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New Wine in Old Bottle: Late-Life Psychosis

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Abstract

Psychosis is common in late life and exacts enormous costs to society, affected individuals, and their caregivers. A multitude of etiologies for late-life psychosis exist, the two most prototypical being schizophrenia and psychosis of Alzheimer's Disease (AD). As such, this review will focus on the non-affective, neuropsychiatric causes of chronic psychosis in the elderly, specifically schizophrenia, delusional disorder, and the psychosis of AD and other dementias. As evidenced in this review, the current research regarding the onset and course of late-life schizophrenia reflects a more favorable prognosis than that painted by the Kraepelinian notion of schizophrenia as "dementia praecox." Antipsychotics are useful in controlling the symptoms of late-life schizophrenia, but their use among older adults warrants increased vigilance because of older adults' increased proclivity to side effects. Psychosocial interventions can be effective, usually in conjunction with medication. Meanwhile, psychosis of AD occurs in nearly half of people with AD and is associated with increased hospitalizations, institutionalization, caregiver distress, and mortality. Despite the profound consequences of psychotic symptoms associated with dementias, the extant literature does not afford clinicians clear, consistent guidance on how to provide optimal treatment to specific patients. Second generation antipsychotics are usually the choice treatment for psychosis, but the black box warning regarding their associated 1–2% increased absolute risk in stroke and overall mortality in patients with dementia complicates their use. Using second generation antipsychotics in low doses for brief periods and discontinuing them when possible is the best clinical practice for dementia-related psychosis. Psychosocial interventions for the treatment of psychosis with AD appear promising in empirical research, but more rigorous study is needed.

Keywords

schizophrenia; psychosis; late-life; dementia; age

Introduction

Psychosis, most simply defined by the presence of hallucinations and/or delusions, is relatively common in older adults. Multiple etiologies for late-life psychosis exist, as any pathological process affecting the brain can manifest as psychosis. Neuropsychiatric

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etiologies of psychosis include chronic conditions, such as early-onset schizophrenia, late-onset schizophrenia, delusional disorder, psychosis associated with various dementias, affective disorders with psychotic features, as well as certain chronic neurological conditions. Additionally, psychosis can be seen in more acute, sometimes reversible conditions, such as delirium, alcohol and/or substance use or withdrawal, and certain neurological diseases. Our review will focus on the non-affective neuropsychiatric etiologies of late life psychosis. Within this focus, we will distinguish between those conditions that develop in early adulthood and persist into later life versus those with a late-life illness onset.

History

Much of the research on late-life psychosis, especially that regarding late-life schizophrenia, is predicated on an historical understanding of the longitudinal course of psychosis. Kraepelin is often credited with first conceptualizing and describing schizophrenia as *dementia praecox* in 1896. However, this term was first used by Morel in 1860 to illustrate a case of an adolescent boy with the acute onset of psychotic symptoms and cognitive deterioration [1, 2]. The term *dementia praecox* references the course (progressive) and age of onset (early) of schizophrenia and has laid the foundation for many current conceptualizations and mis-conceptualizations of late-life psychosis. Jeste et al. [3] have summarized this historical background. In contrast to our current conceptualization of dementia, Kraepelin's use of "dementia" suggested a progressive personality deterioration in regards to volition and emotion. Meanwhile, the term "praecox" referenced an age of onset in adolescence or early adulthood [4]. Kraepelin also distinguished between two other phenomenologically distinct groups, which led to his categorical descriptions of *paraphrenia* and *paranoia*. Kraepelin used the term *paraphrenia* to describe patients who had a mostly paranoid presentation and generally a later age of onset [5]. He used the term *paranoia* to depict patients who had chronic, well-organized delusions, but did not manifest perceptual disturbances, personality deterioration, or a formal thought disorder. In many ways, this later term is similar to the DSM-IV-TR construct of delusional disorder.

