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Elderly Patients with Schizophrenia and Depression: Diagnosis and Treatment

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Abstract

Background—The treatment of older patients with schizophrenia and depressive symptoms poses many challenges for clinicians. Current classifications of depressive symptoms in patients with schizophrenia include: Major Depressive Episodes that occur in patients with schizophrenia and are not classified as schizoaffective disorder, Schizoaffective Disorder, and Schizophrenia with subsyndromal depression in which depressive symptoms do not meet criteria for Major Depression. Research indicates that the presence of any of these depressive symptoms negatively impacts the lives of patients suffering from schizophrenia-spectrum disorders.

Purpose—The purpose of this paper is to review the literature related to older patients with schizophrenia-spectrum disorders and co-occurring depressive symptoms, and to guide mental health professionals to better understand the diagnosis and treatment of depressive symptoms in patients with schizophrenia.

Conclusions—The treatment of elderly patients with schizophrenia and depressive symptoms includes first reassessing the diagnosis to make sure symptoms are not due to a comorbid condition, metabolic problems or medications. If these are ruled out, pharmacological agents in combination with psychosocial interventions are important treatments for older patients with schizophrenia and depressive symptoms. A careful assessment of each patient is needed in order to determine which antipsychotic would be optimal for their care; second-generation antipsychotics are the most commonly used antipsychotics. Augmentation with an antidepressant medication can be helpful for the elderly patient with schizophrenia and depressive symptoms. More research with pharmacologic and psychosocial interventions is needed, however, to better understand how to treat this population of elderly patients.

Keywords

Schizophrenia; Depression; Older Adult; Treatment

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Introduction

The diagnosis and treatment of patients with schizophrenia and co-occurring depression in the elderly is challenging for both clinicians and researchers due to the overlap of symptomatology between schizophrenia and depressive disorders. The purpose of this review is to assist mental health professionals in understanding some of the key diagnostic and treatment challenges faced in caring for older patients with schizophrenia-spectrum disorders, i.e., schizophrenia, schizoaffective disorder and schizophreniform disorder. A review of this literature was recently reported by Kasckow and Zisook (1), and this article serves to be an update to this review with recent advances.

The classification of depressive symptoms in schizophrenia is a complex task. Current classifications of depressive symptoms in patients with schizophrenia include: 1) Major Depressive Episodes that occur in patients with schizophrenia and are not classified as schizoaffective disorder; 2) Schizoaffective Disorder; and, 3) Schizophrenia with subsyndromal depression in which depressive symptoms do not meet criteria for Major Depression.

Depressive Symptoms in Patients with Schizophrenia

In patients without schizophrenia, depression in older adults differs from that in younger individuals in several ways. Community dwelling elders are not likely to experience a first-episode major depression unless they have a history of recurrent major depression beginning earlier in life, but may experience clinically important subthreshold or minor depressions. In addition, elderly depressed individuals are more likely to present with greater medical and/or neurological comorbidities, and a greater chance of concomitant cognitive impairment, the latter which can make diagnosing depression more challenging (2).

Research demonstrates that patients with schizophrenia are more likely than the general population to experience depressive symptoms (3). The National Comorbidity Study reported that 59% of patients with schizophrenia met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for major or minor depression (4,5). Furthermore, depressive symptoms in patients with schizophrenia can be associated with impairment, decreased functioning, rehospitalization and suicide (6–9). In a study of 267 patients aged 18–70, depressive symptoms accounted for nearly 50% of suicidal ideation in patients with schizophrenia (10). Diwan et al. (11) examined factors related to depression in a multiracial urban sample of older persons with schizophrenia. The authors examined 198 persons aged 55 or older who lived in the community and compared them to a community comparison group (n=113). Depressive symptoms were considered to be present if patients had a score of 16 or greater on the Center for Epidemiologic Studies Depression Scale. The schizophrenia group had significantly more persons with clinical depression than the community comparison group (32% versus 11%). In a logistic regression, six variables were related to presence of depression: physical illness, quality of life, presence of positive symptoms, proportion of confidants, coping by using medications, and coping with conflicts by keeping calm.

Detection of depression in patients with schizophrenia requires an understanding of the range of depressive states which these patients may experience. In addition, it is important to understand conditions that could be confused for depression (12). As stated above, the spectrum of depressive/mood symptoms in patients with schizophrenia range from at least one major depressive episode in which schizoaffective disorder is ruled out, to patients with depressive symptoms which do not meet criteria for major depressive disorder but consist of subsyndromal symptoms that are still clinically significant.

Generally, the origin of depressive symptoms in schizophrenia can vary significantly and may be hard to determine in some cases (13). However, depressive symptoms may be the result of: 1) a core component of schizophrenia, like positive and negative symptoms (14–16); 2) an expression of, or response to, severe psychosis (17) and presumed likely to improve with treatment of psychosis (12,18,19); 3) a major depressive episode after a psychotic episode comprising postpsychotic depression (20); or, 4) the result of first-generation antipsychotic medications which cause akinesia (21).

Differentiation of Depressive Symptoms from Negative Symptoms

A key issue in the differential diagnosis of depressive symptoms in patients with schizophrenia is disentangling the contribution of negative symptoms. Based on *DSM-IV* classification, negative symptoms of schizophrenia include affective flattening, avolition and anhedonia. These symptoms are similar to depressive symptoms in that individuals with these symptoms often appear melancholic, unmotivated, unable to concentrate and affectively indifferent (22). However, unique features of depressive symptoms include the presence of depressed mood, cognitive problems, early morning awakening and appetite disturbance. Furthermore, individuals with depressed symptoms may have a “painful affect” with “blue mood,” while patients with schizophrenia exhibit “diminished” or “empty” affect (23,24). Furthermore, the long-term persistence of such symptoms is more consistent with negative symptomatology.

Depressive Symptoms Due to Posttraumatic Stress Disorders or Substance Dependence

At times, it may be difficult to differentiate depressive symptoms from other disorders. In particular, it is difficult to differentiate between Major Depression and Posttraumatic Stress Disorder (PTSD) due to the similarity of symptoms, which include feeling depressed, sleep problems, social withdrawal, memory and concentration problems, irritability and lack of hope for future (25), similar predictor variables (26) and high rates of comorbidity (25,27–29). Both depression and PTSD are common in the elderly population (30,31).

Recent research indicates that the nature of depressive and PTSD symptoms differ, and the disorders can occur independently (25,32,33). Furthermore, older patients may experience PTSD symptoms differently than younger populations (31). It is suggested that such variations in symptom presentation and the course of the disorder are due to a combination of factors which include the aging process, social attitudes of the population and comorbid conditions (34,35). Older adults tend to focus on and report somatic, rather than psychological, symptoms and attribute psychological symptoms of distress such as loss of libido, depression, guilt and loss of interest to aging or medical problems (34).

In the elderly, it may be easy to overlook depressive symptoms emanating from drug or alcohol use (36,37). Clinicians often underestimate how often elderly people may abuse alcohol or other substances, in part as an abortive attempt to ameliorate the effects of deteriorating health, major adverse life changes or losses including the death of a loved one or retirement (37). These changes can lead to boredom or demoralization, which results in the use of alcohol or other substances to alleviate the boredom (37) or seek equanimity. Ultimately, the use of a substance to alleviate such symptoms can lead to increased depressive symptoms and increase the risk that depression becomes a chronic condition (38,39).

Detecting substance abuse in the elderly can be difficult for a variety of reasons. For example, elderly people often drink fewer drinks than is considered abuse for younger

individuals, but drink more frequently and may be more sensitive to the effects of alcohol so that less quantities of alcohol are sufficient to cause intoxication as well as abuse or dependence (40). Furthermore, cognitive deficits may inhibit an elderly individual's ability to monitor alcohol consumption (37). Since elderly people are often on many prescription medications, these may also cause depressive symptoms. Furthermore, certain medications can cause depressive symptoms, and this can potentially be exaggerated in the elderly due to alcohol use, as well as drug-drug interactions (41–43).

Depressive Symptoms during Acute Psychotic Episodes

Depressive symptoms in patients with schizophrenia can be associated with the acute phase of the disorder and the severity of positive symptoms. The majority of depressive symptoms during the acute psychotic phase of schizophrenia improves with antipsychotic treatment (20,44). Levels of depressive symptoms are often less severe in the postpsychotic phase; however, these symptoms may persist or may even worsen in some individuals. When depressive symptoms persist in the postpsychotic phase there appears to be a poorer prognosis. Furthermore, the acute and depressive symptomatology detected in the postpsychotic phase of patients with schizophrenia appears to differ not only temporally but also phenomenologically; a mixed anxiety/depression state appears to occur more frequently during the acute phase, while a more pure depressive state is seen later after the acute psychotic syndrome (18,19,45–48).

There are several rating scales available for helping diagnose depression in patients with schizophrenia, including the Calgary Depression Rating Scale and the Psychotic Depression Scale (PDS) (46,49,50). Hausmann and Fleischhacker (51) also recommend the Calgary Depression Rating Scale and also the Hillside Akathisia Scale to help establish the right diagnosis.

Depression may also occur as part of a prodromal syndrome of schizophrenia. In one study of 203 patients, it had been determined that in 81% of all patients depressive symptoms occurred about four years prior to hospitalization for patients' first psychotic break (52–54). The Interview for the Retrospective Assessment of the Onset of Schizophrenia is a semi-structured interview which can help determine whether this is the case. This may be a concern for older patients since they may acquire late onset schizophrenia or very late onset schizophrenia-like psychosis (55).

Schizophrenia and Major Depressive Episodes

A substantial proportion of patients with schizophrenia can also experience at least one full episode of major depression in which the depressive symptoms are not present substantially during the active or residual phases; these individuals would be diagnosed with schizophrenia and major depression as separate co-occurring disorders, not schizoaffective disorder (56). In about 60% of patients with schizophrenia, major depressive episodes can occur sometime during their lifetime (57).

The presence of a major depressive episode following an acute psychotic episode constitutes postpsychotic depression (58). Postpsychotic depression has been reported to occur in 30 to 50% of patients with schizophrenia (21,59) and usually occurs after the first psychotic break (18,20). The definition of postpsychotic depression varies depending on whether one is using *DSM-IV* or *The International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)* criteria. With the *DSM-IV*, all depressive states occurring any time after a psychotic episode would qualify as postpsychotic depression. With the *ICD-10*, diagnosing postpsychotic depression requires that depressive symptoms develop within a year period following the acute psychotic episode.

Often postpsychotic depression can be mistaken for an extrapyramidal-like syndrome as the secondary effect of antipsychotic medication (60). Iqbal et al. (61) noted that postpsychotic depression can occur independently of the symptoms of schizophrenia. In up to 30% of multiple episode cases, depression can arise up to several months after recovery from an acute psychotic episode (23); in first-episode cases, this can occur up to 50% of the time (20). Schwartz and Meyers (62) determined that, in a majority of patients, depressive symptoms remit within three weeks.

