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Co-Occurring Depressive Symptoms in the Older Patient with Schizophrenia

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Abstract

Clinicians treating older patients with schizophrenia are often challenged by patients presenting with both depressive and psychotic features. The presence of co-morbid depression impacts negatively on quality of life, functioning, overall psychopathology and the severity of co-morbid medical conditions. Depressive symptoms in patients with schizophrenia include major depressive episodes (MDEs) that do not meet criteria for schizoaffective disorder, MDEs that occur in the context of schizoaffective disorder and subthreshold depressive symptoms that do not meet criteria for MDE. Pharmacological treatment of patients with schizophrenia and depression involves augmenting antipsychotic medications with antidepressants. Recent surveys suggest that clinicians prescribe antidepressants to 30% of inpatients and 43% of outpatients with schizophrenia and depression at all ages. Recent trials addressing the efficacy of this practice have evaluated selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, fluvoxamine and citalopram. These trials have included only a small number of subjects and few older subjects participated; furthermore, the efficacy results have been mixed. Although no published controlled psychotherapeutic studies have specifically targeted major depression or depressive symptoms in older patients with schizophrenia, psychosocial interventions likely play a role in any comprehensive management plan in this population of patients.

Our recommendations for treating the older patient with schizophrenia and major depression involve a stepwise approach. First, a careful diagnostic assessment to rule out medical or medication causes is important as well as checking whether patients are adherent to treatments. Clinicians should also consider switching patients to an atypical antipsychotic if they are not taking one already. In addition, dose optimization needs to be targeted towards depressive as well as positive and negative psychotic symptoms. If major depression persists, adding an SSRI is a reasonable next step; one needs to start with a low dose and then cautiously titrate upward to reduce depressive symptoms. If remission is not achieved after an adequate treatment duration (8–12 weeks) or with an adequate dose (similar to that used for major depression without schizophrenia), switching to another agent or adding augmenting therapy is recommended.

We recommend treating an acute first episode of depression for at least 6–9 months and consideration of longer treatment for patients with residual symptoms, very severe or highly co-morbid major depression, ongoing episodes or recurrent episodes. Psychosocial interventions aimed at improving adherence, quality of life and function are also recommended. For patients with schizophrenia and subsyndromal depression, a similar approach is recommended.

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Psychosis accompanying major depression in patients without schizophrenia is common in elderly patients and is considered a primary mood disorder; for these reasons, it is an important syndrome to consider in the differential diagnosis of older patients with mood and thought disturbance. Treatment for this condition has involved electroconvulsive therapy (ECT) as well as combinations of antidepressant and antipsychotic medications. Recent evidence suggests that combination treatment may not be any more effective than antidepressant treatment alone and ECT may be more efficacious overall.

The goals of this paper are to review the major psychiatric syndromes in older patients involving depression and psychosis (table I). The review focuses on patients with schizophrenia and accompanying depressive syndromes: (i) major depressive episodes (MDE) that do not meet criteria for schizoaffective disorders; (ii) MDE that occur in the context of schizoaffective disorders; and (iii) subthreshold depressive symptoms that do not meet criteria for MDE (e.g. minor and subsyndromal depression). Also included is a discussion of major depressive disorder with psychotic features. These four syndromes may overlap and the classification is imperfect. They likely lie on a continuum, or spectrum, of depression severity with overlapping symptoms and treatment requirements.

We exclude discussion of elderly patients with bipolar affective disorder in this review since our purpose is to focus on elderly patients with primary thought disorders; however, major depression with psychosis is included since this is an important syndrome to consider in the differential diagnosis of schizophrenia disorders with accompanying depressive symptoms. In each section covering one of the four diagnostic categories, we first discuss key diagnostic and clinical issues, followed by an elaboration of management strategies. Since many of the studies addressing psychosis and depression include younger patients and mixtures of younger and older patients, we provide the mean age and age range whenever possible.

1. General Issues in Understanding Depressive Symptoms in Patients with Schizophrenia

The Epidemiologic Catchment Area study indicated that patients with schizophrenia were 29 times more likely than the general population to have a lifetime diagnosis of MDE.[1] Similarly, the National Comorbidity Study suggested that 59% of patients with schizophrenia met *Diagnostic and Statistical Manual of Mental Disorders* (3rd edition) [DSM-III][2] criteria for major or minor depression.[3] Depressive syndromes and symptoms in patients with chronic schizophrenia add an additional burden to the challenges of living with this serious illness. Depressive symptoms are associated with disability, recurrence of illness, demoralization and poor motivation, and risk of suicidality.[4–7] Schwartz and Cohen[8] found that depressive symptoms accounted for nearly 50% of the suicidal intent seen within a sample of 267 patients with schizophrenia between the ages of 18 and 70 years and a mean age ± SD: 37.2 ± 10.2 years. Furthermore, a large population study of 7217 people in Finland aged >30 years conducted over a 17-year period highlighted that schizophrenia with accompanying depressive symptoms leads to elevated risks for natural and unnatural mortality.[9]

The spectrum of mood disorders in patients with schizophrenia includes patients with schizophrenia who have both schizophrenia and MDE as separate, co-occurring disorders, patients who have schizophrenia and MDE that are considered facets of the same disorder (schizoaffective disorder), and patients with schizophrenia who have clinically significant symptoms of depression never fully meeting criteria for MDE. There is a considerable overlap between schizophrenia and depressive disorders from a diagnostic standpoint.