More modern concepts of late-life psychosis began to develop with the work of E. and M. Bleuler. E. Bleuler is recognized as being the first scientist to popularize the term *schizophrenia*. In contrast to Kraepelin, he did not believe that the disorder was necessarily characterized by illness course or age of onset [6]. The work of his son, M. Bleuler, on late onset schizophrenia (LOS) demonstrated that the illness could first present later in life [3, 7]. A substantial amount of research was completed in the United Kingdom in the mid-20th century on LOS, usually termed *paraphrenia*. Although LOS was initially met with much resistance in the United States, there has been a growing body of literature on LOS in the United States since the late-20th century. The age of onset and the course of the illness have remained centralizing foci of this research.

Late-Life Schizophrenia

The term "late life schizophrenia" refers to schizophrenia in older adults regardless of when their symptoms first manifested. In particular, it is comprised of older individuals with schizophrenia who first developed symptoms in early adulthood as well as individuals whose symptoms first emerged in later life [8]. As the aging population rapidly grows, the proportion of older adults with schizophrenia is expected to increase in an unprecedented fashion [9].

Understanding the epidemiology of late-life schizophrenia is complex, as different nomenclatures, definitions of late-onset schizophrenia, diagnostic criteria, and heterogeneity

of clinical samples have been applied in the existing literature [10]. The Epidemiologic Catchment Area (ECA) study is most often cited for prevalence rates of late-life schizophrenia. This survey of psychopathology in the general United States population reported 1-year schizophrenia prevalence rates of 0.6% among individuals aged 45–64 and 0.2% for individuals aged 65 years and older. The ECA reported a lifetime prevalence of schizophrenia among people aged 45–64 of 1.0% and among people aged 65 years and older of 0.3% [11]. Several methodological limitations of this study likely resulted in an underestimation of late-life schizophrenia, including lack of age-appropriate diagnostic interview questions; additionally, there may be a premature death rate among persons with schizophrenia that lowers the prevalence in later life [8, 10, 12–14].

The cost of caring for people with late-life schizophrenia is disproportionate to the numbers of individuals with this disorder. The healthcare costs of late-life schizophrenia are estimated to be at least as much as those among teenagers and young adults with schizophrenia [8, 14]. Although the lifetime prevalence of schizophrenia is 1% (versus, for example, 20–25% in major depression), schizophrenia across all age groups accounts for the greatest proportion of mental health care expenditures [8, 15]. One report comparing the annual health care costs for adults with schizophrenia to adults with dementia, depression, and physical illness found that for individuals over age 65, the annual cost of care for schizophrenia was the most expensive [16]. Nursing home care accounted for the vast majority of such expenditures. Overall, there is an increase in the costs associated with schizophrenia as people age [17].

The emotional cost of caring for older adults with schizophrenia is also great, especially for spousal caregivers. In a study specifically looking at family caregivers of older adults with psychotic disorders, Patterson et al. [18] found that spousal caregivers more frequently provide assistance with instrumental activities of daily living and experience a sense of loss of identity and anticipated lifestyle than do other family member caregivers. Despite the literal and figurative costs of caring for older adults with schizophrenia, there is a relative dearth of research on this important and vulnerable segment of society. Cohen et al. [19] found that only 1% of the literature on schizophrenia focuses on late-life schizophrenia.

Early Onset Schizophrenia in Later Life

Psychiatric Symptoms—Historically, people with schizophrenia were thought to have a progressively worsening psychological, functional, and cognitive course as they aged. Much of the literature on community dwelling individuals with schizophrenia challenges this notion [1]. A pattern of progressive deterioration has been shown in studies examining chronically institutionalized people with schizophrenia [20, 21]. However, most individuals with schizophrenia currently do not reside in such institutions and those chronically residing in institutions generally epitomize the most severe manifestations of schizophrenia [19].