Iqbal et al. (59) determined that, in the months prior to developing postpsychotic depression, patients developed greater loss, humiliation and feelings of entrapment in comparison to those who relapsed and did not develop depression. Patients who developed a postpsychotic depression were also more likely to see themselves in a lower status with lower self-esteem, better insight and a heightened awareness of the diagnosis (61). Wittmann and Keshavan (63) presented three cases studies of patients with schizophrenia with depression following the first episode of psychosis; they insightfully demonstrated that grief and mourning occur as patients attempt to actively cope with their realization of their illness. Recovery depends on mourning illness-related loss, developing personal meaning for the illness, moving forward with insight as well as acquiring a new identity.

One study in middle-aged and older patients by Mauri et al. (64) examined 43 patients with schizophrenia (mean age 55 ± 9 years) with the residual subtype of schizophrenia who had been treated with antipsychotics for an average of 25 ± 4 years. The average duration of illness was 30 ± 7 years, and most of the time that patients were ill they had spent most of their time in a chronic mental hospital. At the time of their evaluation, 70% had depressive symptoms constituting postpsychotic depression; 42% had mild symptoms (21-item Hamilton Depression Rating Scale [HAMD] score of 10–19); 16% had moderate severity (21-item HAMD score of 20–29); and, 12% had severe depressive symptoms (21-item HAMD score of 30–49).

Schizoaffective Disorder

About 10 to 30% of patients with schizophrenia-spectrum disorders meet criteria for schizoaffective disorder (23). Patients with schizoaffective disorder meet the criteria for schizophrenia but also have mood symptoms, either mania or depression. According to the *DSM-IV*, the patient must experience a minimum of a two-week period in which psychosis is present without significant mood symptoms (56). Additionally, patients with schizoaffective disorder may present with subsyndromal depressive symptoms and/or postpsychotic depression (1). Schizoaffective disorder is a controversial diagnosis (65), and it is obvious that there is significant overlap in presentation of depressive symptoms across these disorders. Research on the treatment of depressive symptoms in patients with schizoaffective disorder is scarce, especially in the elderly population.

Schizophrenia with Subsyndromal Depression

Patients with schizophrenia and subsyndromal depression meet criteria for schizophrenia, but do not meet criteria for a major depressive disorder. They have 2 to 4 symptoms of depression for more than 2 weeks, not severe enough for a major depressive disorder and which are not prolonged enough for dysthymic disorder. It is associated with social dysfunction. Subsyndromal symptoms can also occur in patients with schizoaffective disorder (56). Research has indicated that subsyndromal symptoms are more common than major depressive episodes in patients with schizophrenia, with estimated rates varying between 20 to 70% (66,67).

Dysphoria and demoralization are often the main presentations of clinically significant depressive symptoms in patients with schizophrenia once psychotic symptoms are stabilized (59,68). Bartels and Drake (66) labeled subsyndromal symptoms as “persistent hopelessness and low self-esteem in the absence of vegetative symptoms of depression,” and as “chronic demoralization,” in the context of schizophrenia. Thus, some researchers have suggested the development of a diagnosis that relates subsyndromal depression with dysthymia or chronic demoralization (13).

Dysphoria includes depressive and anxiety symptoms which can occur anytime and appear to increase with psychosocial stressors (62,69). Demoralization often arises when patients struggle with insight into their illness with the associated negative impact on their ability to function (68). In addition, demoralization often arises when patients had high prior expectations with accompanying good insight as well as hopelessness, low self-esteem, and suicidal ideation (66). Chronic demoralization can develop more gradually and persist for years (66).

Zisook et al. (70) has performed two cross-sectional studies characterizing middle-aged and older outpatient populations with schizophrenia and subsyndromal symptoms. In the first study, which enrolled patients 45 years and older, it was reported that more than two-thirds of patients with schizophrenia who do not have major depressive episodes have at least mild depressive symptoms (defined as a HAMD 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 (71) examined middle-aged and older outpatients with schizophrenia and subsyndromal depressive symptoms where the age range was 40 to 75. They determined that the most prevalent symptoms cut 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 (insomnia, anorexia, loss of libido, somatic anxiety); and, psychomotor (e.g., retardation and agitation) and functional (diminished work and activities).

In a recent study by Montross et al. (72) examining the prevalence of suicidal ideation and attempts in middle-aged and older patients (≥ 40 years) with schizophrenia and subsyndromal depression, the prevalence of suicidal ideation and suicidal attempts was relatively high: nearly half of the participants reported suicide attempts at least once in their lifetime (72). Past suicide attempts and hopelessness were stronger predictors of suicidal ideology than depression and psychopathology.

Depressive Symptoms in Patients with Schizophrenia: Impact on Functioning and Quality of Life

There is evidence that patients with schizophrenia and subsyndromal depression experience many negative consequences which diminish their quality of life (73). In younger patients with schizophrenia, Rocca et al. (74) provided evidence for a significant relationship between depressive symptoms and functioning and quality of life. The severity of depressive symptoms in these patients was found to influence global functioning and subjective quality of life. Depressive symptoms were not associated with illness severity. Furthermore, Kilzieh et al. (75) examined depressive symptoms in nonelderly institutionalized individuals with schizophrenia who had been ill and dependent on others for at least five years. Only 5% of these patients had a 17-item HAMD score ≥ 16 , and many had a low rate of core symptoms such as guilt, depressed mood and suicidal ideation. The authors noted that the preservation of core functional abilities is likely necessary for depressive symptoms to develop.

In an older cohort, Jin et al. (76) conducted a study with 202 middle-aged and older patients aged 56.1 ± 9.0 to 58.3 ± 10.1 with depressive symptoms. The more depressed individuals exhibited a decrease in quality of life and a need for increased use of health services.

Another study by Cohen et al. (77) examined subjective well-being in patients aged 55 and older with schizophrenia and depressive symptoms. Bivariate and logistic regression analyses revealed five variables to be predictors of subjective well-being: male gender, absence of loneliness, older age, reliable social contacts, and fewer perceived life difficulties. Another study from Great Britain reported that 40% of subjects with schizophrenia aged 65 and older living in the community scored 4 or more on the Geriatric Depression Scale; this scale has a cut-off score of 5. Furthermore, these subjects reported that they “left the house less often” and had less “private leisure activities,” while also reporting more contact with “professional services,” indicating that depressive symptoms may negatively influence such patients’ quality of life. Jeste et al. (78) compared community dwelling older adults without psychiatric diagnoses to older patients with schizophrenia with a mean age of 69.1 ± 4.7 ; these older outpatients with schizophrenia had a mean Hamilton Depression Rating Scale score of 8.1 ± 5.3 . Aging in these patients with schizophrenia was not associated with progressive worsening of quality of well-being or everyday functioning as much as that observed in a normal control group.

Nyer et al. (79) examined the relationship of marital status to depression, positive and negative symptoms, quality of life and suicidal ideation in patients 40 years and older with schizophrenia-spectrum disorders and subsyndromal depression. The authors determined that marriage was an important protective factor against suicidal ideation and had a positive impact on quality of life. The participants’ marital status made up three groups: 1) divorced/widowed/separated; 2) single; and, 3) married/cohabitating. Group 1 had higher quality of life scores than group 2, while group 3 had significantly higher quality of life scores than groups 1 or 2. In addition, group 1 had the highest levels of suicidal ideation and group 3 the lowest (79). Thus, this is another example of the deleterious effects depressive symptoms may have on the quality of life of patients with schizophrenia and subsyndromal depression. Another recent study examined functioning in middle-aged and older patients with schizophrenia and subsyndromal depressive symptoms, characterized by HAMD scores ≥ 8 (1), reported that negative symptoms contributed to the overall functional deficits.

Furthermore, a study by Kasckow et al. (9) examined suicidal behavior in patients aged 40 and older with schizophrenia and subsyndromal depressive symptoms. Thirty-six percent of the 146 subjects had at least mild suicidality based on InterSePT Suicide Scale scores of greater than 0. Logistic regression indicated that Quality of Life scores were predictive of suicidality, but not age, everyday functioning, social functioning, or medication management.

Bowie et al. (80) examined the interactions between neuropsychological performance, symptom severity, and functional capacity on three domains of real-world functioning of older patients with schizophrenia or schizoaffective disorder: 1) interpersonal functioning (ability to form and maintain relationships); 2) community activities (managing finances, engaging in recreational activities and using transportation); and, 3) work skills. They found neuropsychological functioning to be mediated by functional capacity in all three domains. The domain of interpersonal functioning was significantly, and negatively, influenced by depressive and negative symptoms. The domain of community activities was directly influenced by neuropsychological functioning only. With regards to work skills, depression had a main effect. Thus, functional skills in patients with schizophrenia in the community appear to be influenced by multiple factors.

Roseman et al. (81) examined factors which may influence quality of life or functional capacity in middle-aged to older individuals with schizophrenia and subsyndromal depression. The authors concluded that poor insight significantly moderates the relation between negative symptom severity and participants' perceived quality of life, resulting in a decreased perception of quality of life. Neither positive nor depressive symptom severity exhibited a significant role in this interaction. Additionally, increased negative symptom severity directly led to decreased functional capacity. These results demonstrate the clinical importance of subsyndromal depressive symptoms which may reflect the patients' level of insight and perceived quality of life. Furthermore, treatments for patients with schizophrenia and subsyndromal depression may focus on the improvement of not only insight but also of social and daily life skills using psychoeducational tools to improve individuals' functional capacity and, thereby, reduce depressive symptomatology. Thus, the importance of multiple factors in addition to depressive symptoms on quality of life perception and functional capacity is demonstrated.

Treatment

The treatment of schizophrenia, in general, involves pharmacologic treatment with antipsychotic agents in conjunction with psychosocial interventions. The second-generation antipsychotics are now used much more frequently than the first-generation agents. The second-generation antipsychotics provide both serotonin and dopamine receptor antagonism; the pharmacologic effect on serotonin receptors reduces the motor side effects associated with the first-generation agents (82). However, as will be discussed below, the second-generation agents carry other risks such as weight gain, the metabolic syndrome and diabetes (83). One issue that is of current debate is whether there are clinically meaningful differences between each of the second-generation antipsychotics. In a systematic review and meta-analysis, Leucht et al. (84) searched the Cochrane Schizophrenia Group's register (up to May 2007) and MEDLINE (up to September 2007). They examined randomized, blinded studies which compared two or more of the second-generation agents for treatment of schizophrenia in general; 78 studies were examined with 13,558 participants. Olanzapine was found to have superior efficacy compared to aripiprazole, quetiapine, risperidone and ziprasidone. In addition, clozapine had superior efficacy compared to zotepine and risperidone when clozapine doses at 400 mg a day were used. Improvements were noted with regards to positive symptoms. However, the authors concluded that differences in overall efficacy need to be balanced against each agent's specific side effect profiles and cost issues. Furthermore, it is not clear if these findings are applicable to the elderly population.