First[10] points out that diagnostic co-morbidity has become the rule rather than the exception in DSM-IV[11] and the *International Statistical Classification of Diseases and Related Health Problems* (10th edition) [ICD-10].[12] Schizophrenia and major depression are two disorders that are on different levels of the Kraepelinian-defined hierarchy and the diagnostic manuals have attempted to keep them mutually exclusive; however, each successive version of these manuals has made an attempt to reduce diagnostic complexity by reducing diagnostic hierarchies. This, in turn, increases the risk for psychiatric co-morbidities.[10]

Depressive symptoms in patients with schizophrenia may have a multi-factorial aetiology. Bressan et al.[13] states that formulation of alternative non-aetiological approaches towards understanding depressive symptoms may be preferable since it is often not practical or even possible to distinguish factors in clinical settings on the basis of aetiology. Nevertheless, this classification of depressive symptoms has persisted and the key components include deciding whether the depressive symptoms are: (i) a component of the core pathology of the disease of schizophrenia;[14] (ii) a part of reactive post-psychotic depression;[15] or (iii) of pharmacogenic origin, which includes akinetic adverse effects due to medications.[16]

Regarding the latter group, akinesia in patients with schizophrenia is most commonly an adverse effect of conventional antipsychotic drugs. Although conventional antipsychotic drugs are not used as frequently in the elderly population as they were in the past, this is still an important issue to consider. Van Putten and May[17] determined that some of their cases of “postpsychotic depression” could be attributed to a toxic effect of antipsychotic drugs. In their series of 94 patients with schizophrenia, 28 developed a mild akinesia (mean age ± SD: 38.2 ± 14.2 years) and 32 never developed extrapyramidal symptoms (EPS) [mean age ± SD: 37.7 ± 11.4 years]. In those patients who developed akinesia, there was less psychosis with a modest but significant increase in depression ratings. Successful treatment of akinesia resulted in significant improvements in patients’ depressive symptoms. In the modern era, it is important to add that selective serotonin reuptake inhibitors (SSRIs) also may evoke akinesia in vulnerable individuals.[18]

2. Major Depressive Episodes that Do Not Meet Criteria for Schizoaffective Disorders

2.1 Classification and Diagnostic Issues

The essential criteria of MDE that do not meet criteria for schizoaffective disorders are that the individual meets criteria for schizophrenia and also has at least one full episode of major depression. However, schizoaffective disorder has been ruled out because symptoms of depression are not present “for substantial portions of the total duration of the active or residual periods of the illness”.[19]

Surprisingly little is known about the characteristics and prevalence of MDE in patients with schizophrenia, a situation that is due, at least in part, to diagnostic conventions. One specific example of an MDE known to occur in people with schizophrenia that may not always meet criteria for schizoaffective disorder is “post-psychotic depression”, classified in the DSM-IV Text Revision (TR), appendix B as “needing further study”.[19] The term “post-psychotic depression” was utilized to describe a state of dysphoria that follows a psychotic episode in schizophrenia.[20] Birchwood et al.[21] claim that a post-psychotic depressive episode can be predicted based on how patients perceive the threat of the psychotic episode, particularly with regard to its effects on their social goals, roles and status. In addition, the degree to which this syndrome affects patients’ perceptions of ‘social shame’ is important.

Post-psychotic depression is one of the diagnostic categories treated differently by the ICD and DSM. The ICD-10 has a specific diagnostic criterion called “post-schizophrenic depression”. The ICD-10 states that post-psychotic depression must occur within *12 months* following the psychotic episode; this time requirement is not required with the DSM-IV criteria. In contrast, an MDE occurring *any time* after a psychotic relapse in a patient with schizophrenia would always be coded by the DSM-IV as “depressive disorder NOS [not otherwise specified]” because post-psychotic depression disorder is classified among the “criteria sets and axes provided for further study”. This categorization likely presumes that depression in people with schizophrenia is somehow different from depression in other people.

Even in the ICD-10 classification system, an MDE occurring more than 12 months after a psychotic episode would be classified as depressive disorder NOS. However, Bressan et al.[13] recommended that diagnosis of post-psychotic depressive episodes should not be restricted to the first year following the psychotic episode. In their series of patients with schizophrenia (mean age ± SD: 38 ± 11 years), many had major depression 1 year after the most recent psychotic episode.

2.2 Treatment Issues

Since the first step in treatment is to optimize antipsychotic medications, we begin with a brief review of first-generation, conventional antipsychotics. These medications have not been shown to have a major impact on depressive symptoms and, as mentioned in section 1, can actually contribute to or worsen depressive symptoms. Next, we discuss the second-generation, atypical antipsychotics, medications that presumably have a more beneficial profile in treating depression. The next step in treating major depression in patients with schizophrenia is to add an antidepressant if their depressive symptoms persist following optimization of treatment with an atypical antipsychotic medication. We then describe the use of antidepressants in patients with schizophrenia, focusing on SSRIs. Finally, after a discussion of the pharmacological management of patients with the various syndromes of schizophrenia involving depressive symptoms, we discuss the role of psychosocial interventions in treating these patients.

Pharmacotherapy is the treatment of choice for elderly patients with psychosis,[22,23] and psychosocial interventions to supplement their antipsychotic medication are also recommended treatment approaches (see section 2.2.4). Atypical antipsychotics are the preferred antipsychotic choices for the elderly patient with psychosis. Age-related changes in both metabolism and receptor sensitivity lead to use of heterogeneous dosing regimens in the elderly.[24] Use of multiple medications for a variety of medical co-morbidities is increasingly common with age and this heightens the importance of appropriate medication choices. In addition, older patients are more sensitive to adverse effects and this, in turn, can affect compliance and drug tolerability. As a result, a prudent approach towards treating the elderly patient involves a ‘start-low’ and ‘go-slow’ approach. Furthermore, required final dosage levels in this population can vary greatly given the heterogeneity of their health status, which can vary from ‘physically fit’ to ‘frail’.

2.2.1 Use of Conventional Antipsychotic Medications in the Elderly—Adverse effects of conventional antipsychotics are particularly problematic for the elderly. First, sedation may create confusion or agitation.[25] Secondly, orthostatic hypotension may heighten the risks of falls and traumatic injury. These adverse effects in combination with anticholinergic potential in low-potency antipsychotics (chlorpromazine and thioridazine) make them non-preferred agents for geriatric patients with schizophrenia. EPS are common in elderly patients using high-potency antipsychotics. EPS include parkinsonism, which in

turn includes rigidity, tremor, bradykinesia and akathisia. Parkinsonism and akathisia develop within the first days of treatment or after dosage increases. They may pose treatment problems if mistakenly attributed to psychosis and treated with further dose increases with medications that created these effects in the first place.[25]