Longitudinal studies examining older adults with early onset schizophrenia (EOS) living in the community demonstrate a more optimistic prognosis. The Vermont Longitudinal Research Project was a 32-year prospective follow-up study of 118 persons retrospectively diagnosed with schizophrenia. Of the 82 participants who were interviewed 20–25 years after the start of the study, 68% no longer experienced signs or symptoms of schizophrenia and 45% no longer experienced any psychiatric symptoms [22]. Harding later summarized 10 longitudinal studies comprising 2429 individuals with schizophrenia followed over an average of 28 years. Forty-six percent to 84% showed significant clinical improvement over time, especially in terms of their positive symptoms, i.e. delusions and hallucinations [23]. Similarly, in the World Health Organization (WHO) 15- and 25-year international prospective study, 48% of the incidence group and 54% of the prevalence group were deemed “globally recovered” [24]. In a cross-sectional study comparing a sample of older

adults with schizophrenia to a control group of older adults without schizophrenia, Jeste et al. [25] found that aging was associated with a decrease in general psychopathology. Aging was not associated with progressive worsening in well-being, psychopathology, or functioning. In contrast to other studies, this study found a relatively stable course for schizophrenia, rather than one hallmarked by striking improvement. Remission rates vary considerably (8%–72%), likely secondary to differing definitions of remission and variations in study populations [26, 27]. Overall, the community based studies summarized above challenge prior notions that the symptoms of schizophrenia progressively worsen with age.

Cognition—With the exception of chronically institutionalized people with schizophrenia, who are known to have a more deteriorative illness course, the literature supports a remarkably stable pattern of neuropsychological functioning in older individuals with schizophrenia [17, 28–30]. For instance, in one study involving 116 community-dwelling individuals with early-onset schizophrenia (≤ 45 years old) versus 122 normal control participants, no difference in the slope of cognitive decline was seen between the group of individuals with schizophrenia and the normal controls [30]. In another study comparing dementia screening measures of individuals with EOS, LOS, AD, and normal controls, a stable cognitive pattern was seen for all groups except for those with AD [31]. Overall, studies involving community dwelling individuals with schizophrenia support a stable cognitive pattern over time, contrasting with the historical concept of progressive deterioration with *dementia praecox*.

Although the pattern of neuropsychological functioning is stable in later life, the baseline cognition of schizophrenia is generally impaired compared to controls. Schizophrenia is associated with mild to moderate cognitive deficits (approximately 1 standard deviation below the mean of demographically comparable normal comparison subjects) across a range of cognitive domains [32]. Notably, there is considerable heterogeneity in terms of the level and pattern of cognitive deficits between people with schizophrenia. Thus, there is no specific pattern of cognitive impairment that is either unique to or common among all people with schizophrenia. Nonetheless, deficits are usually found across a range of cognitive abilities including attention and working memory, learning (but not retention) on measures of episodic memory, executive functions, and psychomotor/processing speed [32, 33]. Crystallized verbal knowledge and retention of information once learned tend to be relatively spared. Studies suggest that the memory impairment seen in late-life schizophrenia is the result of poor organization or registration, rather than poor retrieval of information, as is seen in AD [29, 34–36]. Elderly people with schizophrenia experience the typical subtle changes in cognitive function that occur with normal aging [37], but presence of rapid forgetting is atypical and thus warrants further evaluation for possible co-morbid factors, such as AD or other cortical dementias [29].

Function—Likely related to its relatively stable neurocognitive trajectory, the functional course of schizophrenia appears less pessimistic than previously thought. Patterson and colleagues found that the functioning of older adults with schizophrenia was more impaired than that of normal controls, except in regards to grooming and eating, and that disability was related to greater cognitive impairment, increased extrapyramidal symptoms, and less formal education [38]. In a study comparing middle-aged and older adults with schizophrenia to demographically matched controls, Palmer and colleagues found considerable heterogeneity in the functional status of older adults with schizophrenia [39]. Although the group of people with schizophrenia had a worse functional status than the normal controls, a substantial number of persons with schizophrenia drove automobiles, lived independently, and had been employed at least half of their adult lives after their schizophrenia was diagnosed. Interestingly, positive symptoms were not correlated with functional status, whereas negative, symptoms (e.g. apathy, amotivation) were inversely

correlated with functional status. In a qualitative study among 32 adults with chronic schizophrenia aged 50 and older, considerable heterogeneity was found in perceptions of their own functional status, reiterating that statistically significant changes still fail to capture the individual life stories that should always be considered in clinical evaluations [40].