In addition, Arunpongpaisal et al. (85) reviewed studies examining atypical antipsychotics with other treatments for elderly patients who had a recent diagnosis (within five years) of schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform psychosis or paraphrenia. They stated there is no trial-based evidence upon which to base guidelines for the treatment of late-onset schizophrenia. Thus, there is very little research to help guide the use of antipsychotic agents in older patients with schizophrenia. The most recent Expert Consensus Guidelines for the use of antipsychotic medications in late-life schizophrenia in 2004 (86) suggested that risperidone (1.25–3.5 mg/day) serves as first-line treatment for the treatment of schizophrenia in late life. Quetiapine (100–300 mg/day), olanzapine (7.5–15 mg/day), and aripiprazole (15–30 mg/day) were recommended as second-line approaches. There was limited support for use of clozapine, ziprasidone and high potency conventional agents as additional options for the treatment of schizophrenia in the elderly. The use of antipsychotics to treat elderly patients must be initiated at much lower doses than would be used to treat younger patients (87).

Treating Subthreshold Depressive Symptoms

The treatment of depressive symptoms in patients with schizophrenia varies depending on when they occur, their severity and their persistence (12). Treatment of depression in patients with schizophrenia is accomplished through a combination of pharmacologic and psychosocial approaches (12,68). Because the development of depressive symptoms can be associated with worsening psychosis, clinicians need to carefully consider whether antipsychotic medications should be optimized first prior to initiating antidepressant medication.

Jeste et al. (88) published an 8-week, international, double-blind study with 175 patients with schizophrenia or schizoaffective disorder ≥ 60 years of age in a variety of settings (outpatients, hospital inpatients, and residents of nursing or boarding homes). This study compared risperidone to olanzapine, and the mean age of onset of the disorder in both groups, respectively, was 36.0 and 33.4. Patients had baseline PANSS scores of 50–120 and could not have had a major depressive episode for at least six months. Median doses were 2 mg/day of risperidone and 10 mg/day of olanzapine. PANSS total scores improved significantly at all time points and at endpoint in both groups; between-treatment differences were not significant.

The results not only demonstrated that PANSS total scores improved in both risperidone- and olanzapine-treated patients, but also examined whether antipsychotic monotherapy would help improve depressive symptoms. Indeed, 4 of the 5 PANSS factor scores improved in both risperidone- and olanzapine-treated groups. The 4 factor scores which improved included positive symptoms, negative symptoms, disorganized thoughts and also anxiety/depression. These all improved significantly at all time points and at endpoint in both groups; between-treatment differences were not significant ($p < 0.4$). Baseline mean ($\pm$ standard deviation) HAM-D total scores were 7.5 ± 5.3 in the risperidone group and 8.2 ± 5.4 in the olanzapine group, with the following reductions: risperidone: -1.8 (5.5), $p < 0.01$; olanzapine: -1.5 (5.1), $p < 0.05$; paired t-tests. Thus, the data suggests that second-generation antipsychotics may be helpful in treating subthreshold depressive symptoms in older patients with schizophrenia.

Some investigators have suggested that second-generation antipsychotics are more efficacious than first-generation agents for treating acutely psychotic patients with a mood disorder (14,89,90). A recent review by Furtado and Srihari (91) determined that there are too few data at this time to make any definitive conclusions. In fact, the authors were only able to find three studies which addressed this issue and these were all trials in nonelderly samples. One trial found no significant differences between quetiapine and haloperidol (92). In a second trial, sulpride was compared to chlorpromazine; the group treated with sulpride had more reductions in depressive symptoms based on scores of the Comprehensive Psychopathologic Rating Scale (93). In a third trial, Jasovic (94) used Hamilton Depression Rating Scale scores to compare clozapine to any other antipsychotic plus an antidepressant; use of clozapine lead to greater reductions in Hamilton symptoms. Thus, it is not clear whether second-generation agents are better for treating mood disorders in patients with schizophrenia. Furthermore, it is not clear if this is the case in the elderly.

Augmentation of Antipsychotics with SSRIs in Patients with Schizophrenia

Recent studies have shown that antidepressants are prescribed by clinicians to 30% of inpatients and 43% of outpatients of all ages with schizophrenia and depressive symptoms. Furthermore, selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants and clinicians prefer to treat this population of patients with both

second-generation antipsychotics and an SSRI (95). Despite this high frequency of antidepressant prescription, one quarter of clinicians reported rarely or never prescribing antidepressants in the treatment of patients with schizophrenia and depression. We will discuss below pharmacologic approaches for treating patients with schizophrenia and various presentations of depressive disorders.

Kasckow et al. (96) performed an open-label study of citalopram in chronically hospitalized patients with schizophrenia and depressive symptoms. The authors demonstrated significant improvement in HAMD scores. In this study, 19 patients aged 55 or greater already on antipsychotic medications were augmented with citalopram. Patients had baseline HAMD scores of 12 or greater. Based on two-way repeated ANOVA measures, there were significant ($p < .05$) group effects in HAMD scores and Clinical Global Impression (CGI) scores with the citalopram group (96).

A recent study examined citalopram in middle-aged and older patients with schizophrenia and schizoaffective disorder and subsyndromal depression. Zisook et al. (97) performed a 12-week, double-blind, randomized, placebo-controlled, 2-site study of 198 participants, aged 40 to 75 years old, to examine the effectiveness and safety of citalopram. In this study, subsyndromal depression was defined as having 2 to 4 of the 9 *DSM-IV* symptoms for Major Depression present for the majority of a two-week period. Participants needed to also have a score of 8 or more on the HAMD-17. Participants were randomly assigned to a “flexible-dose treatment” plan with citalopram, or the placebo group, as augmented therapy to their current antipsychotic medication. Nearly all participants were taking second-generation antipsychotics at the time of study participation (90%). The participants in the citalopram group were treated with 20 mg/day for the first week. Dosages could be decreased to 10 mg/day or increased up to 40 mg/day after the first week based on the patient’s response to the medication.

Based on an analysis of covariance of the participants’ improvement scores on the Hamilton Depression Rating Scale and the Calgary Depression Rating Scale, the citalopram group showed significant improvement in depressive and negative symptoms versus the placebo group (all p ’s for each variable < 0.05). Although participants experienced mild side effects/adverse events, there was no significant difference between the citalopram and placebo group in terms of side effects (97).

Further analyses indicated that the citalopram group had significantly higher scores examining social functioning (as per the Social Skills Performance Assessment), mental functioning (as per the SF-12 mental component of the SF-12 Health Survey), and quality of life scale (as per the Heinrichs-Carpenter Quality of Life Scale; QOLS) compared to the placebo group (98). Citalopram treatment led to improvement in medication management (as assessed with the Medication Management Ability Assessment) or physical functioning (as per the Physical Component of the SF-12). In addition, responders had significantly improved endpoint mental SF-12 and QOLS scores compared to nonresponders. Response to citalopram in terms of depressive symptoms mediated the effect of citalopram on mental functioning, but not on the quality of life. Thus, citalopram augmentation of antipsychotic treatment in middle-aged and older patients with schizophrenia and subsyndromal depression not only improves depressive and negative symptomatology, it also appears to improve social and mental health functioning as well as quality of life (98).

Treatment of Patients with Schizophrenia and Major Depression

Studies examining treatment of major depression in elderly patients with schizophrenia are lacking. In younger age patients, there are studies examining whether antidepressants can

improve major depression. Levinson et al. (99) indicated that, for most treatment studies of depressive symptoms during an acute psychotic break, typical antipsychotics are as effective alone as when combined with antidepressants or lithium during the acute psychotic phases. Antidepressants are, however, likely helpful for treating postpsychotic depressive symptoms meeting criteria of major depression (100–102).

Indeed, Dollfus et al. (103) performed a trial comparing olanzapine (5–15 mg) to risperidone (4–8 mg) for the treatment of postpsychotic depression in patients with schizophrenia; age was not specified. At baseline, patients had Montgomery Asberg Depression Scale (MADRS) scores ≥ 16 ; by 2 and 8 weeks of treatment there were significant decreases of MADRS scores in both groups. In addition, Ciobano et al. (104) examined a nonelderly sample of patients with schizophrenia and postpsychotic depression defined by *DSM-IV* criteria. Patients were treated with either a second-generation antipsychotic and either fluvoxamine (100 mg/day), mirtazapine (30–45 mg/day) or venlafaxine (150–225 mg/day) for 2 months. All of the patients improved; response was quicker in the venlafaxine group and was well tolerated.

The 1999 Expert Treatment Guidelines for Patients with Schizophrenia mention recommendations for treating patients with postpsychotic depression (105). These guidelines recommend treating patients with schizophrenia and major depression first with optimal dosages of second-generation antipsychotics; if the patient still experiences significant depressive symptoms after optimization, the Guidelines recommend enhancing treatment with an SSRI. If successful stabilization of depressive symptoms is not achieved with this approach, then venlafaxine would be the next option followed by bupropion (86). In the elderly, the treatment approaches are not well established.

Schizoaffective Disorder

There is little research on the treatment of depressive symptoms in patients with schizoaffective disorder, especially in the elderly population. Furthermore, treatment guidelines for schizoaffective disorder, in general, are not well established. The pharmacologic treatment of patients with schizoaffective disorder may involve a combination of antipsychotics, antidepressants or antimanic agents, depending on whether patients have manic symptoms versus depressive symptoms (106,107). Flynn et al. (108) reviewed the treatment of hospitalized patients with schizoaffective disorder and demonstrated an increase in the use of divalproex and second-generation antipsychotics. Furthermore, despite lack of sufficient evidenced-based trials, the use of antidepressants in combination with optimal antipsychotic treatment, short or long term, has also been suggested as treatments for patients with schizoaffective disorder (109–111).

Controlled trials have demonstrated the efficacy of second-generation antipsychotic monotherapy as having a positive impact for the treatment of schizoaffective disorder. This has been demonstrated with aripiprazole and ziprasidone. Glick et al. (106) analyzed a subsample of subjects with schizoaffective disorder and without any age limitations who were participants in two 4-week, multicenter, double-blind trials of patients with schizophrenia and schizoaffective disorder. Doses of aripiprazole included 15, 20 or 30 mg/day. There were 123 patients on aripiprazole and 56 on placebo. There were improvements in patients with schizoaffective disorder with PANSS total scores, PANSS positive subscale scores but not with other PANSS subscale scores. In addition, no changes were noted in weight, glucose and total cholesterol, nor with scores from scales assessing movement disorders, including akathisia. With ziprasidone at doses of 120 to 160 mg/day, Gunasekara et al. (107) indicated that ziprasidone in clinical trials appears to improve depressive symptoms in patients with schizophrenia and schizoaffective disorder based on the

Montgomery Asberg Depression Rating Scale and the Brief Psychiatric Rating Scale depression cluster scores. It is not known whether aripirazole or ziprasidone exhibit similar effects in elderly patients with schizoaffective disorder.