One study from Dr Dilip Jeste's research group determined that of a series of 56 elderly patients with a variety of diagnoses including dementia, schizophrenia, bipolar disorder, major depression with psychosis and severe anxiety (mean age ± SD: 71.5 ± 11 years) who were receiving low doses of haloperidol, thioridazine or risperidone, drug-induced parkinsonism was most frequently associated with haloperidol.[26] From a theoretical perspective, it makes sense that these adverse effects can worsen with age, given the decreased dopamine availability observable with increasing age.[25]

Tardive dyskinesia consists of involuntary, repetitive movements that are usually facial but occasionally can involve the whole body. Dr Jeste's research team has also extensively investigated this topic in older patients. Tardive dyskinesia usually develops after a long period of antipsychotic treatment. It is a highly noticeable, socially stigmatizing adverse effect and often irreversible even after full medication withdrawal. Jeste et al.[27] examined the cumulative incidence of tardive dyskinesia 1, 3, 6, 9 and 12 months after the institution of antipsychotic therapy among 307 psychiatric outpatients aged >45 years (mean age ± SD: 66.2 ± 12.2 years). The patients' median dose was 68.4 mg/day of chlorpromazine equivalent. Patients who had never received antipsychotics developed a mean cumulative incidence of tardive dyskinesia of 3.4% and 5.9% at 1 and 3 months, respectively; by 12 months, the rate was 24.6%. Patients who had received antipsychotics prior to study baseline for more than 30 days tended to have a greater 12-month cumulative incidence of tardive dyskinesia (36.9%).

Jeste et al.[28] also demonstrated that atypical antipsychotics have lower risk rates of tardive dyskinesia. They compared the 9-month cumulative incidence of tardive dyskinesia with the atypical antipsychotic risperidone with that of the conventional agent haloperidol in middle-aged and older patients (mean age ± SD of the risperidone group 66 ± 12.6 years; mean age ± SD of the haloperidol group 66.1 ± 11.9 years). Study participants were psychiatric patients with diagnoses of schizophrenia, dementia, mood disorders, other conditions with psychotic symptoms or severe behavioural disturbances. The median daily dose of each medication was 1 mg. Patients treated with haloperidol were significantly more likely to develop tardive dyskinesia than patients treated with risperidone ($p < 0.05$); the risperidone group had a 5- to 6-fold lower risk.

Because so many adverse effects complicate the use of first-generation, conventional antipsychotics, especially in older patients, coupled with the lack of evidence regarding their antidepressant efficacy, these medications are not considered first-line antipsychotics when targeting depression in patients with schizophrenia.

2.2.2 Atypical Antipsychotic Medications—In contrast to first-generation antipsychotics, second-generation, or atypical, antipsychotics have been demonstrated to be effective in certain forms of depression,[29] and one of these, quetiapine, is the only US FDA approved monotherapy for bipolar depression.[30] Atypical antipsychotics have been available since the 1990s and are considered first-line treatments for geriatric patients with psychosis. In addition to clozapine, there are five new antipsychotic drugs that are available for use in the US: these are, listed in order of FDA approval, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. The atypical antipsychotic medications are strong antagonists at serotonin receptors and also have central dopamine receptor antagonistic effects. As stated in section 2.2, the elderly require much lower starting dosages and slower

titration rates of atypical antipsychotics than those used for younger patients.[25] Atypical antipsychotics alleviate both positive and negative symptoms and have lower rates of EPS and tardive dykinesia than conventional antipsychotics. The latter considerations are important since these two problems are exaggerated in the elderly.[25] Furthermore, use of clozapine in this population needs to be carefully considered given its anticholinergic properties and propensity for agranulocytosis and seizures.[25]

The Expert Consensus Guidelines[31] recommend risperidone 0.5–2 mg/day as first-line treatment for elderly patients with schizophrenia. Second-line choices included quetiapine 100–300 mg/day, olanzapine 7.5–15 mg/day and aripiprazole 15–30 mg/ day. Available research data on the safety and efficacy of risperidone,[32–37] quetiapine[38–40] and olanzapine[41–43] are based mostly on single-agent open-label studies and their findings are consistent with the recommendations expressed in the Expert Consensus Guidelines. The guidelines also recommend that follow-up appointments begin 1 week after starting an antipsychotic agent. If a dose appears to be inadequate, it is recommended that clinicians wait 2 weeks before altering the dose. In addition, when changing a dose, follow-up should occur within 10 days. Furthermore, once a patient is stable, periodic follow-up appointments should be scheduled no more than 2 months apart in order to adequately monitor therapeutic benefit and tolerability. Once a patient is receiving maintenance treatment, follow-up appointments can then be extended to 3-month intervals. Although the guidelines do not specify which agents are ideal for elderly patients with schizophrenia and MDE, the data on bipolar depression may support consideration of quetiapine when MDE or depression symptoms are prominent.

For patients with EPS, quetiapine is considered to be a first-line option; olanzapine and aripiprazole are considered second-line treatments. All antipsychotics carry the risk of causing a metabolic syndrome with varying degrees of severity, including diabetes mellitus. For patients with diabetes, dyslipidaemia or obesity, experts recommended avoiding clozapine, olanzapine and conventional antipsychotics, particularly the mid- and low-potency agents.[31]

Clearly, patients with diabetes taking any atypical antipsychotic drugs should be monitored for possible worsening of glucose control; furthermore, when starting treatment in individuals with risk factors for diabetes, fasting glucose should be monitored at baseline and periodically during treatment. In addition, weight, height, waist circumference, blood pressure and lipids require periodic monitoring. If diabetes develops, antihyperglycaemic treatment may be warranted. Consensus guidelines from the American Diabetic Association and American Psychiatric Association for dealing with patients with obesity or diabetes who are taking atypical antipsychotic medications can serve as a useful guide for managing these agents.[44] Of course, any decision to use any antipsychotic medication requires careful assessment of all of the associated benefits and risks.

Additional safety guidelines recommended by the Expert Consensus Guidelines include avoidance of risperidone and preference for quetiapine or olanzapine in patients with prolactin-related disorders such as galactorrhoea or gynaecomastia.[31] Furthermore, avoidance of clozapine, ziprasidone and conventional antipsychotics is recommended in patients with corrected QT interval prolongation or congestive heart failure.[45]

2.2.3 Use of Antidepressant Medications in Patients with Schizophrenia and Depressive Symptoms—Siris[4] reported that practitioners prescribed antidepressants to 30% of inpatients and 43% of outpatients with schizophrenia and depression at all ages. Furthermore, these studies revealed that SSRIs were the most frequently prescribed antidepressants, and the preferred combination was an atypical antipsychotic plus an SSRI.

