished appetite or libido.

The main clinical signs of post-psychotic depression are a depressed affect and a generalized psychomotor slowness. It should be stressed that PPD, according to its present DSM definition, is the occurrence of these symptoms during the residual phase of schizophrenia, i.e., following the disappearance of the symptoms meeting criterion A for schizophrenia. Although not included in the definition of PPD, Cutler and Siris [2] reported that approximately one-quarter of schizophrenic and schizoaffective patients with PPD experienced panic attacks, indicating that symptoms of anxiety may be part of the clinical picture of PPD in patients with schizophrenia. Many cases are also associated with suicidal ideation with or without guilt feelings. Shuwall and Siris [3] investigated the relationship of suicidal ideation, anxiety and psychosis in a group of schizophrenic and schizoaffective patients with PPD. Their findings suggest that in these patients the presence of psychosis and/or anxiety is associated with higher levels of suicidal ideation independent of the level of depression.

PPD = post-psychotic depression

Historical development and diagnostic difficulties

Symptoms of depression are common in patients with schizophrenia and probably constitute a diverse group of states of various etiologies rather then a single specific syndrome. Following Bleuler's initial description in 1911 [4], numerous researchers addressed different aspects of depressive symptoms, using a wide range of definitions and criteria for these symptoms. In 1920, Mayer-Gross [5] described despair or denial of the future as a mode of reacting to a psychotic experience. Mayer-Gross was the first to refer to the aspect of a post-psychotic phenomenon, which he referred to as a reaction to the psychotic experience. Eissler, in 1951 [6], presented a description of the syndrome as the "phase of relative clinical muteness" following the acute phase of schizophrenia. In 1966 Semrad [7] discussed the dynamic aspects of the post-psychotic period and suggested that during this stage, as the patient progresses out of his narcissistic regressed position with its major use of denial, projection and distortion, he or she functions more as a "depressed" patient.

In 1976, McGlashan and Carpenter [8,9] thoroughly depicted the clinical picture of PPD and were the first to confer upon it the status of a syndrome. However, several authors continued to disagree on both the etiology of the syndrome and, more important, its existence as an independent clinical entity. Goplerud and Depue [10,11], in opposition to McGlashan and Carpenter, showed that a clearly differentiated episode of depression in the aftermath of acute psychosis reportedly occurred in approximately 25% of all patients hospitalized with a diagnosis of acute schizophrenia. Moreover, there was a high congruence of the pre-morbid functioning, symptomatol-

ogy and clinical course in patients with PPD following acute schizophrenic episodes and in patients in the depressed phase of a bipolar affective-like disorder misdiagnosed as acute schizophrenia.

In 1980, Silva and Yesavage [12] reported on a patient with a remarkable correlation ($r = 0.94$) of schizophrenia and affective symptoms. Although at first glance this seemed to confirm the findings of Goplerud and Depue, Silva and Yesavage highlighted the difficulties in diagnosing schizoaffective disorder. The proposed solutions included the frequent use of an appropriate rating and diagnostic scale, improving statistical methods, and "recognizing that PPD is common and may mimic primary affective disorders."

As time went on, more precise criteria were set and better methods developed for the diagnosis of schizophrenia and mood disorders. It became clear that the arguments of Goplerud and Depue were not relevant. Not only schizoaffectives but also patients clearly diagnosed as schizophrenics demonstrated depressive episodes during their illness.

In the early 1980s some authors suggested that PPD may be drug related. Since various drugs, including antihypertensives, anxiolytics, antibiotics, antidepressants, corticosteroids, choline, indomethacin, levodopa, metronidazole, oral contraceptives, sulfonamides and physostigmine, have been reported to produce depression as a side effect, so might neuroleptics, used in the treatment of schizophrenia, produce a depressive syndrome. Moreover, it was claimed that extrapyrimidal side effects, usually found during treatment with neuroleptics, may also mimic depressive syndrome. It is interesting to mention that PPD was described as early as 1920 whereas the first neuroleptic drug, chlorpromazine, was first introduced in the early 1950s.

In light of the fact that depression may develop spontaneously and independently of neuroleptic medication, Ananth and Ghadirian [13] suggested that PPD includes three types of depression: pendular (primarily disease related), chronic (primarily environment related), and amine depletion (drug related). Thus, PPD is a clinical entity with different etiologies, with drug-induced depression constituting one subgroup of PPD.

