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ORIGINAL ARTICLE

A Conceptual Analysis of Post-psychotic Depression

Octavian Vasiliu[1], Andrei G. Mangalagiu[1], Bogdan M. Petrescu[1], Cristian A. Cândea[1], Corina Tudor[1], Cristina F. Pleșa[2,3], Diana G. Vasiliu[4], Cristian Năstase[5], Carmen A. Sirbu[2,3]

[1] Department of Psychiatry, "Dr. Carol Davila" University Emergency Central Military Hospital, Bucharest, Romania
[2] Department of Neurology, "Dr. Carol Davila" University Emergency Central Military Hospital, Bucharest, Romania
[3] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[4] Regina Maria Foundation, Bucharest, Romania
[5] Department of Neurosurgery, "Dr. Carol Davila" University Emergency Central Military Hospital, Bucharest, Romania

Correspondence: Octavian Vasiliu, octavvasiliu@yahoo.com

Abstract: *The conundrum of post-psychotic depression (PPD) is still present in the psychiatric literature, for more than a century since it was first described by Mayer-Gross. After a short existence in the DSM-IV and ICD-10, this nosological construct was excluded from newer versions of the mental disorders classifications. Therefore, an exploratory analysis of the PPD concept was considered useful both from clinical and theoretical perspectives. There is a high prevalence of depressive symptoms in patients with schizophrenia spectrum disorders (SSD) and, although not all of them represent cases of PPD, they are considered risk factors for suicide. The arguments and contra-arguments for/against PPD were reviewed, and the potential pharmacological interventions for this disorder were analyzed. The explored evidence indicates that PPD is worth further investigation, and in order to differentiate it from schizoaffective disorder, negative symptoms of SSD, or depressive manifestations within the acute psychotic episodes, clearly defined criteria should be found. The use of validated scales, like the Calgary Depression Scale for Schizophrenia and the InterSePT Scale for Suicidal Thinking, is recommended for the initial assessment of depression and suicidal risk in patients with SSD, but also for their monitoring during the acute and maintenance phases. Besides the administration of combined, antidepressant and antipsychotic treatment, the use of clozapine, and the recommendation to initiate treatment for SSD with atypical antipsychotics whenever possible, there is a dearth of studies exploring specific interventions for PPD. Future studies are expected to address the validity of the nosological construct of PPD and the most adequate therapeutic and prophylactic interventions in patients with SSD.*

Keywords: *post-psychotic depression, schizophrenia spectrum disorders, atypical antipsychotics, clozapine, typical anti-psychotics, antidepressants*

INTRODUCTION

Depression that may appear in the context of schizophrenia is considered a complex and heterogeneous group of disorders [1,2]. Mayer-Gross was the first author who described in 1920 the reaction to a psychotic experience that manifests itself as a clinical version of depression [3]. He considered "despair" as the main clinical characteristic of this depression that follows a full-blown psychotic episode, and considered this manifestation to be determined by the patient's increased awareness about the severity of his/her illness [3,4]. A few decades later, Semrad also explored the psychodynamic mechanisms for post-psychotic depression (PPD), emphasizing the denial, projection, and distortion of reality after the remission of acute psychotic episodes [5]. PPD was described by several authors as "retarded depression, with strong neurasthenic and schizoid components" emerging after the patient is discharged from the hospital, and often ignored by mental health specialists [6]. Depressive manifestations in patients with SSD have been conceptualized as a psychological reaction to acute psychosis, as previously mentioned, but also as a comorbidity of two distinct pathologies or a proof for the existence of a continuum between schizophrenia and mood disorders [2]. According to psychoanalysts, PPD is a reaction to psychosis, which appears after the remission of the psychotic episode, more specifically, after the Ego regained a significant proportion of its strengths [7,8].

Some authors, however, reported, based on the analysis of the temporal relationship between the onset of depressive and psychotic symptoms in 27 patients, that the first reports on mood manifestations were frequently at the same time same as the onset of psychosis [9]. Therefore, PPD is a controversial concept, as no specific pattern for its onset could be detected, leading to the assumption that depressive manifestations may be only associated with acute psychotic manifestations.