Interestingly, one-quarter of practising psychiatrists rarely or never prescribed antidepressant medications in patients with schizophrenia, perhaps wary of the possibility of increasing psychotic symptoms or being otherwise uncertain about whether the benefits outweighed the risk.[4] Indeed, the results of double-blind trials discussed below are mixed.

There are seven peer-reviewed published, double-blind, placebo-controlled trials examining SSRIs in the treatment of depressive symptoms in patients with schizophrenia. As mentioned, these trials have provided mixed results. Furthermore, there are very few older patients in these double-blind trials, which are summarized below. Even in these studies, it is not always clear when patients had MDE versus non-MDE depressive symptoms, the samples were generally small and the methodology was often not rigorous. Table II provides a targeted overview and comparison of these studies.

One placebo-controlled trial with fluvoxamine[47] treated 30 inpatients with schizophrenia. Patients were titrated to a dose of 100 mg/day by the second week and this was maintained for 4 weeks and then reduced to 50 mg/day by week 6; the drug was stopped 1 week later. The mean age of the fluvoxamine-treated group was 41 years (range 26–62) with a mean Hamilton Depression Rating Scale (HDRS) score ± SD of 7.7 ± 5.0; for the placebo group, the mean age was 42 years (range 18–62) and the mean HDRS score ± SD was 7.7 ± 4.8. The difference in mean HDRS scores between the two groups at the end of the study period was not significant.

One placebo-controlled study with sertraline treating patients with remitted schizophrenia and major depression showed no benefit of sertraline.[48] The sertraline group had a mean age of 26.7 years (range 20–67) and the placebo group had a mean age of 38.8 years (range 21–57). Mean baseline Calgary Depression Rating Scale (CDRS) scores ± SD were 14 ± 3.5 and mean baseline HDRS scores ± SD were 20.6 ± 4.1 for both groups combined. For inclusion in the study, patients were required to have been receiving stable doses of antipsychotic medications and needed to be clinically stable, defined as a period of at least 1 month when the patient maintained a score of 4 or less, which indicates moderate symptoms that affect the patient's behaviour, on all positive symptoms of the Positive and Negative Symptoms Scale (PANSS).[48]

With fluoxetine, two of three studies demonstrated no benefit over placebo with regard to the treatment of depressive symptoms in patients with schizophrenia. In the first trial,[49] the treatment group had a mean age ± SD of 36.8 ± 6.4 years and a mean HDRS score ± SD of 13.3 ± 10.0 (n = 18); the placebo group had a mean age ± SD of 32.8 ± 6.0 years and a mean HDRS score ± SD of 12.6 ± 9.0 (n = 15). The second trial used depressive symptoms from the Brief Psychiatric Rating Scale (BPRS) as the outcome measure; major depression was an exclusion criterion.[50] The mean age ± SD of the fluoxetine-treated group in this trial was 42.2 ± 9.1 years and the mean HDRS score ± SD at baseline was 13.9 ± 4.7 (n = 20). For the placebo group, the mean age ± SD was 42.8 ± 9.4 years (n = 21) and the mean HDRS score ± SD at baseline was 12.8 ± 3.6. A third trial with fluoxetine required patients to have an HDRS score of <20 points for inclusion.[51] Major depression was an exclusion criterion. In the fluoxetine-treated group, the mean baseline HDRS score ± SD was 11.5 ± 4.5 and the mean baseline age ± SD was 46.3 ± 10.6 years (n = 14). For the placebo group, the mean baseline HDRS score ± SD was 12.2 ± 4.0 and the mean baseline age ± SD was 45.4 ± 10.5 years (n = 16). The age range of patients was 18–65 years. Compared with placebo, fluoxetine treatment led to a slight improvement in depressive symptoms in this trial.

Two double-blind trials have evaluated use of citalopram in patients with schizophrenia. One study found citalopram to have a salutary effect on severity of illness based on the Clinical Global Impressions (CGI) scale and a subjective sense of well-being based on a

visual analogue scale.[52] There were no changes on any of the PANSS scores although the placebo effect was marked. No scales to assess depression were used. For inclusion, patients were required to have scores of ≥4 on at least one of the PANSS items: P7 (hostility), N4 (passive apathetic withdrawal), G2 (anxiety) or G6 (depression). In this study, 45 patents were treated with citalopram and 45 received placebo; the age range was reported as 18–64 years.

The other placebo-controlled citalopram trial utilized a crossover design and found that citalopram decreased the frequency of aggressive incidents in 19 chronically violent patients with schizophrenia.[46] Subjects were patients with schizophrenia and were excluded if their score on item 9 (depression) of the BPRS was >3. The mean age ± SD of the patients was 43 ± 13 years and the age range was 18–68 years. No specific assessments of depressive symptoms were made in the study. No significant changes in BPRS scores were noted.

An open-label study[53] examined the effectiveness of citalopram augmentation of antipsychotics in chronically hospitalized inpatients aged ≥55 years with schizophrenia and depressive symptoms for 10 weeks. Patients had HDRS scores of ≥12. Nineteen patients were recruited, nine of whom received citalopram (mean age ± SD: 65.4 ± 12.7 years) and ten who received no citalopram (mean age ± SD: 59.2 ± 8.2 years). Patients received stable doses of antipsychotic medications for at least 2 weeks prior to initiation of citalopram. Based on two-way repeated-measure ANOVAs, the citalopram group significantly improved ($p < 0.05$ for HDRS and CGI scores).

