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Schizophrenia Spectrum and Other Psychotic Disorders

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Delusions, hallucinations, and other psychotic symptoms can accompany a number of conditions in late life. These symptoms may be more common than previously thought; Swedish investigators found that, in a sample of 85-year-old people, the prevalence of psychotic symptoms was 10.1%, with 6.9% experiencing hallucinations, 5.5% having delusions, and 6.9% experiencing paranoid ideation (Ostling and Skoog 2002).

Conditions, such as delirium and substance-induced psychosis, which cause acute psychotic symptoms, that tend to resolve when the underlying condition is treated are discussed elsewhere in this volume. In this chapter, we review the epidemiology, presentation, and treatment of chronic late-life psychotic disorders that are not secondary to a mood disorder or a general medical condition other than dementia. Thus, we discuss early-onset schizophrenia, late-onset schizophrenia, very late-onset schizophrenia-like psychosis (with onset after age 60), delusional disorder, psychosis of Alzheimer's disease, and psychosis associated with other dementias.

Schizophrenia

Early-Onset Schizophrenia

Typically, individuals with schizophrenia develop the disease in the second or third decade of life (American Psychiatric Association 2000). Although mortality rates in general, and suicide and homicide rates in particular, are higher among individuals with schizophrenia than in the general population (Hannerz et al. 2001; Hiroch et al. 2001; Joukamaam et al. 2001), many people with early-onset schizophrenia are now living into older adulthood. Thus, most of the older adults with schizophrenia have had an early onset followed by a chronic course of illness spanning several decades. The prevalence

of schizophrenia among adults between ages 45 and 64 is approximately 0.6%, and prevalence estimates for schizophrenia among elderly individuals range from 0.1% to 0.5% (Castle and Murray 1993; Copeland et al. 1998; Keith et al. 1991).

Longitudinal follow-up of patients with schizophrenia indicates considerable heterogeneity of outcomes. A minority of patients experience remission of both positive and negative symptoms (Ciompi 1980; Harding et al. 1987; Huber 1997). Auslander and Jeste (2004) reported that nearly 10% of community-dwelling older patients with schizophrenia met strict research criteria for sustained remission. A small proportion of patients experience deterioration of symptoms. The course in a majority of patients is largely unchanged over time (Belitsky and McGlashan 1993; Cohen 1990; Harvey et al. 1999), although there is generally an improvement in positive symptoms (Jeste et al. 2003). A possibility of survivor bias (- i.e., that the sickest patients die young, and the hardier ones survive into older age) should be kept in mind in studying older patients with early-onset illness.

Factors associated with poor prognosis for early-onset schizophrenia include chronicity, insidious onset, premorbid psychosocial or functional deficits, and prominent negative symptoms (Ram et al. 1992). In a sample of chronically institutionalized patients with schizophrenia, older age was associated with lower levels of positive symptoms and higher levels of negative symptoms (Davidson et al. 1995). However, Harding (2002) noted that the strength of the association between predictors of outcome and actual outcome in patients with schizophrenia weakens over time.

Cognition in Older Patients With Schizophrenia

The pattern of cognitive deficits in schizophrenia differs significantly from that in Alzheimer's disease (AD); patients with AD have less efficient learning and more rapid forgetting than patients with schizophrenia (Heaton et al. 2001). Among community-dwelling older outpatients with schizophrenia, cognitive functioning seems to remain relatively stable, other than the changes expected from normal aging (Heaton et al. 2001). A small proportion of chronically institutionalized older patients with schizophrenia have cognitive decline greater than that expected for their age (Putnam and Harvey 2000).

Depression in Older Patients With Schizophrenia

Depression is a common source of comorbidity in older patients with schizophrenia. Studies have shown depressive symptoms to be distinct from negative symptoms (Baynes et al. 2000). Depression is also a major predictor of suicidality in this population (Montross et al. 2006). Subsyndromal depression has been found to be associated with greater morbidity (Diwan et al. 2007; Zisook et al. 2007). Detection and management of subsyndromal depression may have an important role to play in management of this population.

Functional Capacity

The level of functional impairment varies considerably among older adults with schizophrenia. In a study of a group of middle-aged and older schizophrenia outpatients, Palmer et al. (2002) found that 30% had been employed at least part-time since the onset of psychosis, 43% were current drivers, and 73% were living independently. In general, worse neuropsychological test performance, lower educational level, and negative symptoms but not positive symptoms are associated with poorer functional

capacity in older outpatients with schizophrenia (Evans et al. 2003).

Quality of Life

Self-appraisal is considered to be essential in studies of quality of life for patients with schizophrenia. Several studies have found poorer self-assessed quality of life to be associated with depression, positive and negative symptoms, cognitive deficits, financial strain, poor social support, and poor social skills (Vahia et al. 2007). These findings suggest that a multimodal approach to management of these patients is necessary to improve quality of life.

Late-Onset Schizophrenia

Historically, schizophrenia has been considered a disease of younger adulthood. Kraepelin (1971) termed schizophrenia *dementia praecox* to distinguish it from organic disorders arising in late life and to indicate a poor prognosis with a course of progressive deterioration. However, in later years, Kraepelin himself observed that some cases arose for the first time in older age and that progressive decline was not a universal feature of the disease. Bleuler (1943) and Roth (1955) developed this concept further, with studies describing the late-onset phenotype as a distinct entity from the early-onset form. A literature review found that approximately 23% of patients with schizophrenia had an onset after age 40, with 3% being older than age 60 (Harris and Jeste 1988). An investigation involving first-contact patients found that 29% of patients had an onset after age 44, with 12% reporting onset after age 64 (Howard et al. 1993). The consensus statement by the International Late-Onset Schizophrenia Group suggested that schizophrenia with an onset after age 40 should be called “late-onset schizophrenia” and should be considered a subtype of schizophrenia rather than a related disorder (Howard et al. 2000). Although DSM-III-R labeled schizophrenia with onset after age 45 as a late-onset type (American Psychiatric Association 1987). Later editions of the DSM have not included age-related specifiers or criteria (American Psychiatric Association 1994, American Psychiatric Association 2000, American Psychiatric Associaion 2013). The DSM-5 included the following text on schizophrenia with later onset “late-onset cases can meet the diagnostic criteria for schizophrenia, but it is not yet clear whether this is the same condition as schizophrenia diagnosed prior to mid-life.”

Risk factors and clinical presentation associated with late-onset schizophrenia are similar to those associated with early-onset schizophrenia (Brodaty et al. 1999; Jeste et al. 1995). Similar proportions of individuals with early-onset or late-onset schizophrenia reported having a family history of schizophrenia (10%–15%). Levels of childhood maladjustment, measured retrospectively, were similar in early- and late-onset schizophrenia patients and higher in both groups than in healthy subjects (Jeste et al. 1997b). Patients with early and late-onset schizophrenia have increased rates of minor physical anomalies relative to healthy subjects (Lohr et al. 1997).

Women predominate among individuals with onset of schizophrenia in middle to late life (Hafner et al. 1998; Jeste et al. 1997b). It has been speculated that -estrogen may serve as an endogenous antipsychotic, masking schizophrenic symptoms in vulnerable women until after menopause (Seeman 1996). However, investigations on efficacy of hormone replacement therapy as an adjunct treatment for postmenopausal women with psychosis (Kulkarni et al. 1996, 2001; Lindamer et al. 2001) have not had promising results.

Neuroimaging studies show that patients with late-onset schizophrenia, compared with patients with early-onset schizophrenia, have more nonspecific structural abnormalities, such as enlarged ventricles and increased white matter hyperintensities (Sachdev et al. 1999), and a larger volume of thalamus on magnetic resonance imaging (Corey-Bloom et al. 1995). A single small study (N=17) employing diffusion tensor imaging (DTI) recently found evidence of abnormal white matter integrity in the left parietal lobe and right posterior cingulum in LOS patients compared with age matched controls, although there were no associations between these abnormalities and symptom levels (Chen et al., 2013). Other imaging studies have ruled out strokes, tumors, or other abnormalities as potential causes of schizophrenia in late life (Rivkin et al. 2000). Finally, long-term neuro-psychological follow-up of a group of patients with late-onset schizophrenia revealed no evidence of -cognitive decline, suggesting a neurodevelopmental rather than a neurodegenerative process (Palmer et al. 2003).