Safety Issues with Pharmacologic Treatments

Antipsychotic Use

The 2004 Expert Consensus Guidelines for the use of antipsychotic agents in the elderly (86) suggest monitoring patients at least every two months once a patient's status is stable, and every three months once maintenance treatment is achieved (1). The available research on the safety and efficacy of risperidone (112–117), quetiapine (118–120) and olanzapine (121–123), based on single-agent, open-label studies, reports findings and treatment suggestions consistent with the reports from the Expert Consensus Guidelines (86).

The second-generation drugs are strong antagonists of serotonin receptors and dopamine antagonists and, indeed, exhibit lower rates of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) compared to first-generation antipsychotics. Orthostatic hypotension is a potentially serious side effect of second-generation antipsychotics, and clozapine does produce severe side effects due to its anticholinergic properties and increased risk for agranulocytosis and seizures and, thus, needs to be used cautiously in elderly patients (78,82,83,86). Additionally, the use of second-generation antipsychotics to treat elderly patients must be initiated at much lower doses than would be used to treat younger patients (86,87).

Determining the best choice for antipsychotic therapy depends on the side effect profile of the particular agent, the patients' co-occurring condition(s) and unique vulnerabilities, and sometimes patient preference. All antipsychotics pose the threat of causing a metabolic syndrome, including increasing body mass, hyperlipidemia or precipitating or worsening diabetes. Therefore, the Expert Consensus Guidelines (86) suggest that patients with diabetes, dyslipidemia or obesity should avoid using clozapine, olanzapine and first-generation antipsychotics. Regardless of the second-generation antipsychotic chosen, patients with diabetes, or at risk for diabetes, must be monitored closely and regularly. This includes monitoring height, weight, abdominal girth, blood pressure, lipids and glucose levels closely throughout the entire course of treatment starting from the initiation of the treatment agent. If diabetes develops, there are additional Consensus Guidelines from the American Diabetes and American Psychiatric Associations which are available for treating patients that are taking second-generation antipsychotics and are diabetic or obese (124).

Ciranni et al. (125) conducted a retrospective cohort chart review of the California Poison Control System electronic database of cases from 1997 to 2006. They examined records of patients who had an acute toxic ingestion of either a second-generation or first-generation antipsychotic medication; the age range was 18 to 65 years. The odds of a major adverse outcome or death was significantly higher for second-generation antipsychotics (OR=1.71, 95% CI=1.09–2.71). In addition, those who took second-generation antipsychotics had higher odds of respiratory depression, coma, and hypotension, while those taking first-generation antipsychotics had higher odds of dystonia or rigidity. Another recent review, by Khaldi et al. (126), examined whether second-generation antipsychotics are able to induce neuroleptic malignant syndrome. From 1986 to 2005, 47 cases were identified with a mean age of 37. Diagnoses included schizophrenia (n=26), schizoaffective disorder (n=9), bipolar disorder (n=3), mental retardation (n=4), and other (n=5). Drugs implicated included clozapine, olanzapine, risperidone, quetiapine and ziprasidone; 29/47 patients received no other medications and 2 deaths occurred, 1 with olanzapine and 1 with risperidone. These

findings emphasize the need to consider potential adverse effects when prescribing these agents. It is not known whether these findings are generalizable to the elderly.

The U.S. Federal Drug Administration (FDA) has issued a black box warning stating that elderly patients with dementia are at increased risk of death with second-generation antipsychotics. It is not known, however, whether this is an issue in elderly patients with schizophrenia without neurodegenerative syndromes when being treated with these agents. The data do suggest that close monitoring be utilized in older patients with schizophrenia and similar disorders.

Often, elderly patients are on many medications. Thus, the combination drug of olanzapine and fluoxetine marketed as Symbyax (127) and approved for bipolar depression and treatment-resistant depression may be helpful for treating the older patient with schizophrenia and clinically significant depressive symptoms.

Clozapine has emerged in both epidemiologic and clinical studies as having a significant effect on suicidal behavior. Clozapine has been shown to have a substantial effect on attempted suicide (128–130) and completed suicide (131–133). In 2002, the FDA Psychopharmacologic Drugs Advisory Committee voted to recommend that the FDA approve the use of clozapine for the treatment of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder (134). It is not clear whether this is applicable to elderly patients and, furthermore, how the increased safety risks in the elderly are balanced with potential efficacy in suicidal behaviors.

Finally, there were three other important safety guidelines for antipsychotic use in the elderly recommended by the Expert Consensus Panel. These include: 1) treating patients with EPS with quetiapine first, olanzapine or aripiprazole second; 2) the use of quetiapine or olanzapine in patients with prolactin-related disorders like galactorrhea or gynecomastia instead of using risperidone; and, 3) avoiding clozapine, ziprasidone and first-generation antipsychotics in patients with congestive heart failure (135).

Antidepressant Use

There have been case reports suggesting that augmenting antipsychotics with tricyclics or serotonin selective reuptake inhibitors may cause psychosis (136,137). At least with SSRI antidepressants, this has not been supported by larger sized trials (138). However, if clozapine is augmented with SSRIs, then potential adverse effects resulting from drug-drug interactions need to be considered (139).

With tricyclic antidepressants, the elderly are more sensitive to their unwanted actions. Particularly troublesome among older persons are peripheral and central anticholinergic effects such as constipation, urinary retention, delirium and cognitive dysfunction, antihistaminergic effects such as sedation, and antiadrenergic effects such as postural hypotension. In addition to interfering with basic activities, pronounced sedation and orthostatic hypotension pose a significant safety risk to elderly patients since they can lead to falls and fractures.

SSRIs have negligible effects on cholinergic, histaminergic and adrenergic neurotransmission and typically are not associated with the abovementioned adverse symptoms (140). Furthermore, since they do not impede cardiac conduction, they are relatively safe even in overdose situations (141), a critical feature of any drug that is used to treat potentially suicidal patients. According to placebo-controlled trials and postmarketing surveys (142), the most common complaints associated with SSRI therapy include nausea, diarrhea, increased sweating and sexual dysfunction. Most treatment-related symptoms are

mild-to-moderate in severity and gastrointestinal effects appear to abate as therapy continues (142).

Use of Mood Stabilizers as Augmenting Treatments

Prescribing mood stabilizers to augment antipsychotic treatment is common in treating patients with schizophrenia and schizoaffective disorder. More research is needed since the evidence supporting the use of these agents in patients with schizophrenia in general is lacking; furthermore, the utility of using these agents in treating elderly patients with schizophrenia and depressive disorders is even less clear (143). Perhaps lithium augmentation would be helpful for dealing with suicidal risk; however, the evidence for this in older patients with schizophrenia and depressive disorders is lacking (144,145).

A recent meta-analysis of randomized, controlled clinical trials concluded that lithium and carbamazepine were not likely effective treatments in patients with schizophrenia (146). The Texas Medication Algorithm Project guidelines initially included the use of adjunctive mood stabilizers to treat schizophrenia; however, the most recent revision has not included them (147). In a recent study, Chen et al. (148) reported on a one-year observation period in which subjects filled an average of 200 days supply of adjunctive mood stabilizers to augment antipsychotic treatment in patients with schizophrenia. The recipients of these medications had longer antipsychotic treatment durations than those who did not have exposure to mood stabilizers. This analysis included comparisons of patients on valproate, lithium, carbamazepine or combinations of mood stabilizers. The authors stated that the additional intensive treatment accounted for higher costs, although there were no differences in hospitalizations, emergency room visits and nursing home admissions. Longer antipsychotic treatment durations were observed in patients receiving adjunctive mood stabilizers. The authors also stated they could not have determined how much selection bias could have contributed to these outcomes.

Psychosocial Approaches for Treating Patients with Schizophrenia and Depression

Antipsychotic pharmacotherapy improves some symptoms of schizophrenia in late life but others can still remain. The same is true of antidepressant augmentation. Thus, psychosocial therapies in combination with pharmacotherapy are very important additional treatments needed for this patient population in order to alleviate residual symptoms and to improve social functioning and quality of life. There is very little research available for psychosocial treatments targeted toward patients with schizophrenia and depression, and even less for the older patient with schizophrenia and depression.

The care of older patients with schizophrenia is organized within the context of rehabilitation. This involves a “care program approach” involving a team of physicians, nurses, occupational therapists, social workers and others (149,150). There are seven important ideal elements with this plan: 1) optimal treatment of the psychiatric illness; 2) optimal treatment of the physical illness(es) with improved education and awareness of these illnesses; 3) maintenance of daily living skills; 4) maintenance of social contacts; 5) participation in day activities; 6) appropriate management of finances; and, 7) risk assessment. Psychoeducation is a key component of this approach and may need to be modified for older patients because of potential cognitive deficits. Liberman and Eckman (65,151) have described a practically oriented social skills training program for elderly patients with schizophrenia. The model uses role play to enhance patients’ behavioral performance and to enhance communication skills (109).

Assertive Community Treatment is a psychosocial treatment modality important for patients with schizophrenia which has not been studied exclusively in elderly patients with schizophrenia, nor have there been studies targeting elderly patients with schizophrenia and depression. Six studies examining this in patients with schizophrenia in general have been published, which have included subjects age 50 or older. Five studies had favorable results and one study demonstrated mixed findings (14,15,66,67,110,152,153), suggesting that the approach may be helpful for the older patient with schizophrenia in general. With regards to Case Management (CM), there are eight intervention studies involving CM programs with subjects aged 50 or older with schizophrenia. Of these, four reported positive outcomes for CM (19,70,71,109,154), two reported mixed results (71,77), and two found no advantages (11,155). Mohamed et al. (109) pointed out that, although CM does not appear to be as beneficial for older individuals with schizophrenia, studies that included older patients versus younger using 50 as the age cut-off appeared to have better outcomes overall. Clearly more research is needed in this area, especially with regards to older patients with schizophrenia and depressive symptoms.

Other important psychosocial therapeutic strategies that are used to treat patients with schizophrenia include Cognitive Behavioral Therapy, Family Intervention, Social Skills Training, and Cognitive Remediation. These approaches could likely have potentially promising effects in geriatric patients with schizophrenia and depressive symptoms. Each therapeutic approach effectively targets selected domains (156). For Cognitive Behavioral Therapy (CBT), those domains are psychopathology and symptoms. The most consistent effect of CBT has been the improvement of positive and negative symptoms (157–168). Recent meta-analyses of CBT support the findings of individual studies (169,170). For Social Skills Training, goals of treatment include improvement in social skills and attainment of employment.