2.2.4 Psychosocial Treatments—Although no published, controlled psychotherapy studies have specifically targeted MDE or depression symptoms in older patients with schizophrenia, it is clear that psychosocial interventions have a role to play in any comprehensive management plan. Long-term care of older patients with schizophrenia should be organized within the context of rehabilitation. This involves a ‘care programme approach’ comprising a team of physicians, nurses, occupational therapists, social workers and others.[54,55] This approach involves eight important elements: (i) treat the psychiatric illness; (ii) treat physical illness(es); (iii) improve education; (iv) maintain daily living skills; (v) maintain social contacts; (vi) have patients participate in day activities; (vii) make sure finances are managed appropriately and accommodate patients’ needs and wishes; and (viii) maintain appropriate risk assessment. Psychoeducation as a key component of this approach is often modified when implemented in older patients because of potential cognitive deficits. Liberman and Eckman[56] and Liberman et al.[57] have described social skills training for elderly patients with schizophrenia that focuses on approaching problems at a practical level. The model also uses role-play to enhance behavioural performance and highlights patients’ abilities to interpret social messages.[58]

Granholm et al.[59] performed a randomized controlled trial of cognitive behavioural social skills training for middle-aged and older outpatients with chronic schizophrenia. Participants were aged 42–74 years. The mean age ± SD of patients in the experimental group, which consisted of the intervention plus ‘treatment as usual’, was 54.5 ± 7.0 years and this group had a mean HDRS score ± SD of 13.5 ± 9.0. The mean age ± SD for the ‘treatment as usual’ group was 53.1 ± 7.5 years and their mean HDRS score ± SD was 14.2 ± 8.8. Patients receiving combined treatment performed social functioning activities significantly more frequently than the patients receiving ‘treatment as usual’ alone. In addition, the combined treatment group achieved significantly greater cognitive insight, more objectivity in reappraising psychotic symptoms and greater skill mastery. The greater increase in cognitive insight with combined treatment was significantly correlated with a greater reduction in positive symptoms. There were no significant differences between the two groups with regard to changes in HDRS scores. However, improvement in overall cognitive insight was

associated at mid-treatment with a transient increase in depression scores which resolved by the end of treatment.

Assertive community treatment is an important psychosocial treatment modality for patients with schizophrenia that has not been studied exclusively in elderly patients with schizophrenia or in elderly patients with schizophrenia and accompanying depressive symptoms. Six studies examining this modality in patients with schizophrenia in general have been published that have included patients aged ≥50 years.[60–66] Five of these studies[60,61,63–66] reported favourable results and one[62] demonstrated mixed findings, suggesting that the approach may be helpful for the older patient with schizophrenia in general. With regard to case management, there are eight intervention studies involving case management programmes that have included patients aged ≥50 years with schizophrenia. Of these, four reported positive outcomes for case management,[66–69] two reported mixed results[70,71] and two found no advantages.[72,73] Mohamed et al.[66] pointed out that although case management does not appear to be as beneficial for older individuals with schizophrenia, studies that included older patients versus younger patients using 50 years as the age cut-off appeared to have better outcomes overall. Clearly, more research is needed in this area, especially with regard to older patients with schizophrenia and depressive symptoms.

2.2.5 Our Overall Treatment Recommendations—Our recommended approach for treating the elderly patient with schizophrenia and major depression involves a stepwise approach combining various modalities. First, if an elderly person with schizophrenia has an MDE, a careful diagnostic assessment to rule out medical or medication causes is an important initial step. Then, adherence with all prescribed treatments needs to be checked and verified. Next, clinicians should consider switching to an atypical antipsychotic if the patient is not already taking one. Following this, the dose needs to be optimized so as to target depressive as well as positive and negative symptoms. If the MDE persists, adding an SSRI is a reasonable next step. Clinicians should start with a low dose but increase as necessary to reduce depressive symptoms.

The goal of treatment, as with all MDEs, is remission. If remission is not achieved after adequate treatment duration (8–12 weeks) and dose (similar to doses used for MDE in older patients who do not have schizophrenia), it is time to consider either switching or augmenting therapy. Unfortunately, in the absence of any good data comparing the effectiveness of switch or augmentation strategies in these patients, the best we can do is to recommend using similar strategies appropriate for older patients with treatment-resistant MDE.[74] Once remission is achieved, the next goals are recovery from the episode and prevention of new episodes. Again, in the absence of systematically gathered data to guide decisions, we recommend treating an acute, first episode for at least 6–9 months and considering longer treatment for a patient with residual symptoms, very severe or highly co-morbid MDEs, ongoing stressors or recurrent episodes. Provision of psychosocial interventions aimed at improving adherence, hope, quality of life and function is also recommended.

3. Schizoaffective Disorder

3.1 Classification and Diagnostic Issues

Schizoaffective disorder is a controversial diagnostic category.[75] Current convention requires that schizoaffective disorder be diagnosed only when there is an MDE, manic episode or mixed episode concurrent with symptoms that meet DSM-IV-TR criteria A for schizophrenia.[19] In addition, there must also be sustained psychotic symptoms in the

absence of mood symptoms and the mood symptoms must occur for a substantial portion of the duration of the active and residual periods of illness.[19]

3.2 Treatment

Optimal treatment of depressive symptoms in patients with schizoaffective disorder has been relatively unstudied, especially in the elderly; this may explain why treatment guidelines have not yet been established. Nonetheless, despite the paucity of data in this area, some authors recommend use of adjunctive antidepressants in combination with optimal antipsychotic treatment for both the short- and long-term treatment of many patients with schizoaffective disorder,[76,77] although others emphasize greater caution in treating this population.[78] Our recommended approach toward treating the elderly patient with schizoaffective disorder and depressive symptoms is the same as for patients with schizophrenia with MDE (see section 2.2.5). However, because major depression is by definition a more lasting feature of the disorder, antidepressant treatments and psychosocial interventions may need to be continued for longer periods.

4. Schizophrenia with Subsyndromal Symptomatic Depression

4.1 Classification and Diagnostic Issues

Patients with schizophrenia and subsyndromal depressive episodes do not fulfil any criteria for the DSM-IV or ICD-10 classifications of depressive disorders accompanying schizophrenia. If subsyndromal depression is present, a diagnosis of depressive disorder NOS is coded, based on both DSM-IV and ICD-10 criteria. Bressan et al.[13] have suggested investigating the possibility of developing a diagnosis corresponding to dysthymia or chronic demoralization that would correspond to subsyndromal depression. This is consistent with the work of Bartels and Drake,[79] who have described chronic demoralization in the context of schizophrenia as a state of “persistent hopelessness and low self esteem in the absence of vegetative symptoms of depression”.