However, a series of studies focused on PPD have tried to delineate the risk factors, clinical features, and prognosis of this nosological entity, as a distinctive pathology from depressive symptoms belonging to acute schizophrenia, mood episodes within a schizoaffective disorder, or adverse events of the antipsychotics or other drugs. For example, a comparison of patients with schizophrenia presenting or not with PPD (N=30 participants in each group) showed that belonging to elementary (or nuclear) families, longer duration of psychotic phase, more frequent hospitalizations, and more sadness and anxiety-somatization during the acute phase of the disease were associated with PPD [10]. A past history of depression was also more frequently reported in the study group vs. controls [10]. Age of onset, sadness during the acute psychosis phase, premorbid adjustment, social support, and life events were significant determinants of severity for PPD, according to the multiple regression analysis [10].

A cohort study with a 10-year follow-up compared the evolution of 29 patients with schizophrenia and PPD vs. only schizophrenia [11]. Patients with PPD presented at an older age with the onset of schizophrenia and more auditory hallucinations; also, they were admitted more often, but their hospitalizations were of shorter duration [11].

A study that explored the main clinical differences between primary depression (N1= 98 patients) and PPD (N2= 71 patients) concluded that depressed mood, reduced energy, and pathological guilt were more frequently detected in patients with primary depression, while sleep disturbance and ideas of reference with a theme of guilt were more consistently associated with PPD [1].

The duration of PPD was estimated by different authors as varying between several days to several months [12], or, more specifically, between 2 and 26 weeks [8].

Depressive symptoms during a psychotic episode may be as frequent as 50%, and they may correlate with the frequency of relapses, defined by re-admission rate and total length of inpatient treatment [13]. By comparison, the prevalence of PPD reported in the literature was around 30-36% [14,15]. Higher rates of PPD were reported in patients with a first episode of psychosis (FEP), up to 50% [3,15]. Older age, a higher familial load of psychoses, a longer duration of untreated psychosis, the presence of an FEP, and a higher number of stressful life events were associated with a higher risk of PPD [14]. Depression was reported by patients with FEP as being linked to the psychotic experience and to the process of recovering from this experience [16]. Feelings of shame, doubt, and embarrassment, but also loss and social isolation, were associated with the presence of the psychotic experience [16]. Also, the onset of PPD has been correlated to the existence of positive symptoms during acute schizophrenia, especially delusions and hallucinations [17]. A study that enrolled 44 patients (aged 10-40 years) with schizophrenia, all of them during their first six months of the illness, explored the risk of developing PPD one year after discharge from the hospital [18]. Four patients were diagnosed with depression in this interval, according to a Hamilton Depression Rating Scale (HAMD) score ≥17 [18]. Only one case recovered from PPD completely during the follow-up [18]. All patients in this trial were undergoing phenothiazine treatment throughout the monitoring period [18].

In a longitudinal study, 17 patients with schizophrenia were monitored for 6 months, using the 18-item Profile for Rating Depressive and Schizophrenic Behavior (PRDSB) [19]. After recovering from acute psychosis, only 2 participants developed major depressive syndrome [19]. However, over 40% of these patients were interviewed only by telephone after their discharge, so a potential bias regarding the sensitivity of the assessment method can not be excluded [19]. Also, the ethnic homogeneity of the study group could be construed as another potential bias that limits the generalizability of the results.