Most studies have found that patients with late-onset schizophrenia have lower levels of positive symptoms and a lower daily antipsychotic dose requirement compared with patients with early onset disease (Vahia et al. 2010). Patients with late-onset schizophrenia tend to have more organized delusions, auditory hallucinations or hallucinations with a running commentary, and persecutory delusions with and without hallucinations (Howard et al. 2000). Data from initial smaller studies suggested a higher prevalence of the paranoid subtype of schizophrenia and lower levels of negative symptoms on average among patients with late-onset schizophrenia (approximately 75%) than among patients with early-onset schizophrenia (approximately 50%) (Jeste et al. 1997b). However, a more recent larger study from our Center, including data collected over 20 years comparing 744 early-onset schizophrenia and 110 late-onset schizophrenia patients, found similar relative proportions of patients with the paranoid subtype and no differences in severity of negative symptoms in the late-onset and early-onset groups (Vahia et al. 2010).

On neuropsychological testing, after correction for age, education, and gender, patients with late-onset schizophrenia tend to have less impairment in learning, abstraction, and flexibility in thinking than patients with early-onset schizophrenia (Jeste et al. 1997b). Compared with patients with early-onset schizophrenia, a greater proportion of patients with late-onset schizophrenia have successful occupational and marital histories and generally higher premorbid functioning.

Sensory deficits, particularly hearing loss, are associated with psychotic symptoms in late life and have been proposed as a risk factor for late-onset schizophrenia (Howard et al. 1994; Raghuram et al. 1980). However, other data suggest that both early- and late-onset schizophrenia patients may be less likely than healthy older adults to receive appropriate correction for vision and hearing impairments (Prager and Jeste 1993). Thus, uncorrected sensory deficits may reflect generally poorer health care utilization by older psychotic patients and may not be a potential cause of psychosis in the elderly population.

In summary, early- and late-onset schizophrenia share similarities in many key clinical characteristics. However there are important differences including the greater proportion of women, lower average severity of positive symptoms, and lower average antipsychotic dose requirement in late-onset schizophrenia. More analyses of large data sets and studies designed to elucidate the pathophysiological pathways underlying early- and late-onset schizophrenia are needed to better understand how these two groups differ from each other (Jeste et al. 2005).

Very-Late-Onset Schizophrenia-Like Psychosis

In its consensus statement, the International Late--Onset Schizophrenia Group proposed the diagnostic term *very-late-onset schizophrenia-like psychosis* (VLOSLP) for patients whose psychosis begins after age 60 (Howard et al. 2000). Table 17–1 compares risk factors for and clinical features of early-onset schizophrenia, late-onset schizophrenia, and VLOSLP. Very late--onset schizophrenia-like psychosis may be difficult to diagnose clinically because its clinical picture can be confused with other conditions (e.g., delirium, psychosis due to underlying medical illness). Nevertheless, new-onset primary psychotic symptoms have been described in older adults. Indeed, Cervantes et al. (2006) described a clinical case of primary-onset psychosis in a 100-year-old patient.

T Comparison of early-onset schizophrenia, late-onset schizophrenia, and very late-onset schizophrenia-like psychosis

Feature	Early-onset schizophrenia	Late-onset schizophrenia	Very-late-onset schizophrenia-like psychosis
Age at onset	Before 40	Middle age (~40–60)	Late life (60+)
Female preponderance	–	+	++
Negative symptoms	++	+	–
Minor physical anomalies	+	+	–
Neuropsychological impairment			
Learning	++	+	?++
Retention	–	–	?++
Progressive cognitive deterioration	–	–	++
Brain structure abnormalities (e.g., strokes, tumors)	–	–	++
Family history of schizophrenia	+	+	–
Early childhood maladjustment	+	+	–
Daily neuroleptic dose	++	+	+
Risk of tardive dyskinesia	+	+	++

+ = mildly present; ++ = strongly present; ?++ = probably strongly present, but limited data exist; – = absent.

Source. Adapted from Palmer et al. 2001.

Factors distinguishing patients with VLOSLP from “true” schizophrenia patients include a smaller genetic load, less evidence of early childhood maladjustment, a relative lack of thought disorder and negative symptoms (including blunted affect), a greater risk of tardive dyskinesia, and evidence of a neurodegenerative rather than a neurodevelopmental process (Andreasen 1999; Howard et al. 1997). Although the term was initially considered a catchall phrase for several different entities, recent research suggests that VLOSLP may be a distinct entity. It has been noted to be more common in immigrant populations, suggesting that psychosocial factors might play a role (Mitter et al. 2005). Imaging studies have shown underlying focal white matter abnormalities in

cerebral tracts (Jones et al. 2005). One study has suggested that the cognitive biases that are common in younger persons with delusions are absent in patients with VLOSLP (Moore et al. 2006). A study by Mazeh et al. (2005) suggested that patients with VLOSLP may have somewhat more stable cognitive and everyday functioning than do chronically institutionalized elderly patients with schizophrenia. In summary, clinical vigilance must be exercised when treating apparent primary-onset psychotic symptoms in older patients, and "organic" causes should be meticulously ruled out.

Delusional Disorder

At least 6% of older adults have paranoid symptoms such as persecutory delusions, but most of these individuals have dementia (Christenson and Blazer 1984; Forsell and Henderson 1998; Henderson et al. 1998). The essential feature of a delusional disorder is a nonbizarre delusion (e.g., a persecutory, somatic, erotomanic, grandiose, or jealous delusion) without prominent auditory or visual hallucinations. Symptoms must be present for at least 1 month. When delusional disorder arises in late life, basic personality features, intellectual performance, and occupational function are preserved, but social functioning is compromised. To diagnose delusional disorder, the clinician must rule out delirium, dementia, psychotic disorders due to general medical conditions or substance use, schizophrenia, and mood disorders with psychotic features. The course of persecutory delusional disorder is typically chronic, but patients with other types of delusions may have partial remissions and relapses.

According to DSM-5, the lifetime prevalence of delusional disorder is estimated to be 0.2% and the most common subtype is persecutory. There are no significant gender differences in its prevalence, although the jealous subtype may be more frequent in men than in women (American Psychaitric Association, 2013). The disorder typically first appears in middle to late adulthood, with an average age at onset of 40–49 years for men and 60–69 years for women.

Risk factors for delusional disorder include a family history of schizophrenia or avoidant, paranoid, or schizoid personality disorder (Kendler and Davis 1981). Evidence supporting hearing loss as a risk factor for paranoia is mixed (Cooper and Curry 1976; Moore 1981). In one neuroimaging study, brain atrophy and white matter hyperintensities did not distinguish older psychotic patients with somatic delusions from those without such delusions (Rockwell et al. 1994). According to Maher (2005), a subset of the population that is prone to primary perceptual abnormalities may be prone to developing delusions as a result. Maher (2005) also pointed out that "normal" persons may demonstrate "delusional" behavior as a result of sensory disturbances. Evans et al. (1996) compared middle-aged and older patients with schizophrenia or delusional disorder and found no differences in neuro-psychological impairment but more severe psychopathology associated with delusional disorder. Finally, immigration and low socioeconomic status may be risk factors for delusional disorder (American Psychiatric Association 2000).

Psychosis of Alzheimer's Disease

Based on a review of 55 studies, Ropacki and Jeste (2005) estimated the median prevalence of psychosis in Alzheimer's disease (AD) to be about 41% (range 12.2%–74.1%). Psychosis is associated with more rapid cognitive decline. Some studies found a

significant association between psychosis and age, age at onset of AD, and illness duration; however, gender, education, and family history of dementia or psychiatric illness showed weak or inconsistent relationships with psychosis. In a large sample of patients with probable AD, Paulsen et al. (2000) found a cumulative incidence of psychotic symptoms of 20% at 1 year, 36% at 2 years, 50% at 3 years, and 51% at 4 years. Delusions, especially of a persecutory nature, tend to be the most common symptom (median prevalence 36%); visual hallucinations (median prevalence 18.7%) and auditory hallucinations (median prevalence 9.2%) are less common (Ropacki and Jeste 2005). These symptoms often need to be inferred from the patient's behavior, because the patient may be unable to verbalize thoughts or perceptions due to cognitive impairment, particularly in the later stages of the disease. In one large naturalistic study of the course of psychotic symptoms in dementia, Devanand et al. (1997) found that hallucinations and paranoid delusions were more persistent than depressive symptoms over time but less prevalent and less persistent than behavioral disturbances, particularly agitation.