Subsyndromal depressive symptoms in schizophrenia are estimated to be more common than MDE; the rates have estimated to vary between 20% and 70%.[79,80] For instance, Stern et al.[81] found that 2 of 17 patients (age range 18–44 years; mean 29.2) exhibited post-psychotic depression within 6 months after psychotic decompensation while 6 of 17 developed “mild to moderate depression for a short period of time”. Indeed, some have argued that depression is a core component of schizophrenia, similar to positive, negative and cognitive features.[82,83] Clinicians and researchers alike attest to the clinical importance of subsyndromal depressive symptoms in patients with schizophrenia.[4] In an international survey of depression in schizophrenia, the majority of the 1128 American psychiatrists who responded felt that depression was a common problem throughout the course of schizophrenia.[4] Seventy-seven percent felt that depression added to overall morbidity and 68% felt that depressive symptoms impacted significantly on family adjustment. More prospective studies are needed to establish the course and impact of depressive symptoms in patients with schizophrenia.[13]

There is a growing literature suggesting that subsyndromal symptoms of depression in patients with schizophrenia are associated with numerous negative consequences. For instance, Jin et al.[84] demonstrated in patients with schizophrenia and depressive symptoms with a mean age ranging from 56.1 ± 9.0 to 58.3 ± 10.2 years that there was diminished quality of life and an increase in health service utilization. In the study by Zisook et al.,[7] in which patients had a mean age ± SD ranging from 58.9 ± 9.9 to 59.8 ± 10.1 years, accompanying depressive symptoms were associated with worse overall symptom severity. In a study by Birchwood et al.,[85] patients with a mean age ± SD of 42.1 ± 12.7 years and subsyndromal depressive symptoms experienced greater demoralization. Furthermore,

Tollefson et al.[86] found that patients with schizophrenia and subsyndromal depression (mean age ± SD: 36.2 ± 10.7 years) also appeared to be at risk for early relapse.

Zisook and colleagues have performed three cross-sectional studies characterizing middle-aged and older outpatient populations with schizophrenia and subsyndromal symptoms. In the first study, which enrolled patients aged ≥45 years (mean age ± SD of groups ranged from 58.9 ± 9.9 to 59.8 ± 10.1 years), Zisook et al.[7] reported that more than two-thirds of schizophrenic patients who did not have MDE had at least mild depressive symptoms (defined as HDRS score ≥7), and over 30% of patients had depressed mood, feelings of guilt and/or feelings of hopelessness. A more recent series by the same group examined middle-aged and older outpatients with schizophrenia and subsyndromal depressive symptoms in whom the age range was 40–75 years and the mean age ± SD was 52.76 ± 7.24 years.[87] The investigators determined that the most prevalent symptoms ranged across several domains of the depressive syndrome: psychological (e.g. depressed mood, depressed appearance, psychic anxiety); cognitive (e.g. guilt, hopelessness, self-depreciation, loss of insight); somatic (e.g. insomnia, anorexia, loss of libido, somatic anxiety); psychomotor (e.g. retardation and agitation); and functional (e.g. diminished work and activities).

A third study by Zisook et al.[88] enrolled 204 subjects age ≥40 years with HDRS scores <8 or ≥8 (mean age ± SD: 52.5 ± 7.1 and 54.0 ± 9.0 years, respectively). They demonstrated that subsyndromal depression was associated with worse overall psychopathology, worse positive and negative symptoms, worse severity of medical conditions, worse physical and mental functioning, and worse anxiety and suicidality.

A study by Cohen et al.[89] examined indices of subjective well-being in patients with schizophrenia and depressive symptoms aged ≥55 years (mean age 63 years). Using bivariate and then logistic regression analysis, they found five variables to be predictors of subjective well-being: male gender, absence of loneliness, older age, reliable social contacts and fewer perceived life difficulties. A more recent study by this group[90] examined 198 patients with schizophrenia aged ≥55 years (mean age ± SD: 61.8 ± 5.5 years) who lived in the community. The mean age ± SD of a comparison group consisting of community dwellers without schizophrenia was 60.9 ± 5.7 years (n = 113). The schizophrenia group had more clinical depression (32% vs 11%; $\chi^2 = 28.23$, df = 1, p = 0.001). With logistic regression, six variables were related to depression: physical illness, quality of life, positive symptoms, proportions of confidants, coping by using medication and coping by keeping calm. One study in the UK by Graham et al.[91] examined patients aged ≥65 years with schizophrenia living in the community and found that 12 of 30 (40%) scored ≥4 on the Geriatric Depression Scale (GDS), which is indicative of a “comorbid diagnosis of probable depression”. The mean age of patients in the study was 73 years. Compared with control patients, patients with schizophrenia were “out of the house” less frequently, had fewer “private leisure activities” and had more contact with “professional services”.

A recent cross-sectional study by Gupta et al.[92] examined depressive symptoms in a group of patients with schizophrenia or schizoaffective disorder with a mean age ± SD of 68.9 ± 10.5 years. The patients were from outpatient clinics, nursing home settings, personal care homes or continuous day treatment programmes. The patients’ mean GDS score ± SD was 4.80 ± 3.94 (n = 79), similar to levels of depressive symptomatology seen in studies by Graham et al.[91]

Kasckow et al.[93] examined suicidality in a group of patients with schizophrenia and subsyndromal depressive symptoms (n = 146) aged ≥40 years. The proportion of patients aged ≥55 years was 29% and those aged ≥65 years was 7%. Thirty-six percent of the sample had at least a mild degree of suicidality, based on InterSePT Suicide Scale scores >0. Age

was not correlated with scores of suicidality. Furthermore, logistic regression demonstrated that only quality-of-life scores and neither age nor performance-based measures assessing everyday functioning, social functioning or medication management were predictive of scores indicative of suicidality.