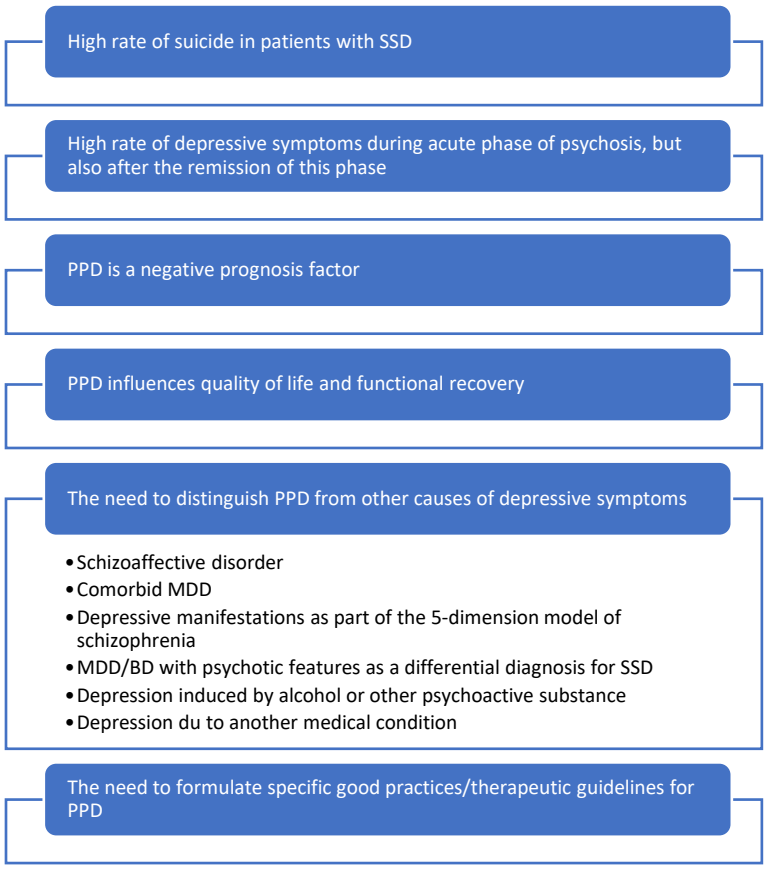
A longitudinal, observational study (N=105 patients with schizophrenia) reported during 12 months of monitoring that depression accompanied acute psychosis in 70% of cases, and remitted together with psychosis, while PPD appeared in 36% of these patients, without a concomitant increase in psychotic symptoms [20].

Focusing the analysis of the PPD concept on the most renowned classifications of mental disorders, this pathology was mentioned for the first time in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), published in 1994 [21]. PPD, according to the cited source, involves the presence of “a Major Depressive Episode that is superimposed on and occurs only during the residual phase of schizophrenia” [21]. The definition of PPD required in the DSM-IV the presence of depressed mood, as a core symptom, and excluded the direct consequences of drug abuse, medication use, or a general medical condition [21]. However, in the fifth edition of the DSM, published in 2013, this nosological entity no longer appears [22].

The tenth edition of the International Classification of Diseases, edited by the World Health Organisation (ICD-10) in 1993, grouped PPD (named "post-schizophrenic depression") together with different types of schizophrenia, in the same chapter, coded F20 [23]. The definition of PPD was "a depressive episode, which may be prolonged, arising in the aftermath of a schizophrenic illness" [29]. It is important, according to the ICD-10, that residual schizophrenic symptoms still be present, although they cannot dominate the clinical status [23]. Newer versions of ICD-10 placed PPD in the category of "other specified depressive episodes" [24]. The latest edition of ICD (ICD-11), the first version published in 2019, did not reference PPD [25].

The convoluted trajectory of the PPD concept from its genesis to the present day is rather difficult to explain, but several important factors contributing to this conundrum represent the main objective of the current review (Figure 1).

Figure 1: Rationale for exploring post-psychotic depression



PPD= postpsychotic depression, SSD= schizophrenia spectrum disorders, MDD= major depressive disorder

The rationale for conducting this review derives from several important clinical and theoretical aspects. First, it is essential to obtain adequate control over depressive symptoms in patients with SSD, because of the high rates of suicide reported in this population [26]. PPD seems to be a factor for negative prognosis in the long-term for patients with schizophrenia, especially because of the higher risk for suicide, but also due to its significant impact on the quality of life and general well-being [17]. Second, the need to delineate clinically PPD from other causes of depression in patients with SSD, in order to find the most adequate therapeutic strategies. To support this, the data presented suggest that PPD is a distinct nosological entity from antipsychotic-induced adverse events, negative symptoms of schizophrenia, depression with psychotic symptoms, or schizoaffective disorders [14,17]. This means that good clinical practices in patients with SSD would involve differentiating between PPD and other frequently reported confounding factors.