In Table 17–2, characteristics associated with psychosis of AD are compared with characteristics of schizophrenia in elderly patients (Jeste and Finkel 2000). Two common psychotic symptoms in AD are misidentification of caregivers and delusions of theft (Jeste et al. 2007). Schneiderian first-rank symptoms, such as hearing multiple voices talking to one another or hearing a running commentary on the patient's actions, are rare (Burns et al. 1990a, 1990b). Disorganization of speech and behavior and negative symptoms are also uncommon (Jeste et al. 2007). Active suicidal ideation and past history of psychosis are rare. Because psychotic symptoms in patients with dementia tend to remit in the late stages of the disease, very long-term maintenance therapy on antipsychotics is typically unnecessary.

T Comparison of psychosis of Alzheimer's disease with schizophrenia in older patients

Feature	Psychosis of AD	Schizophrenia
Prevalence	35%–50% of AD patients	Less than 1% of general population
Bizarre or complex delusions	Rare	Frequent
Misidentification of caregivers	Frequent	Rare
Common form of hallucinations	Visual	Auditory
Schneiderian first-rank symptoms	Rare	Frequent
Active suicidal ideation	Rare	Frequent
Past history of psychosis	Rare	Very common
Eventual remission of psychosis	Frequent	Uncommon
Need for years of maintenance on antipsychotic medication	Uncommon	Very common
Usual optimal daily doses of commonly used atypical antipsychotics:		
Risperidone	0.75–1.5 mg	1.5–2.5 mg
Olanzapine	2.5–7.5 mg	7.5–12.5 mg

Recommended adjunctive psychosocial treatment	Sensory enhancement, structured activities, social contact, behavior therapy[a]	Cognitive-behavioral therapy, social skills training[b]

Note. AD = Alzheimer's disease.
[a]Cohen-Mansfield 2001.
[b]Granholm et al. 2002; McQuaid et al. 2000.
Source. Adapted from Jeste DV, Finkel SI: "Psychosis of Alzheimer's Disease and Related Dementias: Diagnostic Criteria for a Distinct Syndrome. *American Journal of Geriatric Psychiatry* 8:29–34, 2000. Used with permission.

AD patients with psychosis and those without psychosis differ in several important ways. Neuropsychologically, AD patients with psychosis have shown greater impairment in executive functioning, more rapid cognitive decline (Jeste et al. 1992; Stern et al. 1994), and greater prevalence of extrapyramidal symptoms (Stern et al. 1994) than AD patients without psychosis. Delusions in dementia have been associated with dysfunction in paralimbic areas of the frontotemporal cortex (Sultzer 1996). Neuropathologically, dementia patients with psychosis have shown increased neurodegenerative changes in the cortex, increased norepinephrine in subcortical regions, and reduced serotonin levels in both cortical and subcortical areas (Zubenko et al. 1991). In one study, AD patients with psychosis had much higher levels of tau protein in the entorhinal and temporal cortices than did nonpsychotic AD patients (Mukaetova-Ladinska et al. 1995). Furthermore, Wilkosz et al. (2006) have suggested that the misidentification subtype and the paranoid subtype of psychosis of AD may be distinct.

Jeste and Finkel (2000) recommended specific diagnostic criteria for psychosis of AD to facilitate epidemiological, clinical, and therapeutic research. These criteria include the presence of visual or auditory hallucinations or delusions, a primary diagnosis of AD, a duration of at least 1 month, and a chronology indicating that symptoms of AD preceded those of psychosis. Alternative causes of psychosis must be excluded, and sufficient functional impairment should be present for this diagnosis to be made. There is evidence for good interrater and test-retest reliability of these criteria (Jeste et al. 2007).

Psychosis in Other Dementias

Psychosis is also common in other dementias. Visual hallucinations and secondary delusions are common in Lewy body disease, and vascular dementia may also be accompanied by delusions or hallucinations (Schneider 1999). Naimark et al. (1996) found psychotic symptoms in approximately one-third of a sample of patients with Parkinson's disease, with hallucinations being more common than delusions. Psychosis in frontotemporal dementias is poorly characterized but may be as common as psychosis in AD (Srikanth et al. 2005).

Treatment

The modern era of pharmacological treatment for schizophrenia and related disorders began with the introduction of chlorpromazine in the early 1950s. Although this and other conventional agents substantially improved the positive symptoms of schizophrenia (e.g., hallucinations and delusions), a number of treatment liabilities have been recognized over the years, such as movement disorders, sedation, orthostatic hypotension, and increased prolactin concentrations. In addition, older adults have a

significantly higher risk for developing tardive dyskinesia than do younger adults, making use of conventional antipsychotics in this population highly problematic.

Therefore, when atypical antipsychotics—which are associated with significantly lower incidence of tardive dyskinesia—were introduced, they were hailed as the drugs of choice for older adults with psychotic disorders. However, these agents have since been linked to an increased risk of metabolic dysfunction, including diabetes, dyslipidemia, and obesity, thereby leading to a worsened cardiovascular risk profile. In elderly patients with dementia, atypical antipsychotics have been associated with an increased risk of cerebrovascular adverse events and mortality compared to placebo; therefore, leading pharmaceutical regulatory agencies have issued warnings about the use of these agents in patients with dementia (Meeks et. al. 2008). At the same time, because of the paucity of evidence-based pharmacological treatment alternatives to antipsychotics for patients with dementia, clinicians are restricted to off-label treatments, which must be used with caution and close monitoring. Psychosocial treatments for older adults with psychosis have been developed and tested in randomized, controlled trials and show promise as primary or adjunctive treatments.

Treatment of Schizophrenia, Very Late-Onset Schizophrnia-Like Psychosis, and Delusional Disorder

Pharmacological Treatments

Pharmacotherapy for older adults with chronic psychotic disorders can be challenging. Although few randomized, placebo-controlled, double-blind clinical trials have been conducted in this population, some information has become available. Maintenance pharmacotherapy is usually required for older patients with schizophrenia due to risk of relapse. Because older patients are at higher risk of adverse antipsychotic effects, due to age-related pharmacokinetic and pharmacodynamic factors (Hammerlein et al. 1998), coexisting medical illnesses, and concomitant medications, the recommended starting and maintenance doses of anti-psychotics in older adults are much lower than the usual doses in younger adults (American Psychiatric Association 1997). Patients with late-onset schizophrenia respond well to low-dose antipsychotic medication, requiring about 50% of the dose typically taken by older patients with early-onset schizophrenia and 25%–33% of the dose used in younger patients with schizophrenia.

Use of conventional or typical antipsychotics in older adults is problematic because of the higher incidence of tardive dyskinesia in older patients. Aging appears to be the most important risk factor for the development of tardive dyskinesia (American Psychiatric Association 2000; Yassa and Jeste 1992). The cumulative 1-year incidence of tardive dyskinesia is 29% among older patients (mean age 65 years) despite low dosing (Jeste et al. 1999b), whereas the annual cumulative incidence of tardive dyskinesia in young adults is 4%–5% (Kane et al. 1993). The risk of severe tardive dyskinesia is also higher in older patients (Caligiuri et al. 1997). Other side effects of conventional neuroleptics include sedation, anticholinergic effects, cardiovascular effects including orthostatic hypotension, parkinsonian reactions, and neuroleptic malignant syndrome. Despite these side effects, occasionally a conventional antipsychotic may be the most reasonable treatment option for an individual patient, and these agents can be used at flexible, individualized low doses to minimize side effects (Jeste et al. 1999b).

Few efficacy comparisons have been done of conventional antipsychotics versus

atypical antipsychotics in patients with schizophrenia over age 65. In a study of 42 elderly inpatients, Howanitz et al. (1999) found that clozapine (≤300 mg/day) and chlorpromazine (≤600 mg/day) had similar efficacy. Kennedy et al. (2003) compared olanzapine (5–20 mg/day) and haloperidol (5–20 mg/day) in a 6-week trial of 117 patients ages 60 years and older who had schizophrenia and related disorders. Olanzapine (mean modal dose 11.9 mg/day) produced significantly greater symptomatic improvement and was associated wtih fewer motor side effects than haloperidol (mean modal dose 9.4 mg/day) (Kennedy et al. 2003). The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Lieberman et al. 2005), which included adults ages 18–65, found no significant differences in effectiveness between the conventional antipsychotic perphenazine and the atypical antipsychotics risperidone, olanzapine, quetiapine, or ziprasidone, but it is unknown how these findings would translate to patients older than age 65.

Generally, atypical antipsychotics carry a much lower risk of tardive dyskinesia than conventional neuroleptics, even when taken by very high-risk patients such as middle-aged and older adults with borderline tardive dyskinesia (Dolder and Jeste 2003; Jeste et al. 1999a). Clozapine has shown efficacy in reducing tardive dyskinesia in patients with existing tardive dyskinesia (Kane et al. 1993; Lieberman et al. 1991; Simpson et al. 1978; Small et al. 1987); however, other side effects limit its use, particularly in elderly patients. A beneficial effect of other atypical agents, specifically risperidone and olanzapine, on preexisting tardive dyskinesia has also been reported (Jeste et al. 1997a; Kinon et al. 2004; Littrell et al. 1998; Street et al. 2000).