Granholm et al. (171) performed a randomized, controlled trial of Cognitive Behavioral Social Skills Training for middle-aged and older outpatients with chronic schizophrenia. Geriatric patients were included in this study; participants' ages ranged from 42–74 years old. The mean age of subjects in the experimental group, which consisted of the intervention plus "treatment as usual," was 54.5 ± 7.0 with a mean HAMD score of 13.5 ± 9.0 . The average age for the "treatment as usual" group was 53.1 ± 7.5 and the average HAMD score was 14.2 ± 8.8 . Patients receiving the intervention performed social functioning activities more frequently than the patients in "treatment as usual." In addition, the intervention group had 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 greater reduction in positive symptoms. There were, however, no significant differences between the two groups with regards to changes in HAMD scores. However, improvement in overall cognitive insight was associated at mid-treatment with a transient increase in depression scores, but this resolved by the end of treatment.

For Family Therapy, goals are to improve treatment adherence and prevention of relapse and rehospitalization. For Cognitive Remediation, improvement of neurocognitive functioning is the goal. Integrated psychotherapies also offer promise in addressing a wider range of outcomes. Integrated strategies may also be more cost-effective if they can be shown to consistently increase adherence and reduce relapse (172). However, with the possible exception of Integrated Psychological Therapy (173–177), the integrated therapies used to date have not yet demonstrated clear superiority to individual therapeutic approaches in the domains addressed by the individual approaches. Future research needs to examine these psychosocial treatments in geriatric patients with schizophrenia and depressive symptoms.

Conclusions

In this review, we have discussed depressive syndromes in older patients with schizophrenia-spectrum disorders, which include schizophrenia with major depression, schizoaffective disorder, and schizophrenia or schizoaffective disorder with comorbid subsyndromal depression. Although not as much is known about the characteristics of such conditions in the elderly patient, it is evident that comorbid depressive symptoms impact upon patients' quality of life and functioning. Furthermore, a significant proportion of older patients with comorbid depression experience at least mild degrees of suicidal ideation. From a pharmacologic perspective, the treatment of depressive symptoms in patients with schizophrenia requires antipsychotics and antidepressants. Implementing psychosocial interventions is also an important part of patients' treatment plans.

There is still much research which needs to be performed with this patient population. Studies examining other augmentation strategies to antipsychotic and antidepressant treatments, including specific psychotherapeutic approaches such as Cognitive Behavioral Social Skills Training (171), are needed. Furthermore, more research leading to a better understanding of the biologic, psychological and social underpinnings of depressive symptoms in this patient population should result in the development of more effective pharmacologic agents as well as better psychosocial interventions that will improve outcomes in these patients.

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References

1. Kaskow JW, Zisook S. Co-occurring depressive symptoms in the older patient with schizophrenia. *Drugs Aging*. 2008; 25(8):631–647. [PubMed: 18665657]
2. Alexopoulos GS, Borson S, Cuthbert BN, Devanand DP, Muisant BH, Olin JT, et al. Assessment of late life depression. *Biol Psychiatry*. 2002; 52(3):164–174. [PubMed: 12182923]
3. Siris, SG. Depression in the course of schizophrenia. In: Hwang, MY.; Bermanzohn, PC., editors. *Schizophrenia and comorbid conditions*. Washington, DC: American Psychiatric Press, Inc; 2001. p. 31–56.
4. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. *Arch Gen Psychiatry*. 1994; 51(1):8–19. [PubMed: 8279933]
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Text Revision*. 3. Washington, DC: American Psychiatric Association; 2000.
6. Roy A. Suicide in chronic schizophrenia. *Br J Psychiatry*. 1982; 141:171–177. [PubMed: 6126237]
7. Johnson DA. Studies of depressive symptoms in schizophrenia. *Br J Psychiatry*. 1981; 139:89–101. [PubMed: 7030447]
8. Addington DD, Azorin JM, Falloon IR, Gerlach J, Hirsch SR, Siris SG. Clinical issues related to depression in schizophrenia: an international survey of psychiatrists. *Acta Psychiatr Scand*. 2002; 105(3):189–195. [PubMed: 11939972]
9. Kaskow J, Montross L, Golshan S, Mohamed S, Patterson T, Sollanzano E, et al. Suicidality in middle aged and older patients with schizophrenia and depressive symptoms: relationship to functioning and quality of life. *Int J Geriatr Psychiatry*. 2007; 22(12):1223–1228. [PubMed: 17506025]

10. Schwartz RC, Cohen BN. Psychosocial correlates of suicidal intent among patients with schizophrenia. *Compr Psychiatry*. 2001; 42(2):118–123. [PubMed: 11244147]
11. Diwan S, Cohen CI, Bankole AO, Vahia I, Kehn M, Ramirez PM. Depression in older adults with schizophrenia spectrum disorders: prevalence and associated factors. *Am J Geriatr Psychiatry*. 2007; 15(12):991–998. [PubMed: 18056817]
12. Green AI, Canuso CM, Brenner MJ, Wojcik JD. Detection and management of comorbidity in patients with schizophrenia. *Psychiatr Clin North Am*. 2003; 26(1):115–139. [PubMed: 12683263]
13. Bressan RA, Chaves AC, Pilowsky LS, Shirakawa I, Mari JJ. Depressive episodes in stable schizophrenia: critical evaluation of the DSM-IV and ICD-10 diagnostic criteria. *Psychiatry Res*. 2003; 117(1):47–56. [PubMed: 12581820]
14. Tollefson GD, Sanger TM, Lu Y, Thieme ME. Depressive signs and symptoms in schizophrenia. *Arch Gen Psychiatry*. 1998; 55(3):250–258. [PubMed: 9510219]
15. Kay SR, Sevy S. Pyramidal model of schizophrenia. *Schizophr Bull*. 1990; 16(3):537–545. [PubMed: 2287938]
16. Knights A, Hirsch SR. “Revealed” Depression and drug treatment for schizophrenia. *Arch Gen Psychiatry*. 1981; 38(7):806–811. [PubMed: 6113822]
17. Sax KW, Strakowski SM, Keck PE Jr, Upadhyaya VH, West SA, McElroy SL. Relationships among negative, positive, and depressive symptoms in schizophrenia and psychotic depression. *Br J Psychiatry*. 1996; 168(1):68–71. [PubMed: 8770431]
18. Koreen AR, Siris SG, Chakos M, Alvir J, Mayerhoff D, Lieberman J. Depression in first-episode schizophrenia. *Am J Psychiatry*. 1993; 150(11):1643–1648. [PubMed: 8105706]
19. Tollefson GD, Andersen SW, Tran PV. The course of depressive symptoms in predicting relapse in schizophrenia: a double-blind, randomized comparison of olanzapine and risperidone. *Biol Psychiatry*. 1999; 46(3):365–373. [PubMed: 10435202]
20. Birchwood M, Iqbal Z, Chadwick P, Trower P. Cognitive approach to depression and suicidal thinking in psychosis. 1. Ontogeny of post-psychotic depression. *Br J Psychiatry*. 2000; 177:516–521. [PubMed: 11102326]
21. Bressan RA, Costa DC, Jones HM, Eli PJ, Pilowsky LS. Typical antipsychotic drugs -- D(2) receptor occupancy and depressive symptoms in schizophrenia. *Schizophr Res*. 2002; 56(1–2):31–36. [PubMed: 12084417]
22. Winograd-Gurvich C, Fitzgerald PB, Georgiou-Karistianis N, Bradshaw JL, White OB. Negative symptoms: A review of schizophrenia, melancholic depression and Parkinson’s disease. *Brain Res Bull*. 2006; 70(4–6):312–321. [PubMed: 17027767]
23. Siris, SG.; Lavin, MR. Other psychotic disorders. In: Kaplan, HI.; Saddock, BJ., editors. *Comprehensive textbook of psychiatry*. 4. Vol. 1. Baltimore: Williams and Wilkins; 1995. p. 1019–1025.
24. Heald A, Morris J, Soni SD. Characterisation of depression in patients with schizophrenia. *Indian J Med Res*. 2008; 127(6):544–550. [PubMed: 18765872]
25. Bleich A, Koslowsky M, Dolev A, Lerer B. Posttraumatic stress disorder and depression. *Br J Psychiatry*. 1997; 170:479–482. [PubMed: 9307701]
26. O’Donnell ML, Creamer M, Pattison P. Posttraumatic stress disorder and depression following trauma: understanding comorbidity. *Am J Psychiatry*. 2004; 161(8):1390–1396. [PubMed: 15285964]
27. Keane TM, Wolfe J. Comorbidity in post-traumatic stress disorder: an analysis of community and clinical studies. *Journal of Applied Social Psychology*. 1990; 20:1776–1778.
28. Breslau N, Davis GC, Andreski P, Peterson E. Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Arch Gen Psychiatry*. 1991; 48(3):216–222. [PubMed: 1996917]
29. Green BL, Lindy JD, Grace MC, Leonard AC. Chronic posttraumatic stress disorder and diagnostic comorbidity in a disaster sample. *J Nerv Ment Dis*. 1992; 180(12):760–766. [PubMed: 1469374]
30. Beyer JL. Managing depression in geriatric populations. *Ann Clin Psychiatry*. 2007; 19(4):221–238. [PubMed: 18058280]