THE MULTIFACETED CONSTRUCT OF PPD

Although the history of PPD has been over a century, there is a dearth of good-quality studies exploring this pathology's

clinical and epidemiological aspects. However, an analysis of the main dimensions of the PPD construct can be done, based on the available evidence (Table 1).

Table 1: Pros and cons in the analysis of the PPD construct

Pros	Cons
PPD was associated with any type of antipsychotic treatment, therefore it is not an adverse event to the first generation antipsychotics	PPD does not exist because it consists of adverse effects of older antipsychotics
There are longitudinal studies that confirm the persistence of depressive symptoms after the remission of acute psychosis and cases where depression followed a period of psychosis remission	The construct should not be treated as a distinct entity, it only accompanies acute schizophrenia
Negative symptoms and depression do not overlap to the point they are indistinguishable	Negative symptoms cover the presence of depression, therefore depression may be observed only after the remission of those symptoms
There are specific scales for measuring depression in patients with SSD, as well as their suicide risk	PPD can not have its own diagnosis criteria and its severity can not be determined, due to the fact that it is secondary to other symptoms

To begin with the presentation of the reasons why PPD is not yet a fully recognized diagnosis, it must be specified that PPD was correlated by different authors with the effects of first-generation antipsychotics, and they called this phenomenon "pharmacological depression" [27-29]. In a multicenter study (N=211 patients with schizophrenia), depression (quantified with HAMD) was detected in 25% of the cases, all of them treated with fluphenazine (either hydrochloride or decanoate) [30]. This study also showed that depression was associated with a more chronic psychiatric history and a higher rate of relapse [30]. Also, older drugs used to treat SSD, such as chlorpromazine or reserpine, have been associated with lethargy, psychomotor retardation, and anergy, which are acknowledged adverse events of these agents [30].

Secondly, the negative symptoms of schizophrenia may cover the depressive symptoms, making them more difficult to detect [14,17]. Anhedonia, defined as a reduced ability to experience pleasant emotions, is considered both a negative symptom in SSD, and a central manifestation in major depressive disorder (MDD) [31-34]. Therefore, it is considered "a transdiagnostic symptom", and its explained by dysfunctions of the reward and aversion pathways in the central nervous system (CNS) [31]. Furthermore, negative symptoms like alogia and avolition may prevent the detection of depressive symptoms, because they interfere with both the interview and the observation of the patients.

The third aspect refers to a contradiction: although current diagnostic classifications do not include mood symptoms in the core criteria for schizophrenia, these are frequently considered part of the clinical picture, as additional manifestations [35]. According to the five-dimension model of schizophrenia, depression is a core clinical component, together with the positive, negative, agitation-excitement, and disorganization symptoms [36]. However, as mentioned in the introductory chapter, there is no reference to PPD in the latest versions of the ICD or DSM [22,25].

The fourth facet of the PPD controversy is represented by the fact that although differentiating between schizophrenia, schizoaffective disorder, and depressive/bipolar disorder with psychotic features is quintessential, in clinical practice it is frequently difficult to make the right diagnosis. Factorial analysis using validated instruments for psychosis and mood symptoms measurement (e.g., Positive and Negative Syndrome Scale – PANSS, Young Mania Rating Scale – YMRS, Montgomery Depression Rating Scale – MADRS, and Calgary Depression Scale – CDSS) confirmed the existence of very complex structure of the clinical manifestations in patients with schizophrenia [37]. Subclinical mood symptoms have been confirmed by this type of analysis, structured within up to 15 factors – e.g., positive, negative, somatic, anxiety, neurocognitive, disorganization and manic, depressive, psychomotor agitation, hostility/violence [37]. These results support the overlapping model of phenotypes between psychotic mood disorders and SSD, and the possibility of misdiagnosing a patient with a mood disorder and associated psychotic features as having an SSD [37].