Atypical antipsychotics have a less favorable side-effect profile, however, in terms of metabolic function. Common metabolic side effects include excessive weight gain and obesity, glucose intolerance, new--onset type II diabetes mellitus, diabetic ketoacidosis, and dyslipidemia (Allison et al. 1999; Jin et al. 2002, 2004; Wirshing et al. 1998). Although there are no guidelines for management of these side effects specifically in older patients with schizophrenia, the monitoring recommendations developed by the American Diabetes Association et al. (2004) are potentially applicable. Because elderly patients tend to be at higher risk for cardiovascular disease than younger patients, closer monitoring is necessary for older adults.

The short-term benefit of risperidone and olanzapine for treatment of psychotic symptoms in middle-aged and older adults with schizophrenia has been supported in several double-blind trials (Jeste et al 2003, Suzuki et al 2011, Reidel et al 2009, Feldmen et al 2003) and one short-term trial suggests that paloperidone might be of benefit (Tzimos et al 2008). Data supporting the short-term benefit of other atypical antipsychotics come only from open-label or retrospectively designed studies. Although clozapine has been shown to have superior effectiveness compared to other antipsychotics in younger adults (Jones et al. 2006; Lieberman et al. 2005), the medication is difficult to use in elderly persons due to the risk of leukopenia and agranulocytosis, as well as other side effects such as orthostasis, sedation, and anticholinergic effects. The necessity of weekly blood draws also may pose a problem for older patients.

Data from our center raises serious concerns about the longer term safety and effectiveness of atypical antipsychotics in middle-aged and older adults. The use of aripiprazole, olanzapine, quetiapine, and risperidone was studied in 332 outpatients over the age of 40 years, with psychotic symptoms related to a variety of diagnoses including schizophrenia, mood disorders, PTSD, or dementia, over a 2 year period of

time. The high one-year cumulative incidence of metabolic syndrome (36% in 1 year) and high rates of both serious (23.7%) and non-serious (50.8%) adverse events observed were particularly concerning given that no significant improvement in psychopathology was detected (Jin et al 2102). Over half of the study participants discontinued their medication within 6 months, often due to side-effects (51.6%) or lack of efficacy (26%) and the quetiapine arm of the study was discontinued early because the incidence of serious adverse events was found to be twice that of the other three atypical antipsychotics.

The concerns about the long-term safety and efficacy of atypical antipsychotics in middle-aged and older adults combined with the data on the increased risk of strokes and mortality in elderly patients with dementia treated with atypical antipsychotics and the consequent U.S. Food and Drug Administration (FDA) black-box warnings (discussed in "Treatment of Psychosis of Alzheimer's Disease and Other Dementias," later in this chapter), underscore the need for clinicians to exercise caution when using these drugs in older patients with schizophrenia. We strongly recommend educating patients and their caregivers about the potential risks and benefits and encouraging shared decision making. If the decision is made to use an antipsychotic medication, it is generally best to start with a low initial dose (25%-50% of that used in a younger patient) and titrate slowly. In patients who have been on stable doses of antipsychotic medications for long periods of time, clinicians should consider gradual and incremental dose decreases to determine the lowest effective dose. Patients should be monitored closely for medication effectiveness and for possible side effects.

Few data are available specifically regarding the safety and effectiveness of pharmacological treatment of very late-onset schizophrenia-like psychosis or delusional disorder in older patients. A single small retrospective case study of 8 outpatients and 13 inpatients with very late-onset schizophrenia-like psychosis concluded that atypical antipsychotics (aripiprazole, risperidone, olanzapine, and quetiapine) could be helpful at low doses. Alexopoulos et al.'s (2004) survey of 48 experts in geriatric care found antipsychotics to be the only recommended treatment for delusional disorder in older adults, and the most favored recommendation for older adults with delusional disorder was risperidone (0.75–2.5 mg/day), followed by olanzapine (5–10 mg/day) and quetiapine (50–200 mg/day). More research is required regarding pharmacological treatment of these conditions in older adults.

Psychosocial Treatments

Recent years have seen the development and testing of psychosocial interventions for older adults with chronic psychotic disorders. Granholm et al. (2005) conducted a randomized, controlled trial in 76 middle-aged and elderly stable outpatients with schizophrenia to examine the effects of adding cognitive behavioral social skills training (CBSST) to treatment as usual. This training intervention teaches cognitive and behavioral coping techniques, social functioning skills, problem-solving techniques, and compensatory aids for neurocognitive impairments. The investigators found that CBSST led to significantly increased frequency of social functioning activities, greater cognitive insight (more objectivity in reappraising psychotic symptoms), and greater skill mastery. At 12-month follow-up, the CBSST group had maintained their greater skill acquisition and performance of everyday living skills. The greater cognitive insight seen in the cognitive-behavioral social skills training group at the end of the treatment was not

maintained at 12-month follow-up, however, suggesting a possible need for booster sessions (Granholm et al. 2007).

Patterson et al. (2006) conducted a randomized, controlled trial to compare a behavioral group intervention called Functional Adaptation Skills Training (FAST) with a time-equivalent attention control condition. FAST is a manualized behavioral intervention designed to improve everyday living skills (including medication management, social skills, communication skills, organization and planning, transportation, and financial management) of middle-aged and older adults with schizophrenia or schizoaffective disorder. Compared with participants randomized to attention control, the FAST group showed significant improvement in daily living skills and social skills but not medication management. The FAST intervention has also been culturally adapted and pilot-tested in middle-aged and older Spanish-speaking Mexican American patients with schizophrenia or schizoaffective disorder. This intervention, called Programa de Entrenamiento para el Desarrollo de Aptitudes para Latinos (PEDAL), was compared in a randomized, controlled pilot study to a time-equivalent friendly support group (Patterson et al. 2005). The PEDAL group demonstrated a significant improvement in everyday living skills that was maintained at 12-month follow-up.

A 12-month program combining social skills training and a nurse-administered preventive healthcare program (HOPES: Helping Older People Experience Success) was associated with improved community living skills and functioning, greater self-efficacy, and lower levels of negative symptoms in adults over the age of 50 years with serious mental illness including schizophrenia and he improvement in community living skills was maintained at 3 year follow-up (Mueser et al 2010; Bartels et al 2013).

Following an examination of employment outcomes among middle-aged and older adults with schizophrenia who each participated in one of three types of work rehabilitation program, Twamley et al. (2005) reported that the highest rates of volunteer or paid work (81%) and competitive/paid work (69%) occurred for the patients who were placed in a job chosen with a vocational counselor and who then received individualized on-site support. The less successful programs (achieving at best a 44% rate of volunteer or paid work) employed a train-then-place approach.

Treatment of Psychosis of Alzheimer's Disease and Other Dementias

Over the past decade, atypical antipsychotics have for the most part replaced conventional antipsychotics in treating psychosis, aggression, and agitation in patients with dementia because of greater perceived tolerability, lower risk for acute extrapyramidal symptoms, and comparatively lower risk of tardive dyskinesia. Most antipsychotics that are prescribed for older adults are for behavioral disturbances associated with dementia, despite their lacking this FDA-approved indication (Weiss et al. 2000).

Atypical antipsychotics seem to have modest short-term efficacy for treating psychosis of AD (Ballard et al. 2006; Sink et al. 2005); however, studies have not always found a significant advantage over placebo in treating psychotic symptoms (Kindermann et al. 2002; Schneider et al. 2006a). In the CATIE Alzheimer's disease trial—the largest ($N = 421$) non–industry-sponsored trial of atypical antipsychotics for psychosis or agitation/aggression in people with dementia—olanzapine, quetiapine, and risperidone

were no better than placebo for the primary outcome (time to discontinuation for any reason) (Schneider et al. 2006b). Time to discontinuation due to lack of efficacy favored olanzapine and risperidone, whereas time to discontinuation due to adverse events favored placebo. In Schneider and colleagues' meta-analysis of randomized, controlled trials of atypical antipsychotics in dementia, the number needed to treat ranged from 5 to 14, depending on the outcome measure, criterion for improvement, and methodology used (Schneider et al. 2006a). The reviewers found that the overall average treatment effect was approximately 18%, which is remarkably similar to that reported in a meta-analysis of conventional antipsychotics in this population (Schneider et al. 1990). A more recent review identified 18 randomized controlled trials of atypical antipsychotic treatment of agitation and aggression in Alzheimer's disease over periods of 6-12 weeks. The authors identified five clinical trials reporting statistically significant but clinically modest improvement in aggression with risperidone at total doses up to 2 mg daily compared to placebo. The evidence to support the benefit of risperidone for nonaggressive symptoms was less consistent. Evidence to support the value of other atypical antipsycotics was limited and conflicting (Ballard and Corbett 2013).