31. Summers MN, Hyer L, Boyd S, et al. Diagnosis of later-life PTSD among elderly combat veterans. *Journal of Clinical Geropsychology*. 1996; 2:103–115.
32. Blanchard EB, Buckley TC, Hickling EJ, Taylor AE. Posttraumatic stress disorder and comorbid major depression: is the correlation an illusion? *J Anxiety Disord*. 1998; 12(1):21–37. [PubMed: 9549607]
33. Franklin CL, Zimmerman M. Posttraumatic stress disorder and major depressive disorder: investigating the role of overlapping symptoms in diagnostic comorbidity. *J Nerv Ment Dis*. 2001; 189(8):548–551. [PubMed: 11531207]
34. Averill PM, Beck JG. Posttraumatic stress disorder in older adults: a conceptual review. *J Anxiety Disord*. 2000; 14(2):133–156. [PubMed: 10864382]
35. Hyer L, Summers MN, Braswell L, et al. Posttraumatic stress disorder: silent problem among older combat veterans. *Psychotherapy*. 1995; 32(2):348–364.
36. Salzman C, Wong E, Wright BC. Drug and ECT treatment of depression in the elderly, 1996–2001: a literature review. *Biol Psychiatry*. 2002; 52(3):265–284. [PubMed: 12182932]
37. Menninger JA. Assessment and treatment of alcoholism and substance-related disorders in the elderly. *Bull Menninger Clin*. 2002; 66(2):166–183. [PubMed: 12141383]
38. O'Hara, R.; Coman, E.; Butters, MA. Late life depression. In: Snyder, PJ.; Nussbaum, PD.; Robins, DK., editors. *Clinical neuropsychology: a pocket handbook for assessment*. 2. Washington (DC): American Psychology Association (APA); 2005. p. 183–209.
39. Mersy DJ. Recognition of alcohol and substance abuse. *Am Fam Physician*. 2003; 67(7):1529–1532. [PubMed: 12722853]
40. Raue PJ, Alexopoulos GS, Bruce ML, Klimstra S, Mulsant BH, Gallo JJ. The systematic assessment of depressed elderly primary care patients. *Int J Geriatr Psychiatry*. 2001; 16(6):560–569. [PubMed: 11424164]
41. Salzman C. Depressive disorders and other emotional issues in the elderly: current issues. *Int Clin Psychopharmacol*. 1997; 12 (Suppl 7):S37–S42. [PubMed: 9476139]
42. Wood KA, Harris MJ, Morreale A, Rizos AL. Drug-induced psychosis and depression in the elderly. *Psychiatr Clin North Am*. 1988; 11(1):167–193. [PubMed: 2898132]
43. McDonald WM, Salzman C, Schatzberg AF. Depression in the elderly. *Psychopharmacol Bull*. 2002; 36 (Suppl 2):112–122. [PubMed: 12490827]
44. Birchwood M, Iqbal Z, Upthegrove R. Psychological pathways to depression in schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2005; 255(3):202–212. [PubMed: 15995904]
45. Baynes D, Mulholland C, Cooper SJ, Montgomery RC, MacFlynn G, Lynch G, et al. Depressive symptoms in stable chronic schizophrenia: prevalence and relationship to psychopathology and treatment. *Schizophr Res*. 2000; 45(1–2):47–56. [PubMed: 10978872]
46. Addington D, Addington J, Maticka-Tyndale E. Specificity of the Calgary Depression Scale for schizophrenics. *Schizophr Res*. 1994; 11(3):239–244. [PubMed: 8193062]
47. Oosthuizen P, Emsley R, Niehaus D, Koen L, Chiliza B. The relationships between depression and remission in first-episode psychosis. *World Psychiatry*. 2006; 5(3):172–176. [PubMed: 17139353]
48. Addington J, Leriger E, Addington D. Symptom outcome 1 year after admission to an early psychosis program. *Can J Psychiatry*. 2003; 48(3):204–207. [PubMed: 12728745]
49. Micallef J, Fakra E, Blin O. Use of antidepressant drugs in schizophrenic patients with depression. *Encephale*. 2006; 32(2 Pt 1):263–269. French. [PubMed: 16910628]
50. Eiber R, Even C. Actual approaches to post-psychotic depression. *Encephale*. 2001; 27(4):301–307. French. [PubMed: 11686051]
51. Hausmann A, Fleischhacker WW. Depression in patients with schizophrenia. *CNS Drugs*. 2000; 14(4):289–299.
52. Hafner H, Riecher-Rossler A, Hambrecht M, Maurer K, Meissner S, Schmidtke A, et al. IRAOS: an instrument for the assessment of onset and early course of schizophrenia. *Schizophr Res*. 1992; 6(3):209–223. [PubMed: 1571314]
53. Hafner H, Maurer K, Löffler W, an der Heiden W, Munk-Jorgensen P, Hambrecht M, et al. The ABC Schizophrenia Study: a preliminary overview of the results. *Soc Psychiatry Psychiatr Epidemiol*. 1998; 33(8):380–386. [PubMed: 9708025]

54. Bustamante S, Maurer K, Löffler W, Hafner H. Depression in the early course of schizophrenia. *Fortschr Neurol Psychiatr.* 1994; 62(9):317–329. German. [PubMed: 7959515]
55. Howard R, Rabins PV, Seeman MV, Jeste DV. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group. *Am J Psychiatry.* 2000; 157(2):172–178. [PubMed: 10671383]
56. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition.* Washington, DC: American Psychiatric Association; 2000.
57. Martin RL, Cloninger CR, Guze SB, Clayton PJ. Frequency and differential diagnosis of depressive syndromes in schizophrenia. *J Clin Psychiatry.* 1985; 46(11 Pt 2):9–13. [PubMed: 2865255]
58. McGlashan TH, Carpenter WT Jr. An investigation of the postpsychotic depressive syndrome. *Am J Psychiatry.* 1976; 133(1):14–19. [PubMed: 1247119]
59. Iqbal Z, Birchwood M, Chadwick P, Trower P. Cognitive approach to depression and suicidal thinking in psychosis. *Br J Psychiatry.* 2000; 177:522–529. [PubMed: 11102327]
60. Jeczmierni P, Levkovitz Y, Weizman A, Carmel Z. Post-psychotic depression in schizophrenia. *Isr Med Assoc J.* 2001; 3(8):589–592. [PubMed: 11519384]
61. Iqbal Z, Birchwood M, Hemsley D, Jackson C, Morris E. Autobiographical memory and post-psychotic depression in first episode psychosis. *Br J Clin Psychol.* 2004; 43(Pt 1):97–104. [PubMed: 15005909]
62. Schwartz CC, Myers JK. Life events and schizophrenia. II. Impact of life events and symptom configuration. *Arch Gen Psychiatry.* 1977; 34(10):1242–1245.
63. Wittmann D, Keshavan M. Grief and mourning in schizophrenia. *Psychiatry.* 2007; 70(2):154–166. [PubMed: 17661540]
64. Mauri MC, Laini V, Barone R, Clemente A, Volonteri LS, Cerveri G, et al. Post-psychotic depression and residual schizophrenia in a mental health hospital. *Encephale.* 2000; 26(6):21–26. [PubMed: 11217534]
65. Kendler KS, McGuire M, Gruenberg AM, Walsh D. Examining the validity of DSM-III-R schizoaffective disorder and its putative subtypes in the Roscommon Family Study. *Am J Psychiatry.* 1995; 152(5):755–764. [PubMed: 7726316]
66. Bartels SJ, Drake RE. Depressive symptoms in schizophrenia: comprehensive differential diagnosis. *Compr Psychiatry.* 1988; 29(5):467–483. [PubMed: 3053027]
67. Leff, J. Depressive symptoms in the course of schizophrenia. In: DeLisi, LE., editor. *Depression in schizophrenia.* Washington, DC: American Psychiatric Press; 1990. p. 3-23.
68. Siris SG. Depression in schizophrenia: perspective in the era of “Atypical” antipsychotic agents. *Am J Psychiatry.* 2000; 157(9):1379–1389. [PubMed: 10964850]
69. Lysaker PH, Bell MD, Bioty SM, Zito WS. The frequency of associations between positive and negative symptoms and dysphoria in schizophrenia. *Compr Psychiatry.* 1995; 36(2):113–117. [PubMed: 7758296]
70. Zisook S, Nyer M, Kasckow JW, Golshan S, Lehman D, Montross L. Depressive symptom patterns in patients with chronic schizophrenia and subsyndromal depression. *Schizophr Res.* 2006; 86(1–3):226–233. [PubMed: 16750346]
71. Zisook S, Montross L, Kasckow J, Mohamed S, Palmer BW, Patterson TL, et al. Subsyndromal depressive symptoms in middle aged and older patients with schizophrenia. *Am J Geriatr Psychiatry.* 2007; 15(12):1005–1014. [PubMed: 18056819]
72. Montross LP, Kasckow J, Golshan S, et al. Suicidal ideation and suicide attempts among middle-aged and older patients with schizophrenia spectrum disorders and concurrent subsyndromal depression. *The Journal of Nervous and Mental Disease.* 2008; 196(12):884–890. [PubMed: 19077855]
73. Conley RR, Ascher-Svanum H, Zhu B, Faries DE, Kinon BJ. The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. *Schizophr Res.* 2007; 90(1–3):186–197. [PubMed: 17110087]
74. Rocca P, Bellino S, Calvarese P, Marchiaro L, Patria L, Rasetti R, et al. Depressive and negative symptoms in schizophrenia: different effects on clinical features. *Compr Psychiatry.* 2005; 46(4):304–310. [PubMed: 16175763]

75. Kilzieh N, Wood AE, Erdmann J, Raskind M, Tapp A. Depression in Kraepelinian schizophrenia. *Compr Psychiatry*. 2003; 44(1):1–6. [PubMed: 12524629]
76. Jin H, Zisook S, Palmer BW, Patterson TL, Heaton RK, Jeste DV. Association of depressive symptoms and functioning in schizophrenia: a study in older outpatients. *J Clin Psychiatry*. 2001; 62(10):797–803. [PubMed: 11816869]
77. Cohen CI, Talavera N, Hartung R. Predictors of subjective well-being among older, community-dwelling persons with schizophrenia. *Am J Geriatr Psychiatry*. 1997; 5(2):145–155. [PubMed: 9106378]
78. Jeste DV, Barak Y, Madhusoodanan S, Grossman F, Gharabawi G. International multisite double-blind trial of the atypical antipsychotics risperidone and olanzapine in 175 elderly patients with chronic schizophrenia. *Am J Geriatr Psychiatry*. 2003; 11(6):638–647. [PubMed: 14609804]
79. Nyer M, Kasckow J, Fellows I, Lawrence EC, Golshan S, Solorzano E, et al. The relationship of marital status and clinical characteristics in middle-aged and older patients with schizophrenia and depressive symptoms. *Ann Clin Psychiatry*. 2010; 22(3):172–179. [PubMed: 20680190]
80. Bowie CR, Reichenberg A, Patterson TL, Heaton RK, Harvey PD. Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. *Am J Psychiatry*. 2006; 163(3):418–425. [PubMed: 16513862]
81. Roseman AS, Kasckow J, Fellows I, Osatuke K, Patterson TL, Mohamed S, et al. Insight, quality of life, and functional capacity in middle-aged and older adults with schizophrenia. *Int J Geriatr Psychiatry*. 2008; 23(7):760–765. [PubMed: 18205246]
82. Correll CU, Leucht S, Kane JM. Lower risk of tardive dyskinesia associated with second generation antipsychotics: a systematic review of 1 year studies. *Am J Psychiatry*. 2004; 161(3):414–425. [PubMed: 14992963]
83. Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K. First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2008; 192(6):406–411. [PubMed: 18515889]
84. Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, et al. Meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry*. 2009; 166(2):152–163. [PubMed: 19015230]
85. Arunpongpaisal S, Ahmed I, Aqeel N, Suchat P. Antipsychotic drug treatment for elderly people with late-onset schizophrenia. *Cochrane Database Syst Rev*. 2003; 2:CD004162. [PubMed: 12804499]
86. Alexopoulos GS, Streim J, Carpenter D, Docherty JP. Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients. Using antipsychotic agents in older patients. *J Clin Psychiatry*. 2004; 65 (Suppl 2):5–99. [PubMed: 14994733]
87. Kahn S, Kasckow JW, Mulchahey JJ, et al. Antipsychotic use in the older patient with schizophrenia. *Behavioral Health Management*. 2004; 24:S1–S4.
88. Jeste DV, Twamley EW, Eyler Zorrilla LT, Golshan S, Patterson TL, Palmer BW. Aging and outcome in schizophrenia. *Acta Psychiatr Scand*. 2003; 107(5):336–343. [PubMed: 12752029]
89. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry*. 1997; 58(12):538–546. [PubMed: 9448657]
90. Banov MD, Zarate CA Jr, Tohen M, Scialabba D, Wines JD Jr, Kolbrener M, et al. Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. *J Clin Psychiatry*. 1994; 55(7):295–300. [PubMed: 8071290]
91. Furtado VA, Srihari V. Atypical antipsychotics for people with both schizophrenia and depression. *Cochrane Database Syst Rev*. 2008; (1):CD005377. [PubMed: 18254078]
92. Emsley RA, Buckley P, Jones AM, Greenwood MR. Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. *J Psychopharmacol*. 2003; 17(2):210–215. [PubMed: 12870569]
93. Alfredsson G, Harnryd C, Wiesel FA. Effects of sulpiride and chlorpromazine on depressive symptoms in schizophrenic patients -- relationship to drug concentrations. *Psychopharmacology (Berl)*. 1984; 84(2):237–241. [PubMed: 6438683]