However, each of these confounding factors may be addressed. The first argument is precarious because even SSD patients treated with newer antipsychotics may develop depressive symptoms and the effect of these pharmacological agents on depressive symptoms is only small to medium [38]. According to a Cochrane review, based on five reports about

patients diagnosed with both schizophrenia and depression, there was no significant difference in efficacy (evaluated by PANSS scores) between quetiapine and haloperidol, sulpiride was significantly superior to chlorpromazine (reflected in the severity of depressive symptoms), and clozapine was superior to the association of another antipsychotic and an antidepressant (moclobemide/mianserin) [39]. A significant reduction of depressive symptoms in patients with schizophrenia was reported only if a CDSS score at baseline was ≥5, unlike the positive, negative, and general symptoms (scored with PANSS), in a naturalistic study that enrolled adult patients with ≥2 years of treatment with clozapine (N=23) or other atypical antipsychotics (N=23) [40]. At the follow-up visit, patients who received other antipsychotics led o superior results when compared to clozapine on depressive symptoms, but only when the analysis was limited to those with clinically relevant depression [40]. It can easily be deduced that the results of studies exploring the impact of antipsychotics on depressive symptoms in SSD are quite heterogenous, varying from no difference in outcomes between typicals and atypicals, to superiority of clozapine vs. other antipsychotics combined with antidepressants, and to superiority of other atypicals to clozapine, but only in certain subpopulations.

The second argument is even more difficult to support because authors exploring PPD showed that this syndrome "is usually stable phenomenologically, often lengthy, and may be resistant to all treatment modalities" [6]. Even considering the last part as an exaggeration determined by the lack of adequate therapeutic resources when that statement was formulated, there is still enough ground to back up an independent syndrome, with pharmacological and clinical peculiarities. There are authors that contradict the third argument, stating that depression is "a frequent comorbidity in the course of schizophrenia" [7], and not just a cluster of symptoms intrinsic to SSD.

The fourth argument can also be easily disqualified because there are validated instruments, currently in clinical use, that allow for the monitoring of depressive symptoms in patients with SSD. CDSS is an instrument created by Addington et al., first published in 1990, for the purpose of measuring depression in SSD, starting from selected items within HAMD and Present State Examination (PSE) [41]. This instrument was validated on 50 patients with acute psychosis, and it has 11 items, with a Cronbach's alpha of 0.84-0.89 [41,42]. The validity of CDSS in evaluating mood symptoms in patients with SSD was confirmed by subsequent studies and reviews, and this scale was significantly correlated with HAMD and MADRS [43,44]. CDSS differentiated depressive symptoms from other clinical manifestations of SSD and also had good predictive validity [44]. Another study comparing CDSS and HAMD (N=119 in-patients with acute schizophrenia) concluded that CDSS had a higher sensitivity than HAMD in assessing mild or severe depression, while the specificity was comparable high for both instruments [45].

The InterSePT Scale for Suicidal Thinking (ISST) has 12 items and was created to assess suicidal ideation in SSD patients [46]. Two validation studies (N=22 and 980 patients with SSD) confirmed that ISST is reliable and valid if used to assess ongoing suicidal ideation in patients with SSD [46]. Both ISST and CDSS can be used to provide information necessary in the case management of patients with SSD and suicidal risk [47].

Based on its properties, CDSS is considered a first-line instrument to determine the severity of depressive symptoms in patients with SSD, and a review that compared 6 different instruments targeting the same symptoms formulated this recommendation [44]. A study that explored the diagnosis of major depressive episodes in 84 patients with schizophrenia found that CDSS was superior to the Beck Depression Inventory (BDI), HAMD, and PANSS-D when evaluating the Receiver Operating Characteristics (ROC) curves [48].

However, the possibility that PPD symptoms may be, in fact, the continuation of depressive symptoms with onset in the acute psychotic phase, can not be completely excluded [7]. On the other hand, if PPD is detected after a period of psychotic symptoms remission, then it may be considered part of a new episode of schizophrenia [7].