There have been only a few randomized, controlled trials comparing atypical and conventional antipsychotics for treatment of dementia: three trials compared risperidone with haloperidol (Chan et al. 2001; De Deyn et al. 1999; Suh et al. 2004), and one compared quetiapine with haloperidol (Tariot et al. 2006). One of these found superior efficacy of the atypical over the typical agent, and the others reported no significant differences between the two types. In all four studies, haloperidol was associated with more extrapyramidal symptoms.

In addition to the liabilities described above, the use of atypical antipsychotics in elderly patients with -dementia has been associated with both cerebrovascular adverse events (CVAEs) and death, leading to black-box warnings by the FDA. Currently, risperidone, olanzapine, and aripiprazole carry black-box warnings for stroke risk in older patients with dementia. The data for quetiapine in this population are more limited than for risperidone, olanzapine, and aripiprazole. The attribution of risk of CVAEs to atypical antipsychotics is limited, however, in that these studies were not designed to determine a cause-and-effect relationship between atypical antipsychotics and CVAEs, and serious CVAEs were not operationally defined in the trials. Additionally, retrospective database reviews (Gill et al. 2005; Herrmann et al. 2004) did not find any difference in incidence of CVAEs for typical versus atypical antipsychotic use, although none of these studies were originally designed to examine CVAE risk.

In May 2004, the FDA issued a black-box warning that elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk for death compared to those treated with placebo. A 2005 meta-analysis of 15 randomized, controlled trials reported a mortality risk of 3.5% for atypical antipsychotic–treated patients compared with a risk of 2.5% for patients given placebo (odds ratio 1.5, 95%; CI, 1.1–2.2) (Schneider et al. 2005). The causes of death were most commonly cardiac or infectious, the two most common causes of death in patients with dementia (Kammoun et al. 2000; Keene et al. 2001). The data on risk of mortality associated with typical versus atypical antipsychotics have been mixed (Jeste et al. 2008).

Patients with Lewy body dementia and parkinsonian dementia are especially sensitive to side effects such as extrapyramidal symptoms and anticholinergic effects; therefore, very low doses and slow titration schedules should be used to avoid worsening of motor symptoms (Stoppe et al. 1999). Low-dose clozapine has demonstrated efficacy in

reducing symptoms of psychosis, and the drug does not worsen and can even improve the parkinsonian tremor (Bonuccelli et al. 1997; Masand 2000; Parkinson Study Group 1999; Pollak et al. 2004). Several trials of olanzapine in patients with Parkinson's disease have found worsened motor function without demonstrable efficacy in treating psychosis (Chou et al. 2007; Miyasaki et al. 2006). Quetiapine does not appear to worsen motor functioning, but data about its efficacy for psychosis in Parkinson's disease are mixed (Chou et al. 2007; Yeung et al. 2000). The limited data (generally from small, open-label studies) on ziprasidone and aripiprazole do not clearly support the use of these drugs in patients with movement disorders; however, no large randomized, controlled trials have been published to date (Chou et al. 2007). One double-blind, placebo-controlled trial that addressed the treatment of psychosis in dementia with Lewy bodies ($N = 120$) found that twice as many patients treated with rivastigmine (up to 12 mg/day) (63%) versus placebo (30%) had at least 30% improvement in delusions and hallucinations without worsening of motor symptoms (McKeith et al. 2000).

Non-use of active treatment may be a reasonable option for some mild to moderate cases, but in many clinical scenarios, this would be an unacceptably risky alternative. Because of the concerns about safety and effectiveness of antipsychotic medications discussed above and the lack of alternative FDA approved pharmacotherapies for treating psychosis in patients with dementia, most current treatment guidelines recommend nonpharmacological treatment of symptoms as a first-line approach to management of these symptoms unless more aggressive management is deemed necessary to preserve safety. Accordingly there have been a number of studies testing such promising intervention although when strict inclusion criteria are used, such as those of the American Psychological Association, very few of these studies can be considered evidence-based because the results are often inconclusive (Ayalon et al. 2006; Livingston et al. 2005). Recent reviews highlight several promising psychosocial therapies (e.g. individualized daily social interactions and caregiver training) (Ballard and Corbet, 2013).

Key Points

- Schizophrenia may be classified by age at onset into early-onset schizophrenia (onset before age 40), late-onset schizophrenia (onset between ages 40 and 60), and very late-onset schizophrenia-like psychosis (onset after age 60).
- There is considerable heterogeneity of course and outcome with aging in patients with early-onset schizophrenia, although there is generally an improvement in positive symptoms.
- Patients with late-onset schizophrenia are similar to patients with early-onset schizophrenia in terms of risk factors, clinical presentation, family history of schizophrenia, and response to medications. However, women are overrepresented among the late-onset patients. Also, late-onset schizophrenia is characterized by lower average severity of positive symptoms, and a lower average antipsychotic dose requirement.
- Very-late-onset schizophrenia-like psychosis is a heterogeneous entity with varied etiology.
- Patients with psychosis of Alzheimer's disease tend to have paranoid delusions and visual or auditory hallucinations, as well as greater risk of agitation, faster cognitive

decline, and greater likelihood of being institutionalized than patients with Alzheimer's disease without psychosis.

- Older adults have a much higher risk for developing tardive dyskinesia than younger patients. Although atypical antipsychotics are associated with significantly lower risk of tardive dyskinesia than conventional agents, they have problematic metabolic liabilities.
- Psychosocial treatments have an important place as an adjunctive treatment for older adults with schizophrenia.
- There are currently no FDA-approved treatments for psychosis and agitation in dementia; however, off-label use of medications, as well as certain psychosocial interventions, may be appropriate.
- There are concerns about longer-term safety as well as effectiveness of atypical antipsychotics in older patients with psychotic disorders. Additionally, atypical antipsychotic use in patients with dementia has been associated with an increased risk of cerebrovascular adverse events and mortality, leading to FDA black-box warnings for this population.
- Principles of pharmacotherapy for older adults with psychosis include careful consideration of indications, shared decision making, and use of the lowest effective doses for the shortest possible time periods.

References

Alexopoulos GS, Streim J, Carpenter D, et al: Using antipsychotic agents in older patients. J Clin Psychiatry 65:5–99, 2004

Allison DB, Mentore JL, Heo M, et al: Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 156:1686–1696, 1999

American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al: Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. J Clin Psychiatry 65:267–272, 2004

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Press, 1987

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC, American Psychiatric Association, 2013

American Psychiatric Association: Practice guidelines for the treatment of patients with schizophrenia. Am J Psychiatry 154:1–63, 1997

Andreasen NC: I don't believe in late onset schizophrenia, in Late-Onset Schizophrenia. Edited by Howard R, Rabins PV, Castle DJ. Philadelphia, PA, Wrightson Biomedical, 1999, pp 111–123

Auslander LA, Jeste DV: Sustained remission of schizophrenia among community-dwelling older outpatients. Am J Psychiatry 161:1490–1493, 2004

Ayalon L, Gum AM, Feliciano L, et al: Effectiveness of nonpharmacological interventions for the management of neuropsychiatric symptoms in patients with dementia: a systematic review. Arch Intern Med 166:2182–2188, 2006

Ballard C, Waite J, Birks J: Atypical antipsychotics for aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev, Issue 1, Art. No.: CD003476, 2006

Ballard C, Corbett A: Agitation and aggression in people with Alzheimer's disease. Curr Opin Psychiatr 26(3) 252-9

Bartels SJ, Pratt SI, Mueser KT et al: Long-term outcomes of a randomized trail of integrated skills training and preventative healthcare for older adults with serious mental illness. Am J Geriatr Psychiatry 2013 pii: S1064-7481(13)00231-5 (e-pub ahead of print).