94. Jasovic-Gasic, M.; Crnobaric, C.; Miljevic, C. Antidepressants versus clozapine in the treatment of depressive syndrome in schizophrenia. *Proceedings of the 10th European College of Neuropsychopharmacology Congress*; 1997 Sep 13–17; Vienna, Austria.
95. Siris SG, Addington D, Azorin J, Fallon IR, Gerlach J, Hirsch SR. Depression in schizophrenia: recognition and management in the USA. *Schizophr Res*. 2001; 47(2–3):185–197. [PubMed: 11278136]
96. Kasckow JW, Mohamed S, Thallasinos A, Carroll B, Zisook S, Jeste DV. Citalopram augmentation of antipsychotic treatment in older schizophrenia patients. *Int J Geriatr Psychiatry*. 2001; 16(12):1163–1167. [PubMed: 11748776]
97. Zisook S, Kasckow JW, Golshan S, Fellows I, Solorzano E, Lehman D, et al. Citalopram augmentation for subsyndromal symptoms of depression in middle-aged and older outpatients with schizophrenia and schizoaffective disorder: a randomized controlled trial. *J Clin Psychiatry*. 2009; 70(4):562–571. [PubMed: 19192468]
98. Kasckow J, Lanouette N, Patterson T, Fellows I, Golshan S, Solorzano E, et al. Treatment of subsyndromal depressive symptoms in middle-age and older adults with schizophrenia: effect on functioning. *Int J Geriatr Psychiatry*. 2010; 25(2):183–190. [PubMed: 19711335]
99. Levinson DF, Umapathy C, Musthaq M. Treatment of schizoaffective disorder and schizophrenia with mood symptoms. *Am J Psychiatry*. 1999; 156(8):1138–1148. [PubMed: 10450252]
100. Siris SG, Morgan V, Fagerstrom R, Rifkin A, Cooper TB. Adjunctive imipramine in the treatment of postpsychotic depression. A controlled trial. *Arch Gen Psychiatry*. 1987; 44(6):533–539. [PubMed: 3555386]
101. Hogarty GE, McEvoy JP, Ulrich RF, DiBarry AL, Bartone P, Cooley S, et al. Pharmacotherapy of impaired affect in recovering schizophrenic patients. *Arch Gen Psychiatry*. 1995; 52(1):29. [PubMed: 7811160]
102. Kirli S, Caliskan M. A comparative study of sertraline versus imipramine in postpsychotic depressive disorder of schizophrenia. *Schizophr Res*. 1998; 33(1–2):103–111. [PubMed: 9783350]
103. Dollfus S, Guillard P, Cazenave M, et al. Antipsychotics in the treatment of schizophrenic patients with a post-psychotic depression. *European Psychiatry*. 2004; (Suppl 1):126s. Abstract only.
104. Ciobanu AM, Dragan A, Beldie A, et al. Treatment of post-psychotic depression (PPD) in schizophrenia. *European Psychiatry*. 2008; 23:S109. Abstract only.
105. McEvoy JP, Scheifler PL, Frances A. The Expert Consensus Guidelines Series: treatment of schizophrenia. *J Clin Psychiatry*. 1999; 60(Suppl 11):1–80.
106. Glick ID, Mankoski R, Eudicone JM, Marcus RN, Tran QV, Assuncao-Talbot S. The efficacy, safety, and tolerability of aripiprazole for the treatment of schizoaffective disorder: results from a pooled analysis of a sub-population of subjects from two randomized, double-blind, placebo-controlled, pivotal trials. *J Affect Disord*. 2009; 115(1–2):18–26. [PubMed: 19230981]
107. Gunasekara NS, Spencer CM, Keating GM. Spotlight on ziprasidone in schizophrenia and schizoaffective disorder. *CNS Drugs*. 2002; 16(9):645–652. [PubMed: 12153335]
108. Flynn J, Grieger TA, Benedek DM. Pharmacologic treatment of hospitalized patients with schizoaffective disorder. *Psychiatr Serv*. 2002; 53(1):94–96. [PubMed: 11773657]
109. Danileviciute V. Schizoaffective disorder: clinical symptoms and present-day approach to treatment. *Medicina (Kaunas)*. 2002; 38(11):1057–1065. Lithuanian. [PubMed: 12532717]
110. Azorin JM, Kaladjian A, Fakra E. Current issues on schizoaffective disorder. *Encephale*. 2005; 31(3):359–365. French. [PubMed: 16142051]
111. Levinson DF, Umapathy C, Musthaq M. Treatment of schizoaffective disorder and schizophrenia with mood symptoms. *Am J Psychiatry*. 1999; 156(8):1138–1148. [PubMed: 10450252]
112. Ritchie CW, Chiu E, Harrigan S, Hall K, Hassett A, Macfarlane S, et al. The impact upon extrapyramidal side effects, clinical symptoms and quality of life of a switch from conventional to atypical antipsychotics (risperidone or olanzapine) in elderly patients with schizophrenia. *Int J Geriatr Psychiatry*. 2003; 18(5):432–440. [PubMed: 12766921]

113. Barak Y, Shamir E, Weizman R. Would a switch from typical antipsychotics to risperidone be beneficial for elderly schizophrenic patients? A naturalistic, long-term, retrospective, comparative study. *J Clin Psychopharmacol.* 2002; 22(2):115–120. [PubMed: 11910255]
114. Hwang JP, Yang CH, Yu HC, Chang JW, Cheng CY, Tsai SJ. The efficacy and safety of risperidone for the treatment of geriatric psychosis. *J Clin Psychopharmacol.* 2001; 21(6):583–587. [PubMed: 11763005]
115. Verma S, Orenge CA, Kunik ME, Halle D, Molinari VA. Tolerability and effectiveness of atypical antipsychotics in male geriatric inpatients. *Int J Geriatr Psychiatry.* 2001; 16(2):223–227. [PubMed: 11241729]
116. Davidson M, Harvey PD, Vervaeke J, Gagliano CA, De Hooge JD, Bray G, et al. A long-term, multicenter, open-label study of risperidone in elderly patients with psychosis. On behalf of the Risperidone Working Group. *Int J Geriatr Psychiatry.* 2000; 15(6):506–514. [PubMed: 10861916]
117. Madhusoodanan S, Brecher M, Brenner R, Kasckow J, Kunik M, Megron AE, et al. Risperidone in the treatment of elderly patients with psychotic disorders. *Am J Geriatr Psychiatry.* 1999; 7(2): 132–138. Erratum in: *Am J Geriatr Psychiatry* 1999; 7(3):268. [PubMed: 10322240]
118. Madhusoodanan S, Brenner R, Alcantra A. Clinical experience with quetiapine in elderly patients with psychotic disorders. *J Geriatr Psychiatry Neurol.* 2000; 13(1):28–32. [PubMed: 10753004]
119. Tariot PN, Salzman C, Yeung PP, Pultz J, Rak IW. Long-term use of quetiapine in elderly patients with psychotic disorders. *Clin Ther.* 2000; 22(9):1068–1084. [PubMed: 11048905]
120. McManus DQ, Arvanitis LA, Kowalczyk BB. Quetiapine, a novel antipsychotic: experience in elderly patients with psychotic disorders. Seroquel Trial 48 Study Group. *J Clin Psychiatry.* 1999; 60(5):292–298. [PubMed: 10362435]
121. Hwang JP, Yang CH, Lee TW, Tsai SJ. The efficacy and safety of olanzapine for the treatment of geriatric psychosis. *J Clin Psychopharmacol.* 2003; 23(2):113–118. [PubMed: 12640211]
122. Barak Y, Shamir E, Zemishlani H, Mirecki I, Toren P, Weizman R. Olanzapine vs. haloperidol in the treatment of elderly chronic schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry.* 2002; 26(6):1199–1202. [PubMed: 12452546]
123. Madhusoodanan S, Brenner R, Suresh P, Concepcion NM, Florita CD, Menon G, et al. Efficacy and tolerability of olanzapine in elderly patients with psychotic disorders: a prospective study. *Ann Clin Psychiatry.* 2000; 12(1):11–18. [PubMed: 10798821]
124. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 2004; 27(2):596–601. [PubMed: 14747245]
125. Ciranni MA, Kearney TE, Olson KR. Comparing acute toxicity of first- and second-generation antipsychotic drugs: a 10-year, retrospective cohort study. *J Clin Psychiatry.* 2009; 70(1):122–129. [PubMed: 19192473]
126. Khaldi S, Kornreich C, Choubani Z, Gourevitch R. Neuroleptic malignant syndrome and atypical antipsychotics: a brief review. *Encephale.* 2008; 34(6):618–624. French. [PubMed: 19081460]
127. DeBattista C, Hawkins J. Utility of atypical antipsychotics in the treatment of resistant unipolar depression. *CNS Drugs.* 2009; 23(5):369–377. [PubMed: 19453199]
128. Altamura AC, Bassetti R, Bignotti S, Pioli R, Mundo E. Clinical variables related to suicide attempts in schizophrenic patients: a retrospective study. *Schizophr Res.* 2003; 60(1):47–55. [PubMed: 12505137]
129. Spivak B, Mester R, Wittenberg N, Maman Z, Weizman A. Reduction of aggressiveness and impulsiveness during clozapine treatment in chronic neuroleptic-resistant schizophrenic patients. *Clin Neuropharmacol.* 1997; 20(5):442–446. [PubMed: 9331521]
130. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry.* 1995; 152(2):183–190. [PubMed: 7840350]
131. Walker AM, Lanza LL, Arellano F, Rothman KJ. Mortality in current and former users of clozapine. *Epidemiology.* 1997; 8(6):671–677. [PubMed: 9345668]