PPD may be confounded with negative symptoms of SSD, as previously mentioned. The discussion about primary and secondary negative symptoms is a very complex topic, that clearly exceeds the objective of this paper. As a general definition, primary negative symptoms are intrinsic to schizophrenia, a specific clinical dimension, while secondary negative symptoms derive from the presence of positive symptoms, depression, antipsychotics' pharmacodynamical properties, substance use disorders (SUDs), and social withdrawal [49-51]. After the remission of psychotic symptoms, the depressive symptoms were still present, although their rate decreased from 60% during the acute psychotic episode, to 40% after 5 years follow-up [52].

In conclusion, a correct diagnosis of PPD should include a clinical and psychometric evaluation of psychotic and depressive symptoms, a thoroughly-conducted screening for comorbidities (organic, toxic, or psychiatric) [53-55], an analysis of the risk factors for the persistence of depressive symptoms [56,57], a clear collection of personal medical history (in order to establish the temporal succession of psychotic and depressive manifestations), and an accurate pharmacological anamnesis.

THERAPEUTIC INTERVENTIONS FOR PPD

Adapting the type and dosage of antipsychotic agents in patients with SSD was signaled by different authors as a method to decrease the risk of PPD [2]. Re-evaluation of the main drugs administered during the acute phase of psychosis or the prescription of adjuvant antidepressants or ECT has also been suggested as a case management strategy in PPD [2]. Psychotherapeutic, social, and institutional support are useful options for patients with PPD [2].

A review (n=20 articles) exploring the results of available pharmacological and psychosocial treatments of PPD after the first episode of psychosis did not find support for one intervention in favor of another [58]. Online psychotherapy and treatment with ω-3 polyunsaturated fatty acids (PUFA) have been associated with some favorable results [58].

Olanzapine (5-15 mg/day) was compared to risperidone (4-8 mg/day) in the treatment of PPD (according to the DSM IV criteria) in patients with schizophrenia (N=76), and a clinically significant decrease in MADRS scores (-4 points vs. baseline) was reported after 8 weeks of treatment with either antipsychotic [59]. This study used a randomized, double-blind, parallel-group design. The comparative analysis of the two interventions did not detect any significant MADRS differences at the end-point [59]. A high response rate (≥20% reduction in MADRS scores) was observed during antipsychotic treatment [59]. In order to control for possible confounders of PPD, patients with akinetic symptoms were excluded from this trial [59]. The same team reported on another randomized, placebo-controlled trial, with 24 patients diagnosed with schizophrenia or schizoaffective disorder and PPD or negative symptoms, who continued their six-month adjunctive imipramine to fluphenazine decanoate/ benztropine mesylate treatment or were tapered to placebo + fluphenazine decanoate/benztropine during one year [60]. More patients receiving a placebo relapsed into PPD, at a statistically significant level; also, patients who received placebo experienced relapses into psychoses [60]. Yet another trial conducted by the same team showed that double-blind, controlled discontinuation of imipramine after stabilization (N=14 participants with schizophrenia undergoing treatment with fluphenazine + benztropine) led to relapse into PPD in all patients with placebo vs. only two out of eight in the antidepressant-receiving group (significant difference, p=0.009) [61].

A controlled trial investigated the effects of imipramine hydrochloride for PPD for six weeks, in a double-blind manner [62]. All patients (N=33) were diagnosed with schizophrenia or schizoaffective disorder and received a stable dosage of fluphenazine decanoate and one week-trial with benztropine mesylate was initiated to rule out akinesia; all participants were either non-psychotic or only residually psychotic at baseline [62]. The PPD diagnosis was based on current major or minor depression for at least four weeks, and a HAMD score ≥12 for at least three consecutive weeks [62]. The depressive symptoms (according to HAMD and SADS, Schedule for Affective Disorders and Schizophrenia scores) were controlled better with imipramine vs. placebo and their global clinical status (according to the CGI scores) also improved more consistently in patients receiving the active drug [62]. The psychotic symptoms and tolerability profile did not change significantly between groups [62]. The use of adjunctive imipramine to fluphenazine was further explored by the same team, in a larger and more heterogenous study group [63]. The positive effects of the combined treatment were still detected in the total sample, but the significance of the results was lower [63]. These differences were explained in a post-hoc analysis by the higher level of psychotic symptoms severity, and by "more refractoriness of depression" due to failed previous trials of antidepressants [63].