Baynes D, Mulholland C, Cooper SJ, et al: Depressive symptoms in stable chronic schizophrenia: prevalence and relationship to psychopathology and treatment. Schizophr Res 45:47–56, 2000

Belitsky R, McGlashan TH: The manifestations of schizophrenia in late life: a dearth of data. Schizophr Bull 19:683–685, 1993
Bleuler M: Die spatschizophrenen Krankheitsbilder. Fortschr Neurol Psychiatr Grenzgeb 15:259–290, 1943
Bonuccelli U, Ceravolo R, Salvetti S, et al: Clozapine in Parkinson's disease tremor: effects of acute and chronic administration. Neurology 49:1587–1590, 1997
Brodaty H, Sachdev P, Rose N, et al: Schizophrenia with onset after age 50 years, 1: phenomenology and risk factors. Br J Psychiatry 175, 410–415, 1999
Burns A, Jacoby R, Levy R: Psychiatric phenomena in Alzheimer's disease, I: disorders of thought content. Br J Psychiatry 157:72–76, 1990a
Burns A, Jacoby R, Levy R: Psychiatric phenomena in Alzheimer's disease, II: disorders of perception. Br J Psychiatry 157:76–81, 1990b
Caligiuri MP, Lacro JP, Rockwell E, et al: Incidence and risk factors for severe tardive dyskinesia in older patients. Br J Psychiatry 171:148–153, 1997
Castle DJ, Murray RM: The epidemiology of late-onset schizophrenia. Schizophr Bull 19:691–700, 1993
Cervantes AN, Rabins PV, Slavney PR: Onset of schizophrenia at age 100. Psychosomatics 47:356–359, 2006
Chambless DL, Hollon SD: Defining empirically supported therapies. J Consult Clin Psychol 66:7–18, 1998
Chan WC, Lam LC, Choy CN, et al: A double-blind randomised comparison of risperidone and haloperidol in the treatment of behavioural and psychological symptoms in Chinese dementia patients. Int J Geriatr Psychiatry 16:1156–1162, 2001
Chen L, Chen X, Liu W et al: White matter microstructure abnormalities in patients with late-onset schizophrenia identified by a voxel-based diffusion tensor imaging. Psychiatry Res 212 (3):201-7
Chou KL, Borek LL, Friedman JH: The management of psychosis in movement disorder patients. Expert Opin Pharmacother 8:935–943, 2007
Christenson R, Blazer D: Epidemiology of persecutory ideation in an elderly population in the community. Am J Psychiatry 141:1088–1091, 1984
Ciompi L: Catamnestic long-term study on the course of life and aging of schizophrenics. Schizophr Bull 6:606–618, 1980
Cohen CI: Outcome of schizophrenia into later life: an overview. Gerontologist 30:790–797, 1990
Cohen-Mansfield J: Nonpharmacologic interventions for inappropriate behaviors in dementia: a review and critique. Am J Geriatr Psychiatry 9:361–381, 2001
Cooper AF, Curry AR: The pathology of deafness in the paranoid and affective psychoses of later life. J Psychosom Research 20:97–105, 1976
Copeland JRM, Dewey ME, Scott A, et al: Schizophrenia and delusional disorder in older age: community prevalence, incidence, comorbidity and outcome. Schizophr Bull 19:153–161, 1998
Corey-Bloom J, Jernigan T, Archibald S, et al: Quantitative magnetic resonance imaging of the brain in late-life schizophrenia. Am J Psychiatry 152:447–449, 1995
Davidson M, Harvey PD, Powchik P, et al: Severity of symptoms in chronically institutionalized geriatric schizophrenic patients. Am J Psychiatry 152:197–207, 1995
De Deyn P, Rabheru K, Rasmussen A, et al: A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 53:946–955, 1999
Devanand DP, Jacobs DM, Tang MX, et al: The course of psychopathologic features in mild to moderate Alzheimer disease. Arch Gen Psychiatry 54:257–263, 1997
Diwan S, Cohen CI, Bankole AO, et al: Depression in older adults with schizophrenia spectrum disorders: prevalence and associated factors. Am J Geriatr Psychiatry 15:991–998, 2007
Dolder CR, Jeste DV: Incidence of tardive dyskinesia with typical versus atypical antipsychotics in very high risk patients. Biol Psychiatry 53:1142–1145, 2003
Evans JD, Paulsen JS, Harris MJ, et al: A clinical and neuropsychological comparison of delusional disorder and schizophrenia. J Neuropsychiatry Clin Neurosci 8:281–286, 1996
Evans JD, Heaton RK, Paulsen JS, et al: The relationship of neuropsychological abilities to specific domains of functional capacity in older schizophrenia patients. Biol Psychiatry 53:422–430, 2003
Forsell Y, Henderson AS: Epidemiology of paranoid symptoms in an elderly population. Br J Psychiatry 172:429–432, 1998
Gill SS, Rochon PA, Herrmann N, et al: Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. Br Med J 330:445, 2005
Granholm E, McQuaid JR, McClure FS, et al: A randomized controlled pilot study of cognitive behavioral social skills training for older patients with schizophrenia (letter). Schizophr Res 153:167–169, 2002
Granholm E, McQuaid JR, McClure FS, et al: A randomized, controlled trial of cognitive behavioral social skills training for middle-aged and older outpatients with chronic schizophrenia. Am J Psychiatry 162:520–529, 2005
Granholm E, McQuaid JR, McClure FS, et al: Randomized controlled trial of cognitive behavioral social skills training for older people with schizophrenia: 12-month follow-up. J Clin Psychiatry 68:730–737, 2007

Hafner H, Van Der Heiden W, Behrens S, et al: Causes and consequences of the gender differences in age at onset of schizophrenia. Schizophr Bull 24:99–113, 1998
Hammerlein A, Derendorf H, Lowenthal DT: Pharmacokinetic and pharmacodynamic changes in the elderly: clinical implications. Clin Pharmacokinet 35:49–64, 1998
Hannerz H, Borga P, Borritz M: Life expectancies for individuals with psychiatric diagnoses. Public Health 115:328–337, 2001
Harding C: Changes in schizophrenia across time, in Schizophrenia Into Later Life. Edited by Cohen CI. Washington, DC, American Psychiatric Publishing, 2002, pp 19–42
Harding CM, Brooks GW, Ashikaga T, et al: Aging and social functioning in once-chronic schizophrenic patients 22–62 years after first admission: the Vermont story, in Schizophrenia and Aging. Edited by Miller NE, Cohen GD. New York, Guilford Press, 1987, pp 74–82
Harris MJ, Jeste DV: Late-onset schizophrenia: an overview. Schizophr Bull 14:39–55, 1988
Harvey PD, Silverman JM, Mohs RC, et al: Cognitive decline in late-life schizophrenia: a longitudinal study of geriatric chronically hospitalized patients. Biol Psychiatry 45:32–40, 1999
Heaton RK, Gladsjo JA, Palmer BW, et al: Stability and course of neuropsychological deficits in schizophrenia. Arch Gen Psychiatry 58:24–32, 2001
Henderson AS, Korten AE, Levings C, et al: Psychotic symptoms in the elderly: a prospective study in a population sample. Int J Geriatr Psychiatry 13:484–492, 1998
Herrmann N, Mamdani M, Lanctot KL: Atypical antipsychotics and risk of cerebrovascular accidents. Am J Psychiatry 161:1113–1115, 2004
Hiroch U, Appleby L, Mortensen PB, et al: Death by homicide, suicide, and other unnatural causes by people with mental illness. Lancet 358:2110–2112, 2001
Howanitz E, Pardo M, Smelson DA: The efficacy and safety of clo-zapine versus chlorpromazine in geriatric schizophrenia. J Clin Psychiatry 60:41–44, 1999
Howard R, Castle D, Wessely S, et al: A comparative study of 470 cases of early and late-onset schizophrenia. Br J Psychiatry 163:352–357, 1993
Howard R, Almeida O, Levy R: Phenomenology, demography and diagnosis in late paraphrenia. Psychol Med 24:397–410, 1994
Howard R, Graham C, Sham P, et al: A controlled family study of late-onset non-affective psychosis (late paraphrenia). Br J Psychiatry 170:511–514, 1997
Howard R, Rabins PV, Seeman MV, et al: Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. Am J Psychiatry 157:172–178, 2000
Huber G: The heterogeneous course of schizophrenia. Schizophr Res 28:177–185, 1997
Jeste DV, Finkel SI: Psychosis of Alzheimer's disease and related dementias: diagnostic criteria for a distinct syndrome. Am J Geriatr Psychiatry 8:29–34, 2000
Jeste DV, Harris MJ, Pearlson GD, et al: Late-onset schizophrenia: studying clinical validity. Psychiatr Clin North Am 11:1–14, 1988
Jeste DV, Wragg RE, Salmon DP, et al: Cognitive deficits of patients with Alzheimer's disease with and without delusions. Am J Psychiatry 149:184–189, 1992
Jeste DV, Harris MJ, Krull A, et al: Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. Am J Psychiatry 152:722–730, 1995
Jeste DV, Klausner M, Brecher M, et al: A clinical evaluation of risperidone in the treatment of schizophrenia: a 10-week, open-label, multicenter trial involving 945 patients. Psychopharmacology 131:239–247, 1997a
Jeste DV, Symonds LL, Harris MJ, et al: Non-dementia non--praecox dementia praecox? Late-onset schizophrenia. Am J Geriatr Psychiatry 5:302–317, 1997b
Jeste DV, Lacro JP, Bailey A, et al: Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. J Am Geriatr Soc 47:716–719, 1999a
Jeste DV, Rockwell E, Harris MJ, et al: Conventional versus newer antipsychotics in elderly patients. Am J Geriatr Psychiatry 7:70–76, 1999b
Jeste DV, Barak Y, Madhusoodanan S, et al: An international multisite double-blind trial of the atypical antipsychotic risperidone and olanzapine in 175 elderly patients with chronic schizophrenia. Am J Geriatr Psychiatry 11:638–647, 2003
Jeste DV, Blazer DG, First M: Aging-related diagnostic variations: need for diagnostic criteria appropriate for elderly psychiatric patients. Biol Psychiatry 58:265–271, 2005
Jeste DV, Meeks TW, Kim DS, et al: Diagnostic categories and criteria for neuropsychiatric syndromes in dementia: research agenda for DSM-V, in Diagnostic Issues in Dementia: Advancing the Research Agenda for DSM-V. Edited by Sunderlan T, Jeste DV, Baiyewu O, et al. Washington, DC, American Psychiatric Publishing, 2007, pp 77–98
Jeste DV, Blazer D, Casey D, et al: ACNP White Paper: update on the use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology 33:957–970, 2008