4.2 Treatment

It remains relatively unclear whether antidepressants are indicated as an augmentation strategy in patients with schizophrenia who also have depressive symptoms but who do not meet criteria, in terms of number, duration or severity, for a full depressive syndrome.[94] In the elderly, even less evidence is available to support such practice and much more research is needed. Our recommended approach toward treating the elderly patient with schizophrenia and subsyndromal depression in general is to start the patient on an atypical antipsychotic (if not taking one already) and optimize the dose. If optimization of atypical antipsychotic monotherapy has been attempted and the patient still has significant depressive symptoms that require further treatment, we recommend adding an SSRI. Clearly, the clinician needs to weigh the costs and benefits associated with extending treatment duration.[24]

5. Major Depression with Psychosis

5.1 Classification and Diagnostic Issues

Major depression can present with psychotic features and is labelled as “severe with psychotic features”.[19] In DSM-IV-TR,[19,95] this syndrome requires the criteria of major depression and also symptoms of mood-congruent or mood-incongruent hallucinations or delusions.

In general, major depression with psychosis is not uncommon among patients with major depression. In a recent report, Ohayon and Schatzberg[96] sampled 19 000 patients and found that 19% of those who met criteria for major depression had psychotic features, making the prevalence of major depression with psychosis 4%. This survey was performed in five countries in patients with an age range of 15–100 years. The percentage of patients aged ≥65 years ranged from 17.5% to 19.7% depending on the country; likewise, the percentage of those aged 55–64 years ranged from 12.7% to 14.1%. MDE without psychotic features was less prevalent in patients aged ≥65 years. For instance, in the ≥65 years age group, there were significantly different point prevalences in major depression without psychosis in the 25- to 34-year-old group (2.4%; 95% CI 1.9, 3.0) versus the ≥65-year-old group (1.3%; 95% CI 0.9, 1.7; $p < 0.05$ via χ^2). In another series of inpatients admitted to hospital units for depression, 25% had psychotic depression.[95,97] The mean age ± SD of the non-psychotic patients was 38.9 ± 15.8 years and that of the psychotic patients was 40.9 ± 16.0 years.

Based on research by Meyers and Greenberg,[98] psychotic depression occurs at a rate of 40% in hospitalized elderly depressed patients. In their series of 161 patients, the mean age ± SD was 71.7 ± 6.6 years. In a different study that examined elderly depressed community dwellers, 3.6% had psychotic depression.[99] Patients in this series were aged ≥60 years. Thus, psychosis accompanying major depression in the elderly is not uncommon. The same is true of the ‘old-old’. In one study involving a series of patients aged ≥85 years, hallucinations were associated with major depression with an odds ratio of 3.9.[100]

Based on a study by Schwartz et al.,[101] in which the median age of patients was 28 years (range 15–58), patients have re-occurrences of psychotic features when they have a recurrence of depressive syndromes. A literature review by Nelson and Charney[102]

indicates that the form and content of delusional thinking is usually consistent when depression recurs.

Psychotic features are often classified as mood congruent or mood incongruent. However, one series of studies determined that 50–60% of patients hospitalized for major depression with psychotic features had both mood-congruent and mood-incongruent features.[103] The mean age ± SD of the mood-congruent group was 47.8 ± 12.4 years compared with 41.6 ± 10.7 years in the mood-incongruent group. In addition, in this study about half of the patients with mood-incongruent states had at least one co-occurring mood-congruent symptom. Furthermore, about two-thirds of patients with mood-congruent features had at least one mood-incongruent symptom. Thus, this sub-classification of major depression with psychotic features into mood congruent or mood incongruent may be unnecessary since both can be detected simultaneously.[19,103]

Delusions in patients experiencing major depression with psychosis are more common than hallucinations.[95] The typical delusional presentation in this syndrome focuses on guilt, hypochondriasis, nihilism, persecution and often jealousy. These delusions differ from those in patients with dementia in that patients with dementia generally have less systematized and less congruent delusions.[95,104] Furthermore, in inpatients with major depression and psychosis, clinicians find it difficult to differentiate depressive delusions from overvalued ideas of hopelessness and worthlessness.[105] In addition, psychotic features in patients with major depression are associated with less insight relative to those with no psychosis.[95] Furthermore, a study by Leyton et al.,[104] in which patients had a mean age ± SD of 38.4 ± 2.3 years, demonstrated that patients with depression and psychosis tended to have been ill for longer periods of time and to have had more recurrent episodes of depression.

A study by Pini et al.[106] revealed that patients with depression and psychosis had insight impairment as severe as that detected in patients with schizophrenia, schizoaffective disorder and bipolar disorder. The mean age ± SD of patient groups in that study varied from 33.6 ± 9.5 to 36.2 ± 12.7 years, with the minimum age for inclusion being 16 years. Furthermore, the pattern of neuropsychological impairment in patients with psychotic depression is similar to that detected in patients with schizophrenia. This was shown in a study by Jeste et al.,[107] which enrolled patients with a minimum age of 45 years, and a mean age ± SD ranging from 56.8 ± 10.3 to 61.3 ± 12.0 years, depending on the group. Another study by Hill et al.[108] found similar results for a younger group (mean age ± SD ranging from 25.2 ± 8.8 to 29.8 ± 10.6 years).

5.2 Treatment

Treatments for depression with psychosis have involved electroconvulsive therapy (ECT) and combinations of antidepressant and antipsychotic medications. The Expert Consensus Guidelines for the treatment of elderly patients with major depression with psychosis recommends both antipsychotic/antidepressant combination therapy or ECT.[31] Preferable antipsychotics include risperidone 0.75–2.25 mg/day as the first-line choice in combination with an antidepressant. Olanzapine 5–10 mg/day and quetiapine 50–200 mg/day are also recommended as second-line options. No consensus recommendation is given for aripiprazole or ziprasidone.[31]

There are limited studies evaluating the treatment of geriatric patients with psychotic depression. One study by Mulsant et al.[109] showed no significant difference between nortriptyline plus perphenazine (50% response) versus nortriptyline plus placebo (44%). The study group consisted of 125 women and 62 men, 180 (96%) of whom were Caucasian. The mean age ± SD of the patients was 62 ± 18 years. This study is consistent with a recent review suggesting that the evidence is not very strong in favour of supporting the premise

that the combination of an antidepressant plus an antipsychotic is any better than an antidepressant alone; however, the authors stated that the combination is clearly superior to an antipsychotic alone.[110] Another study by Meyers et al.,[111] in which patient ages ranged from 50 to 84 years and the mean age ± SD was 71.8 ± 8.4 years, compared the efficacy and safety of continuation combination therapy with nortriptyline plus perphenazine with that of nortriptyline plus placebo in 29 patients who achieved remission after ECT. No difference in relapse rates was noted and the group with the added antipsychotic actually experienced more adverse events. Another trial by Flint and Rifat[112] compared response rates in elderly patients with psychotic depression treated with 6 weeks of ECT (mean age ± SD: 75.7 ± 6.0 years) or nortriptyline and perphenazine (mean age ± SD: 75.5 ± 5.1 years). The frequency of response to drugs was lower than that to ECT.