In a continuation trial, four out of five patients previously stabilized on imipramine + fluphenazine decanoate + benztropine for PPD relapsed into depression six months after the tapering of the antidepressant [64]. The control group, consisting of four patients who did not discontinue imipramine, did not present depressive relapses [64]. The same research team reported on ten PPD patients with good responses to imipramine who relapsed six months after discontinuation of the antidepressant, that was added to fluphenazine decanoate and benztropine [65].

A 24-week double-blind trial compared haloperidol (mean dose 17.5 mg/day) and thiothixene (mean dose 31.8 mg/day) in 46 outpatients with schizophrenia, from their efficacy and safety properties [66]. One of the outcomes was the incidence of treatment-emergent depression, assessed by the Hamilton Depression Rating Scale (HAMD) and Zung Self-Rating Depression Scale (ZSRS) [66]. Haloperidol was superior to thiothixene on the "cognitive disturbance" HAMD factor [66]. Clinically significant symptoms were reported in five patients treated with haloperidol and three receiving thiothixene [66]. The impact on the psychotic symptoms was also more important for haloperidol, according to the Brief Psychiatric Rating Scale (BPRS) scores [66].

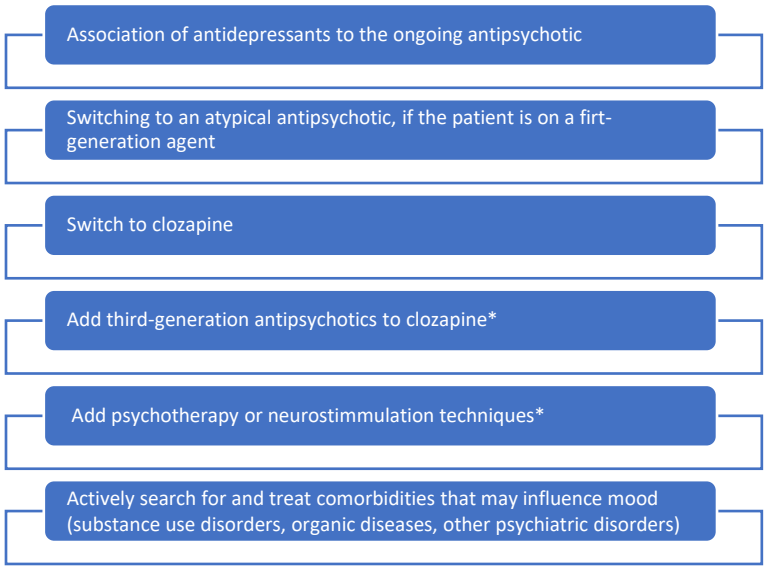
In a trial that compared the antidepressant effects of fluphenazine decanoate (mean dose 32.8 mg fortnightly) and flupenthixol decanoate (mean dose 36.9 fortnightly) administered two-weekly in a group of 48 out- and inpatients with schizophrenia during 15 weeks [67]. No significant differences could be found between groups regarding the number and severity of mood impairments and depression

[67]. Nineteen patients developed depression, and the addition of clomipramine was necessary for five participants, with a mean duration of four weeks, and an average dose of 75 mg/day [67]. The onset of depressive symptoms was reported between days 14 and 70 for outpatients and between days 7 and 77 for inpatients [67]. The onset of depression was unrelated to the antipsychotic dose [67]. The instruments used to assess depression in this trial were HAMD, von Zeersen's self-evaluation scale, and AMP-system [67].