Jin H, Meyer JM, Jeste DV: Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. Ann Clin Psychiatry 14:59–64, 2002

Jin H, Meyer JM, Jeste DV: Atypical antipsychotics and glucose dysregulation: a systematic review. Schizophr Res 71:195–212, 2004

Jones DK, Catani M, Pierpaoli C, et al: A diffusion tensor magnetic resonance imaging study of frontal cortex connections in very-late-onset schizophrenia-like psychosis. Am J Geriatr Psychiatry 13:1092–1099, 2005

Jones PB, Barnes TR, Davies L, et al: Randomized controlled trial of the effect on quality of life of second- vs. first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 63:1079–1087, 2006

Joukamaam M, Heliovaara M, Knekt P, et al: Mental disorders and cause-specific mortality. Br J Psychiatry 147:498–502, 2001

Kammoun S, Gold G, Bouras C, et al: Immediate causes of death of demented and non-demented elderly. Acta Neurol Scand 176:96–99, 2000

Kane JM, Woerner MG, Pollack S, et al: Does clozapine cause tardive dyskinesia? J Clin Psychiatry 54:327–330, 1993

Keene J, Hope T, Fairburn CG, et al: Death and dementia. Int J Geriatr Psychiatry 16:969–974, 2001

Keith SJ, Regier DA, Rae DS: Schizophrenic disorders, in Psychiatric Disorders in America: the Epidemiologic Catchment Area Study. Edited by Robins LN, Regier DA. New York, Free Press, 1991, pp 33–52

Kendler KS, Davis KL: The genetics and biochemistry of paranoid schizophrenia and other paranoid psychoses. Schizophr Bull 7:689–709, 1981

Kendler KS, Tsuang MT, Hays P: Age at onset in schizophrenia: a familial perspective. Arch Gen Psychiatry 44:881–890, 1987

Kennedy JS, Jeste DV, Kaiser CJ, et al: Olanzapine vs. haloperidol in geriatric schizophrenia: analysis of data from a double-blind controlled trial. Int J Geriatr Psychiatry 18:1013–1020, 2003

Kindermann SS, Dolder CR, Bailey A, et al: Pharmacologic treatment of psychosis and agitation in elderly patients with dementia: four decades of experience. Drugs Aging 19:257–276, 2002

Kinon BJ, Jeste DV, Kollack-Walker S, et al: Olanzapine treatment for tardive dyskinesia in schizophrenia patients: a prospective clinical trial with patients randomized to blinded dose reduction periods. Prog Neuropsychopharmacol Biol Psychiatry 28:985–996, 2004

Kraepelin E: Dementia Praecox and Paraphrenia (1919). Translated by Barclay RM. Huntington, NY, Krieger, 1971

Kulkarni J, de Castella A, Smith D, et al: A clinical trial of the effects of estrogen in acutely psychotic women. Schizophr Res 20:247–252, 1996

Kulkarni J, Riedel A, de Castella A, et al: Estrogen: a potential treatment for schizophrenia. Schizophr Res 48:137–144, 2001

Lieberman JA, Saltz BL, Johns CA, et al: The effects of clozapine on tardive dyskinesia. Br J Psychiatry 158:503–510, 1991

Lieberman JA, Stroup TS, McEvoy JP, et al: Effectiveness of anti-psychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209–1223, 2005

Lindamer LA, Buse DC, Lohr JB, et al: HRT in postmenopausal women with schizophrenia: positive effect on negative symptoms? Biol Psychiatry 49:47–51, 2001

Littrell KH, Johnson CG, Littrell S, et al: Marked reduction of tardive dyskinesia with olanzapine. Arch Gen Psychiatry 55:279–280, 1998

Livingston G, Johnston K, Katona C, et al: Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry 162:1996–2021, 2005

Lohr JB, Alder M, Flynn K, et al: Minor physical anomalies in older patients with late-onset schizophrenia, early-onset schizophrenia, depression, and Alzheimer's disease. Am J Geriatr Psychiatry 5:318–323, 1997

Maher B: Delusional thinking and cognitive disorder. Integr Physiol Behav Sci 40:136–146, 2005

Masand PS: Atypical antipsychotics for elderly patients with neurodegenerative disorders and medical conditions. Psychiatr Ann 30:203–208, 2000

Mazeh D, Zemishlani C, Aizenberg D, et al: Patients with very-late-onset schizophrenia-like psychosis: a follow-up study. Am J Geriatr Psychiatry 13:417–419, 2005

McKeith I, Del Ser T, Spano P, et al: Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 356:2031–2036, 2000

McQuaid JR, Granholm E, McClure FS, et al: Development of an integrated cognitive-behavioral and social skills training intervention for older patients with schizophrenia. J Psychother Pract Res 9:149–156, 2000

Meeks TW, Jeste DV: Beyond the black box: What is the role for antipsychotics in dementia? Curr Psychiatr 7(6) 50-65

Mitter P, Reeves S, Romero-Rubiales F, et al: Migrant status, age, gender and social isolation in very late-onset schizophrenia-like psychosis. Int J Geriatr Psychiatry 20:1046–1051, 2005

Miyasaki JM, Shannon K, Voon V, et al: Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 66:996–1002, 2006

Montross L, Kasckow J, Golshan S, et al: The continued need for suicide assessments among middle-aged and older patients with schizophrenia. Paper presented at the annual meeting of the American Association for Geriatric Psychiatry, San Juan, Puerto Rico, March 2006

Moore NC: Is paranoid illness associated with sensory defects in the elderly? J Psychosom Res 25:69–74, 1981

Moore R, Blackwood N, Corcoran R, et al: Misunderstanding the intentions of others: an exploratory study of the cognitive etiology of persecutory delusions in very late-onset schizophrenia-like psychosis. Am J Geriatr Psychiatry 14:410–418, 2006

Mueser KT, Pratt SI, Bartels SJ et al: Randomized trial of social rehabilitation and integrated healthcare for older people with severe mental illness. J Consult Clin Psychol 78(4) 561-73

Mukaetova-Ladinska EB, Harrington CR, Xuereb J, et al: Biochemical, neuropathological, and clinical correlations of neurofibrillary degeneration in Alzheimer's disease, in Treating Alzheimer's and Other Dementias. Edited by Bergener M, Finkel SI. New York, Springer, 1995, pp 57–80

Naimark D, Jackson E, Rockwell E, et al: Psychotic symptoms in Parkinson's disease patients with dementia. J Am Geriatr Soc 44:296–299, 1996

Ostling S, Skoog I: Psychotic symptoms and paranoid ideation in a nondemented population-based sample of the very old. Arch Gen Psychiatry 59:53–59, 2002