Further studies produced inconclusive data. In the work of Hogarty and Munetz [14], equal numbers of non-depressed patients on drug and placebo manifested PPD. They found no evidence that drugs contributed to the depression or that the depressive signs were primarily extrapyramidal. Although these data were conclusive, they showed only that PPD was not neuroleptically induced and did not rule out or confirm its existence as a distinct clinical entity.

It became progressively evident that researchers were referring to different clinical entities with common clinical signs and symptoms that resembled a depressive episode. In 1982, Mandel et al. [15] conducted an extensive trial of 211 schizophrenic patients and found that depression had developed within 5 months of discharge in 25% of them. The depressed patients had a more chronic psychiatric history and, contrary to the hypothesis that depression is a favorable prognostic indicator, were more likely to relapse. This 25% incidence agreed with the 1976 estimate of McGlashan and Carpenter. Thus, by the middle of the 1980s, two general groups of researchers could be identified: those who claimed that PPD was merely a primarily extrapyramidal syndrome, neuroleptically induced [16,17], and those who claimed that PPD was a clinical entity, not related to medications [18–20].

As mentioned above, the lack of a uniform definition of PPD has led to the use of various criteria systems and definitions for this disorder by different researchers. In their retrospective study on 46 schizophrenic patients Minu and Ushijima [21] defined the term "post-psychotic collapse" as the state of underactivity that emerged after an improvement in acute psychotic symptoms, such as hallucinations, delusions, excitement and catatonic symptoms. Patients in this state claim to have lost their energy and vitality and wish to lie on their beds for most of the day.

As mentioned above, the timing of the depressive symptoms in relation to the course of the disease is of major importance. Green and colleagues [22] examined the temporal relationship between onset of depressive and psychotic symptoms in 27 patients with recent-onset schizophrenia or schizoaffective disorder. They found that the highest frequency of occurrence of depressive symptoms was simultaneous with the occurrence of the psychosis, and that no post-psychotic pattern exists. This study was strongly criticized on several grounds – namely, the scaling system used by the researches to rank the symptoms [23], and the 8 week period of follow-up following the psychotic event compared with the widely accepted 10–45 weeks following hospital discharge [24].

In 1994 PPD was defined in the DSM classification of the American Psychiatric Association [25]. Hopefully, the establishment of these uniform and universal criteria will enable the further study of PPD in a more uniform manner, which, in the future, will allow us to more easily analyze and compare the data from the different sources and to further understand this common and important clinical problem.

Negative symptoms and PPD

It should be stressed that anhedonia, apathy, abulia (inability to make decisions), alogia (inability to speak) and diminished drive for social interactions can sometimes be a manifestation either of negative symptoms or of PPD. Siris [26] in 1988 showed that half of 46 patients with PPD had signs that could also be attributed to negative symptoms and concluded that the two disorders could not be clearly differentiated. In contrast, Barnes [27], in 1989, following Pogee-Gelle et al. [28] in 1982, examined 194 chronic schizophrenic patients, 13% of whom had depressed mood. His data showed no significant correlation between depression and any of the following: negative symptom, parkinsonism, tardive dyskinesia, use of anticholinergic drugs or the current dose of antipsychotic medication. However, it is noteworthy that Siris did not distinguish between

schizophrenia and schizoaffective disorder and that his sample was smaller than that of Barnes.

We therefore subscribe that PPD is not the same entity as negative symptoms, since the former is a distinct period characterized by depressed mood as a primary symptom that does not correlate with the existence of negative symptoms as mentioned above [25]. We subscribe to the position of Siris [29], who found a clear difference between akinesia on the one hand and PPD on the other.