ECT has been shown to be efficacious in the treatment of psychotic depression. One study of this treatment method recruited 55 inpatients with major depression with or without psychosis, with a mean age of 50.4 years and an age range of 20–70 years.[113] In patients with depression and psychosis, ECT was associated with a higher likelihood of achieving a 50% reduction in depressive symptoms as well as in achieving a remission. Another series of patients with psychotic depression and a mean age ± SD of 48.6 ± 16.5 years demonstrated a response rate of 86% with ECT.[114]

As part of a Consortium for the Research in ECT, O'Connor et al.[115] studied age effects of ECT in a group of patients with major depression, 30% of whom were psychotic. The mean age ± SD of the total sample (n = 253) was 56 ± 16.2 years. The group with psychosis exhibited a greater change from baseline in terms of HDRS scores. Furthermore, the most pronounced effect of an acute ECT treatment course was seen in the middle-aged and elderly depressed patients with psychosis. This included, respectively, a group of patients aged 46–64 years and another group aged 65–85 years; the young group included patients aged 18–45 years.

6. Summary and Conclusions

We have discussed depressive syndromes in the context of patients with primary thought disorders or psychosis in whom depression is the primary problem. We have also discussed what is known with regard to these conditions in the elderly patient. While this review is intended to help clinicians evaluate and treat elderly patients, we realise that we have more questions than answers regarding the optimal treatment strategies for older patients with schizophrenia and depression. While the diagnosis of major depression with psychosis clearly appears to be within the realm of an affective disorder and clinicians agree that it requires treatment with ECT or a combination of antipsychotics and antidepressants, less clear is how we distinguish and treat the different depressive syndromes in elderly patients with schizophrenia. Our understanding at this stage is mostly theoretical and more research is needed to better understand these syndromes. Much more research is also needed to better refine our treatment approaches in this group of elderly patients.

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Table I

Diagnostic features and treatment considerations in elderly patients with psychosis and depressive symptoms

Major depression with psychosis	Schizophrenia with major depressive episodes	Schizoaffective disorder	Schizophrenia with subsyndromal depression
Diagnostic features			
Major depression in which psychosis occurs only with mood disturbance	Schizophrenia with episodes of major depression	Schizophrenia with episodes of mania and/or major depression	Schizophrenia without major depressive and/or manic episodes
Predominantly a mood disorder	Predominantly a thought disorder	Predominantly a thought disorder	Predominantly a thought disorder
Can have cognitive deficits	Includes post-psychotic depression	Requires 2-week psychosis without mania and/or major depression	Can have cognitive deficits
	Does not meet criteria for schizoaffective disorder	Mood symptoms are present for substantial portions of the total duration of the active or residual periods of the illness	
		Can present with subsyndromal depressive symptoms	
		Includes post-psychotic depression Can have cognitive deficits	
Somatic treatment			
ECT or antidepressant + atypical antipsychotic	First optimize dose of atypical antipsychotic; if needed, add antidepressant, preferably an SSRI	First optimize dose of atypical antipsychotic; if needed, add antidepressant, preferably an SSRI	First optimize atypical antipsychotic monotherapy; if needed, add antidepressant, preferably an SSRI

ECT = electroconvulsive therapy; **SSRI** = selective serotonin reuptake inhibitor.

Table II

Double-blind trials examining selective serotonin reuptake inhibitor augmentation of antipsychotic agents in patients with schizophrenia[a]

Study	n	Baseline depression	Medication	Duration (wk)	Results
Silver and Nassar[47]	30	Mean HDRS score 7.7 (placebo and fluvoxamine groups)	Fluvoxamine	7	No differences in HDRS Scores
Addington et al.[48]	48	Schizophrenia with major depression; mean HDRS score 20.6; mean CDRS score 14.0 (for both groups combined)	Sertraline	6	No difference in CDRS or HDRS scores
Buchanan et al.[49]	33	Mild-to-moderate depression; mean HDRS score 13.3 (fluoxetine), 12.6 (placebo)	Fluoxetine augmentation of clozapine	8	No difference in HDRS scores
Goff et al.[50]	41	Mild-to-moderate depressive symptoms; major depression excluded; mean HDRS score 13.9 (fluoxetine), 12.8 (placebo)	Fluoxetine augmentation of depot antipsychotic	6	No difference in HDRS scores
Spina et al.[51]	30	Mild-to-moderate depressive symptoms; mean HDRS score 11.5 (fluoxetine), 12.2 (placebo)	Fluoxetine	12	HDRS scores better in fluoxetine group
Salokangas et al.[52]	90	Not specified except that scores of ≥4 on PANSS P7 (hostility), N4 (passive apathetic withdrawal), G2 (anxiety) and G6 (depression) were required for inclusion	Citalopram	12	No depression outcomes assessed; improvement in CGI and subjective well-being, based on a visual analogue scale
Vartiainen et al.[46]	19	Not specified except that subjects were patients with schizophrenia and were excluded if their score on item 9 (depression) of the BPRS was >3	Citalopram	24	No depression outcomes assessed; lower frequency of aggressive incidents with citalopram

[a] All studies were double blind and placebo controlled except Vartiainen et al.,[46] which was a double-blind, placebo-controlled, crossover study.

BPRS = Brief Psychiatric Rating Scale; **CDRS** = Calgary Depression Rating Scale; **CGI** = Clinical Global Impressions scale; **HDRS** = Hamilton Depression Rating Scale; **PANSS** = Positive and Negative Syndrome Scale.