132. Meltzer HY, Alphas L, Green AI, Altamura AC, Anand R, Bertoldi A, et al. International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry*. 2003; 60(1):82–91. [PubMed: 12511175]
133. Reid WH, Mason M, Hogan T. Suicide prevention effects associated with clozapine therapy in schizophrenia and schizoaffective disorder. *Psychiatr Serv*. 1998; 49(8):1029–1033. [PubMed: 9712207]
134. <http://www.docguide.com/dg.nsf/c199ac7acbf21b1b852565f30052a091/f183c9483736e9fc85256c680056ee80?OpenDocument>
135. Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTC interval, torsade de pointe, and sudden death. *Am J Psychiatry*. 2001; 158(11):1774–1782. [PubMed: 11691681]
136. Kramer MS, Vogel WH, DiJohnson C, Dewey DA, Sheves P, Cavicchia S, et al. Antidepressants in 'depressed' schizophrenic inpatients. A controlled trial. *Arch Gen Psychiatry*. 1989; 46(10): 922–928. [PubMed: 2679483]
137. Silver H, Jahjah N, Kushnir M. Psychotic symptoms in schizophrenics during chronic fluvoxamine treatment. A report of two cases. *Schizophr Res*. 1995; 16(1):77–79. [PubMed: 7547649]
138. Zisook S, Kasckow JW, Golshan S, Fellows I, Solorzano E, Lehman D, et al. Citalopram augmentation for subsyndromal symptoms of depression in middle-aged and older outpatients with schizophrenia and schizoaffective disorder: a randomized controlled trial. *J Clin Psychiatry*. 2009; 70(4):562–571. [PubMed: 19192468]
139. Centoorino F, Baldessarini RJ, Frankenburg FR, Kando J, Volpicelli SA, Flood JG. Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *Am J Psychiatry*. 1996; 153(6):820–822. [PubMed: 8633698]
140. Ekselius L, von Knorring L, Eberhard G. A double-blind multicenter trial comparing sertraline and citalopram in patients with major depression treated in general practice. *Int Clin Psychopharmacol*. 1997; 12(6):323–331. [PubMed: 9547134]
141. Thomson Healthcare Inc. 2000 Physicians' desk reference. Montvale (NJ): Thomson Healthcare Inc; 1999.
142. Solai LK, Mulsant BH, Pollack BG. Selective serotonin reuptake inhibitors for late life depression. *Drugs Aging*. 2001; 18(5):355–368. [PubMed: 11392444]
143. Citrome L. Adjunctive lithium and anticonvulsants for the treatment of schizophrenia: what is the evidence? *Expert Rev Neurother*. 2009; 9(1):55–71. [PubMed: 19102669]
144. Lerner Y, Mintzer Y, Schestatzky M. Lithium combined with haloperidol in schizophrenic patients. *Br J Psychiatry*. 1988; 153:359–362. [PubMed: 3150693]
145. Collins PJ, Larkin EP, Schubsachs AP. Lithium carbonate in chronic schizophrenia -- a brief trial of lithium carbonate added to neuroleptics for treatment of resistant schizophrenic patients. *Acta Psychiatr Scand*. 1991; 84(2):150–154. [PubMed: 1683094]
146. Leucht S, Kissling W, McGrath J. Lithium for schizophrenia. *Cochrane Database Syst Rev*. 2007; (3):CD003834. [PubMed: 17636738]
147. Miller AL, Hall CS, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2003 update. *J Clin Psychiatry*. 2004; 65(4):500–508. [PubMed: 15119912]
148. Chen H, Kennedy WK, Dorfman JH, Fincham JE, Reeves J, Martin BC. The effect of adjunctive mood stabilizers on antipsychotic utilization pattern and health resource utilization for Medicaid enrollees with schizophrenia. *Curr Med Res Opin*. 2007; 23(6):1351–1365. [PubMed: 17559734]
149. Quinlaven R, Hough R, Crowell A, Beach C, Hofstetter R, Kenworthy K. Service utilization and cost of care for severely mentally ill clients in an intensive case management program. *Psychiatr Serv*. 1995; 46(4):365–371. [PubMed: 7788458]
150. Franklin JL, Solovitz B, Mason M, Clemons JR, Miller GE. An evaluation of case management. *Am J Public Health*. 1987; 77(6):674–678. [PubMed: 3578614]

151. Nierenberg AA, Katz J, Fava M. A critical overview of the pharmacologic management of treatment-resistant depression. *Psychiatr Clin North Am.* 2007; 30(1):13–29. [PubMed: 17362800]
152. Stern MJ, Pillsbury JA, Sonnenberg SM. Postpsychotic depression in schizophrenics. *Compr Psychiatry.* 1972; 13(6):591–598. [PubMed: 4637572]
153. Jin H, Zisook S, Palmer BW, Patterson TL, Heaton RK, Jeste DV. Association of depressive symptoms with worse functioning in schizophrenia: a study of older outpatients. *J Clin Psychiatry.* 2001; 62(10):797–803. [PubMed: 11816869]
154. Birchwood M, Mason R, MacMillan F, Healy J. Depression, demoralization and control over psychotic illness: a comparison of depressed and non-depressed patients with a chronic psychosis. *Psychol Med.* 1993; 23(2):387–395. [PubMed: 8332655]
155. Graham C, Arthur A, Howard R. The social functioning of older adults with schizophrenia. *Aging Ment Health.* 2002; 6(2):149–152. [PubMed: 12028883]
156. Patterson TL, Leeuwenkamp OR. Adjunctive psychosocial therapies for the treatment of schizophrenia. *Schizophr Res.* 2007; 100(1–3):108–119. [PubMed: 18226500]
157. Bechdolf A, Kohn D, Knost B, Pukrop R, Klosterkotter J. A randomized comparison of group cognitive-behavioral therapy and group psychoeducation in acute patients with schizophrenia: outcome at 24 months. *Acta Psychiatr Scand.* 2005; 112(3):173–179. [PubMed: 16095471]
158. Bechdolf A, Veith V, Schwarzer D, Schormann M, Stamm E, Janssen B, et al. Cognitive-behavioral therapy in the pre-psychotic phase: an exploratory study. *Psychiatry Res.* 2005; 136(2–3):251–255. [PubMed: 16122813]
159. Drury V, Birchwood M, Cochrane R, Macmillan F. Cognitive therapy and recovery from acute psychosis: a controlled trial. I. Impact on psychotic symptoms. *Br J Psychiatry.* 1996; 169(5):593–601. [PubMed: 8932888]
160. Gumley A, Karatzias A, Power K, Reilly J, McNay L, O'Grady M. Early intervention for relapse in schizophrenia: impact of cognitive behavioral therapy on negative beliefs about psychosis and self-esteem. *Br J Clin Psychol.* 2006; 45(Pt 2):247–260. [PubMed: 16719982]
161. Kemp R, Hayward P, Applewhaite G, Everitt B, David A. Compliance therapy in psychotic patients: randomized controlled trial. *BMJ.* 1996; 312(7027):345–349. [PubMed: 8611831]
162. Kemp R, Kirov G, Everitt B, Hayward P, David A. Randomised controlled trial of compliance therapy. 18-month follow-up. *Br J Psychiatry.* 1998; 172:413–419.
163. Kuipers E, Garety P, Fowler D, Dunn G, Bebbington P, Freeman D, et al. London-East Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis. I: effects of the treatment phase. *Br J Psychiatry.* 1997; 171:319–327. [PubMed: 9373419]
164. Sensky T, Turkington D, Kingdon D, Scott JL, Scott J, Siddle R, et al. A randomized controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. *Arch Gen Psychiatry.* 2000; 57(2):165–172. [PubMed: 10665619]
165. Startup M, Jackson MC, Evans KE, Bendix S. North Wales randomized controlled trial of cognitive behavior therapy for acute schizophrenia spectrum disorders: two-year follow-up and economic evaluation. *Psychol Med.* 2005; 35(9):1307–1316. [PubMed: 16168153]
166. Tarrier N, Wittkowski A, Kinney C, McCarthy E, Morris J, Humphreys L. Durability of the effects of cognitive-behavioural therapy in the treatment of chronic schizophrenia: 12-month follow-up. *Br J Psychiatry.* 1999; 174:500–504. [PubMed: 10616627]
167. Tarrier N, Lewis S, Haddock G, Bentall R, Drake R, Kinderman P, et al. Cognitive-behavioural therapy in first-episode and early schizophrenia. 18-month follow-up of a randomised controlled trial. *Br J Psychiatry.* 2004; 184:231–239. [PubMed: 14990521]
168. Temple S, Ho BC. Cognitive therapy for persistent psychosis in schizophrenia: a case-controlled clinical trial. *Schizophr Res.* 2005; 74(2–3):195–199. [PubMed: 15721999]
169. Pfammatter M, Junghan UM, Brenner HD. Efficacy of psychological therapy in schizophrenia: conclusions from meta-analyses. *Schizophr Bull.* 2006; 32(1):S64–S80. [PubMed: 16905634]
170. Zimmermann G, Favrod J, Trieu VH, Pomini V. The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: a meta-analysis. *Schizophr Res.* 2005; 77(1):1–9. [PubMed: 16005380]

171. Granholm E, McQuaid JR, McClure FS, Auslander LA, Perivoliotis D, Pedrelli P, et al. A randomized, controlled trial of cognitive behavioral social skills training for middle-aged and older outpatients with chronic schizophrenia. *Am J Psychiatry*. 2005; 162(3):520–529. [PubMed: 15741469]
172. Stant AD, TenVergert EM, Groen H, Jenner JA, Nienhuis FJ, van de Willige G, et al. Cost-effectiveness of the HIT programme in patients with schizophrenia and persistent auditory hallucinations. *Acta Psychiatr Scand*. 2003; 107(5):361–368. [PubMed: 12752032]
173. Patterson TL, McKibbin C, Taylor M, Goldman S, Davila-Fraga W, Bucardo J, et al. Functional adaptation skills training (FAST): a pilot psychosocial intervention study in middle-aged and older patients with chronic psychotic disorders. *Am J Geriatr Psychiatry*. 2003; 11(1):17–23. [PubMed: 12527536]
174. Patterson TL, Bucardo J, McKibbin CL, Mausbach BT, Moore D, Barrio C, et al. Development and pilot testing of a new psychosocial intervention for Latinos with chronic psychosis. *Schizophr Bull*. 2005; 31(4):922–930. [PubMed: 16037481]
175. Patterson TL, Mausbach BT, McKibbin C, Goldman S, Bucardo J, Jeste DV. Functional adaptation skills training (FAST): a randomized trial of a psychosocial intervention for middle-aged and older patients with chronic psychotic disorders. *Schizophr Res*. 2006; 86(1–3):291–299. [PubMed: 16814526]
176. Roder V, Mueller DR, Mueser KT, Brenner HD. Integrated psychological therapy (IPT) for schizophrenia: is it effective? *Schizophr Bull*. 2006; 32 (Suppl 1):S81–93. [PubMed: 16916888]
177. Velligan DJ, Mueller J, Wang M, Dicocco M, Diamond PM, Maples NJ, et al. Use of environmental supports among patients with schizophrenia. *Psychiatr Serv*. 2006; 57(2):219–224. [PubMed: 16452699]