Akinesia and PPD

In 1987, two papers were published almost simultaneously in the *Journal of Clinical Psychiatry*, one by Siris et al. [30] and the other by Van Putten and Marder [31]. Siris was by then an eminent researcher working on the pharmacological treatment of PPD. He was never involved in the discussion on whether PPD was a true syndrome or drug induced. Over the years he studied the effects of adjuvant imipramine or amitryptyline in the treatment of depression following a psychotic episode, and the results were encouraging. In his paper "Akinesia and post-psychotic depression: a difficult differential diagnosis" [28], he argued: "detailed clinical case descriptions highlight the potential symptomatic overlap between the syndrome of akinesia and postpsychotic depression in neuroleptic-treated patients." The cases demonstrate that both syndromes may resemble major depression phenomenologically. However, the response to medication of the two syndromes was not identical. Therefore, he claimed, a different medication response may be a potentially useful tool for distinguishing between the various PPD-like states in the course of schizophrenia or schizoaffective disorder. He found that PPD was responsive to adjuvant tricyclics, whereas akinesia was not, reinforcing the previous hypothesis of its extrapyramidal origin. The paper of Van Putten and Marder accurately described akinesia as a behavioral state of diminished motor and psychic spontaneity that is difficult to distinguish from the negative symptoms of schizophrenia. The most useful clinical correlates of akinesia are a subjective sense of sedation and excessive sleep. These authors claimed that the disorder interferes with social adjustment and "may manifest as postpsychotic depression." They further claimed that the akinetic syndrome is strongly associated with dysphoric responses to neuroleptics and has even been linked to suicidal and homicidal behavior in extreme cases. These two papers established the existence of two different clinical entities: PPD and akinetic syndrome, both of which may appear after a psychotic episode but which have two completely different and recognized etiologies.

Today, at least two separate clinical entities are recognized: a depression-like syndrome due to extrapyramidal side effects in cases of long-term treatment with neuroleptic drugs, and a pure depressive syndrome, PPD, not primarily related to any kind of drug treatment and clinically characterized by depressed mood, low energy level, low pleasure capacity and low self-esteem. Recent studies have reconfirmed the earlier findings of McGlashan and Carpenter concerning the high incidence, often around 25%, of depression-like symptoms occurring during the post-psychotic course of patients diagnosed as having schizophrenia, even when stringent diagnostic criteria are used and when the diagnosis of depression is made on a syndromic rather than on a merely symptomatic basis.

Treatment

Despite anecdotal experience suggesting that adjunctive antidepressant medication may be useful in treating course-related depressive symptoms in at least some schizophrenic patients, and despite reports of the popular use of this strategy, few well-controlled prospective studies have investigated the addition of an antidepressant medication to the ongoing neuroleptic regimen in schizophrenic patients with depressive symptoms. Moreover, methodological problems may have distorted the results. These include the lack of three important factors: a) a syndromic definition of depression, b) a clear determination of how many patients in the trial were still psychotic and how many were post-psychotic at the time of attempted treatment of the depressive symptoms, and c) an attempt to eliminate the potentially highly confounding neuroleptic side effect of akinesia. Although the favorable response of PPD to imipramine was empirically known, Siris et al. in 1987 [30] conducted the first comprehensive study on the benefit of adjunctive imipramine in the treatment of PPD using the syndromal definition of depression. They showed that patients with an operationally defined syndrome of PPD were more responsive to imipramine added to an ongoing regimen of antipsychotic drugs. Exacerbation of psychotic symptoms did not occur with these regimens [32]. In 1988 Siris and Strahan [33] reported that in nine patients with PPD who were initially responsive to adjunctive imipramine treatment, tapering of the adjunctive imipramine 6 months after the initial response led to the return of depressive symptomatology. The control group, which continued to take imipramine, showed no re-exacerbation of depression. The relapse of depression following discontinuation of imipramine treatment or switching it to placebo was reconfirmed by other studies [34,35]. In addition, it was observed that discontinuation of imipramine also led to relapse into psychosis despite continuation of neuroleptics [35]. Siris et al. [36] reported the superior outcome of adjunctive imipramine treatment for PPD in a 9 week compared to a 6 week regimen. These results show that although imipramine therapy helps contain the appearance of PPD, its effect is not as radical as expected in cases of major affective disorders. Additional trials conducted by Siris and co-workers [35,37] further established the role of treatment with adjunctive imipramine to the neuroleptic regimen in patients with PPD, both in the short and long term.

Conclusions

Evidence indicates that PPD is a distinct entity, occurs in approximately 25% of psychotic patients, and can be treated

with antidepressant medication. Research data suggest that PPD should be differentiated from akinesia, neuroleptic-induced syndrome, and negative symptoms. The inclusion of a definition and diagnostic criteria for PPD in the DSM system has established a more uniform and widely accepted concept that will hopefully enable a better and more informative approach to this important entity.

Furthermore, given the common features of PPD and negative symptoms, and since the "atypical" neuroleptics such as clozapine are thought to act against negative symptoms, further research on the incidence of PPD among schizophrenics treated with these drugs is needed in order to establish whether these drugs can prevent or reduce the incidence of PPD.

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It is a painful thing
To look at your own trouble and know
That you yourself and no one else has made it

Sophocles, 450 B.C.