Ostling S, Borjesson-Hanson A, Skoog I: Psychotic symptoms and paranoid ideation in a population-based sample of 95-year-olds. Am J Geriatr Psychiatry 15:999–1004, 2007

Palmer BW, McClure F, Jeste DV: Schizophrenia in late-life: findings challenge traditional concepts. Harv Rev Psychiatry 9:51–58, 2001

Palmer BW, Nayak G, Jeste DV: A comparison of early and late--onset schizophrenia, in Schizophrenia Into Late Life. Edited by Cohen CI. Washington, DC, American Psychiatric Publishing, 2002, pp 43–55

Palmer BW, Bondi MW, Twamley EW, et al: Are late-onset schizophrenia-spectrum disorders neurodegenerative conditions? Annual rates of change on two dementia measures. J Neuro-psychiatry Clin Neurosci 15:45–52, 2003

Parkinson Study Group: Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. N Engl J Med 340:757–763, 1999

Patterson TL, Bucardo J, McKibbin CL, et al: Development and pilot testing of a new psychosocial intervention for older Latinos with chronic psychosis. Schizophr Bull 31:922–930, 2005

Patterson TL, McKibbin C, Mausbach BT, et al: Functional Adaptation Skills Training (FAST): a randomized trial of a psychosocial intervention for middle-aged and older patients with chronic psychotic disorders. Schizophr Res 86:291–299, 2006

Paulsen JS, Salmon DP, Thal LJ, et al: Incidence of and risk factors for hallucinations and delusions in patients with probable AD. Neurology 54:1965–1971, 2000

Pollak P, Tison F, Rascol O, et al: Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. J Neurol Neurosurg Psychiatry 75:689–695, 2004

Prager S, Jeste DV: Sensory impairment in late-life schizophrenia. Schizophr Bull 19:755–772, 1993

Putnam KM, Harvey PD: Cognitive impairment and enduring negative symptoms: a comparative study of geriatric and nongeriatric schizophrenia patients. Schizophr Bull 26:869–878, 2000

Raghuram R, Keshavan MD, Channabasavanna SM: Musical hallucination in a deaf middle-aged patient. J Clin Psychiatry 41:357, 1980

Ram R, Bromet EJ, Eaton WW, et al: The natural course of schizophrenia: a review of first-admission studies. Schizophr Bull 18:185–207, 1992

Rivkin P, Kraut M, Barta P, et al: White matter hyperintensity volume in late-onset and early-onset schizophrenia. Int J Geriatr Psychiatry 15:1085–1089, 2000

Rockwell E, Krull AJ, Dimsdale J, et al: Late-onset psychosis with somatic delusions. Psychosomatics 35:66–72, 1994

Ropacki SA, Jeste DV: Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. Am J Psychiatry 162:2022–2030, 2005

Roth M: The natural history of mental disorder in old age. J Ment Sci 101:281–301, 1955

Sachdev P, Brodaty H, Rose N, et al: Schizophrenia with onset after age 50 years, 2: neurological, neuropsychological and MRI investigation. Br J Psychiatry 175:416–421, 1999

Schneider LS: Pharmacologic management of psychosis in dementia. J Clin Psychiatry 60:54–60, 1999

Schneider LS, Pollock VE, Lyness S.A: A meta-analysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 38:553–563, 1990

Schneider LS, Dagerman KS, Insel P: Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 294:1934–1943, 2005

Schneider LS, Dagerman K, Insel PS: Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 14:191–210, 2006a
Schneider LS, Tariot PN, Dagerman KS, et al: Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 355:1525–1538, 2006b
Seeman MV: The role of estrogen in schizophrenia. J Psychiatry Neurosci 21:123–127, 1996
Simpson GM, Lee JM, Shrivastava RK: Clozapine in tardive dys-kinesia. Psychopharmacology 56:75–80, 1978
Sink KM, Holden KF, Yaffe K: Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA 293:596–608, 2005
Small JG, Milstein V, Marhenke JD, et al: Treatment outcome with clozapine in tardive dyskinesia, neuroleptic sensitivity, and treatment-resistant psychosis. J Clin Psychiatry 48:263–267, 1987
Srikanth S, Nagaraja AV, Ratnavalli E: Neuropsychiatric symptoms in dementia: frequency, relationship to dementia severity and comparison in Alzheimer's disease, vascular dementia and frontotemporal dementia. J Neurol Sci 236:43–48, 2005
Stern Y, Albert M, Brandt J, et al: Utility of extrapyramidal signs and psychosis as predictors of cognitive and functional decline, nursing home admission, and death in Alzheimer's disease: prospective analyses from the Predictors Study. Neurology 44:2300–2307, 1994
Stoppe G, Brandt CA, Staedt JH: Behavioural problems associated with dementia: the role of newer antipsychotics. Drugs Aging 14:41–54, 1999
Street JS, Tollefson GD, Tohen M, et al: Olanzapine for psychotic conditions in the elderly. Psychiatr Ann 30:191–196, 2000
Suh GH, Son HG, Ju YS, et al: A randomized, double-blind, crossover comparison of risperidone and haloperidol in Korean dementia patients with behavioral disturbances. Am J Geriatr Psychiatry 12:509–516, 2004
Sultzer DL: Neuroimaging and the origin of psychiatric symptoms in dementia. Int Psychogeriatr 8 (suppl 3):239–243, 1996
Tariot PN, Schneider L, Katz IR, et al: Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial. Am J Geriatr Psychiatry 14:767–776, 2006
Twamley EW, Padin DS, Bayne KS, et al: Work rehabilitation for middle-aged and older people with schizophrenia: a comparison of three approaches. J Nerv Ment Dis 193:596–601, 2005
Vahia I, Bankole AO, Reyes P, et al: Schizophrenia in later life. Aging Health 3:383–396, 2007
Vahia IV, Palmer BW, Depp C et al: Is late-onset schizophrenia a subtype of schizophrenia? Acta Psychiatr Scand 122(5):414-26
Weiss E, Hummer M, Koller D, et al: Off-label use of antipsychotic drugs. J Clin Psychopharmacol 20:695–698, 2000
Wilkosz PA, Miyahara S, Lopez OL, et al: Prediction of psychosis onset in Alzheimer disease: the role of cognitive impairment, depressive symptoms, and further evidence for psychosis subtypes. Am J Geriatr Psychiatry 14:352–360, 2006
Wirshing DA, Spellberg BJ, Erhart SM, et al: Novel antipsychotics and new onset diabetes. Biol Psychiatry 44:778–783, 1998
Yassa R, Jeste DV: Gender differences in tardive dyskinesia: a critical review of the literature. Schizophr Bull 18:701–715, 1992
Yeung PP, Tariot PN, Schneider LS, et al: Quetiapine for elderly patients with psychotic disorders. Psychiatr Ann 30:197–201, 2000
Zisook S, Montross L, Kasckow J, et al: Subsyndromal depressive symptoms in middle-aged and older persons with schizophrenia. Am J Geriatr Psychiatry 15:1005–1014, 2007
Zubenko GS, Moossy J, Martinez AJ, et al: Neuropathologic and neurochemical correlates of psychosis in primary dementia. Arch Neurol 48:619–624, 1991

Suggested Readings

Auslander LA, Jeste DV: Sustained remission of schizophrenia among community-dwelling older outpatients. Am J Psychiatry 161:1490–1493, 2004
Chou KL, Borek LL, Friedman JH: The management of psychosis in movement disorder patients. Expert Opin Pharmacother 8:935–943, 2007
Granholm E, McQuaid JR, McClure FS, et al: A randomized, controlled trial of cognitive behavioral social skills training for middle-aged and older outpatients with chronic schizophrenia. Am J Psychiatry 162:520–529, 2005
Howard R, Rabins PV, Seeman MV, et al: Late-onset schizophrenia and very-late-onset schizophrenia-like psychois: an international consensus. Am J Psychiatry 157:172–178, 2000
Jeste DV, Harris MJ, Krull A, et al: Clinical and neuropsychological characteristics of patients with late-onset

schizophrenia. Am J Psychiatry 152:722–730, 1995

Jeste DV, Blazer D, Casey D, et al: ACNP White Paper: update on the use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology 33:957–970, 2008

Kendler KS, Tsuang MT, Hays P: Age at onset in schizophrenia: a familial perspective. Arch Gen Psychiatry 44:881–890, 1987

Ropacki SA, Jeste DV: Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. Am J Psychiatry 162:2022–2030, 2005

Vahia I, Bankole AO, Reyes P, et al: Schizophrenia in later life. Aging Health 3:383–396, 2007