According to a review of 7 studies focused on the use of antidepressants in patients with SSD, tricyclic antidepressants administered in combination with first-generation antipsychotics are a safe choice after the acute psychotic phase is controlled [68]. The risk of exacerbating residual psychotic symptoms is considered minimal by the authors of that review [68]. Still, these antidepressants were ineffective against anergy, considered a core symptom of PPD [68]. This is a controversial conclusion because "anergy" can be easily confounded with several negative signs of schizophrenia (such as avolition, apathy, or even anhedonia) [13,49,50,52,69,70]. The incidence of negative symptoms in patients with SSD is reported to be high, with more than 57% presenting with at least one such symptom, and 41% with at least two negative symptoms [69]. Other authors report a prevalence of negative symptoms that may reach 90% for at least one such manifestation, and up to 60% for at least one depressive symptom in FEP [70]. There is a risk of anticholinergic adverse events because of the pharmacokinetic interactions between the two classes of pharmacological agents [68].

Clozapine is considered a good therapeutic intervention in SSD associating mood disorders [71]. Risperidone was superior to haloperidol in decreasing anxiety and depression scores (at 8 mg/day and 10 mg/day, respectively), and the same atypical antipsychotic was more effective than haloperidol and levomepromazine on the Psychotic Anxiety Scale (at 8.6 mg/day, 9.2 mg/day, and 125 mg/day, respectively) [71]. Another review (n=33 studies focused on treatments for SSD with mood symptoms) concluded that combined treatments are as effective as antipsychotics used in monotherapy for acute psychotic exacerbations with depressive manifestations, although "some evidence" for superiority was detected in the case of antipsychotics [72]. For patients developing a major depressive syndrome after remission of acute psychosis, there has been found evidence to support the administration of antidepressants, as add-ons to antipsychotics [72]. The results regarding therapeutic response to antidepressants in cases of subsyndromal depression were mixed [72].

Figure 2: Potential therapeutic interventions for post-psychotic depression



**= extrapolated recommendations from studies with other populations than patients with post-psychotic depression; not yet enough evidence to support their use*

Newer antidepressants have been launched in clinical use, but their efficacy profile in patients with PPD still remains unexplored [73-77]. Also, older antidepressants may be of interest for this topic, if added to atypical antipsychotics, because, as previously reported, the rate of residual depressive symptoms in this population is quite high [52,78]. Other interventions, besides antidepressants and atypical antipsychotics, are waiting to be investigated in clinical trials for depressive symptoms or major depressive episodes associated with SSD [79-81]. Adding third-generation

antipsychotics to clozapine, in cases of ultra-resistance to treatment SSD cases, would also have to be considered a viable option for controlling depressive and negative symptoms [82,83]. Exploring organic, toxic, and psychiatric risk factors for treatment resistance is important when analyzing the most adequate treatment plan for patients with depression, PPD included [84-85].

CONCLUSIONS

The controversy surrounding the diagnosis of PPD is still under scrutiny, because (1) SSDs associate a high rate of suicide, even after the introduction of new generation antipsychotics, (2) there is a significant impact of depression on the quality of life and functional recovery in SSD patients, and (3) the case management of PPD may differ from the interventions recommended in patients with schizoaffective disorder, major depression with psychotic features, adverse events of different drugs with CNS depressogenic properties, and other conditions that may present themselves with depressive symptoms. The data about efficient interventions for PPD derives from older studies, therefore new trials exploring new generations of antidepressants are needed for this population. Based on the reviewed data, there are elements referring to risk factors, clinical characteristics, epidemiology, and even treatment for PPD, but they need to be validated by prospective, good-quality trials.

Conflicts of interest and sources of funding

None to declare.

Authors' contribution

OV conceived the idea of the review. OV, AGM, BMP, CAC, CT and CFP designed the study. OV, CFP, AGM, CAC, CFP, CT, DGV, CN and CAS screened the studies during the primary search. OV, AGM, CAC, CFP and CAS drafted the first version of the review. OV, CAC, CFP, DGV, CN and CAS revised the manuscript and elaborated the review's conclusions. All authors had full access to the data contained in this review and decided to submit the manuscript for publication.

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