Life Satisfaction and Quality of Life—Although life satisfaction and quality of life are generally lower among older adults with schizophrenia compared to their peers without schizophrenia, most older adults with schizophrenia report a relatively high level of life satisfaction and deny a worsening in their quality of life associated with aging [19, 41]. Life satisfaction is often associated with subjective, rather than objective measures [41], while quality of life has been found to correlate indirectly with positive symptoms [42]. Severity of depressive symptoms, impairment in cognitive functioning, and earlier age of schizophrenia onset influence the mental health quality of life and functioning of older adults with schizophrenia [43], whereas social functional impairment, psychosocial factors including avoidant coping styles and negative life events, and severity of psychotic symptoms influence the overall health-related quality of life of older adults with schizophrenia [44]. Interestingly, patients with schizophrenia report better subjective well-being than do patients with mood, anxiety, or somatoform disorders [45], and older individuals with schizophrenia report better mental health quality of life than do younger adults with schizophrenia [46].

Social connectedness is often related to quality of life. Historically, older adults with schizophrenia were often assumed to be socially isolated. A study comparing middle-aged and older adults with schizophrenia to normal subjects challenges this belief [47]. Although compared to adults without schizophrenia, those with schizophrenia were less likely to be married, have children, and live with others, they were still remarkably socially connected—97% had regular contact with family or friends and 62% had been married at some point in their lives. Furthermore, individuals with schizophrenia were similar to those without schizophrenia in terms of presence of a family confidant, frequency of contact with family, extent of interpersonal difficulties, and amount of instrumental support received.

Predictors of outcome—Several factors predict a negative long-term outcome in late-life schizophrenia. These include premorbid deficits in psychosocial and overall function, prominent negative symptoms, and gradual symptom onset [48]. All of the regression models in the World Health Organization (WHO) 15- and 25-year international follow-up study indicate that the strongest predictors of long-term outcome in schizophrenia are such measures of the early illness course, with the amount of time experiencing psychotic symptoms in the first 2 years of illness being the strongest predictor of symptoms and disability in later life [24]. In light of the symptomatic improvement seen in many older adults with schizophrenia and the finding that early onset characteristics best predict long-term outcome, the authors of the WHO international study concluded that the findings “offer robust reasons for therapeutic optimism and point to a critical ‘window of opportunity’ in the early period of syndromal differentiation”.

Late Onset Schizophrenia and Very Late Onset Schizophrenia-Like Psychosis

Background—The nomenclature to describe schizophrenia that first manifests in later life has changed considerably over time. Historically, as previously described, the onset of schizophrenia was thought to be limited to adolescence or early adulthood. Criteria outlined by Feighner and his colleagues in 1972 restricted the diagnosis of schizophrenia to onset before age 40. Similarly, the DSM-III did not allow for the diagnosis if the onset occurred after age 45. Subsequently, the DSM-III-R permitted the diagnosis of schizophrenia late-

onset type after age 45, and the DSM-IV contains no diagnostic restrictions for age of onset [8]. An international consensus in 2000 proposed that individuals with onset of schizophrenia after the age of 40 be subdivided into late onset schizophrenia (LOS) if the symptoms manifested between ages 40–60 and very-late-onset schizophrenia-like psychosis (VLOSLP) if the symptoms manifested after age 60 [49]. Much of the existing literature does not discern between the latter distinction of LOS and VLOSLP. Rather, onset after age 40 or 45 is often referenced as LOS. As such, this section will summarize what is known about LOS in the broader sense of this definition and will distinguish between LOS and VLOSLP in terms of the international consensus when possible. Table 1 also summarizes some key differences among various diagnoses of late-life psychosis, with the intent to serve as a quick, somewhat simplified, reference for distinguishing among key clinical differences among these diagnoses based on extant literature.

Epidemiology—The overall epidemiology for late-life schizophrenia (i.e. including those with early onsets who have aged) was described previously. Here, we will focus on the epidemiology of LOS and VLOSLP. In M. Bleuler's study of 459 patients with schizophrenia, 14.8% had onset after age 40 [1, 50]. Incidence rates for onset after age 44 are 12.6 per 100,000 population per year [49] and incidence rates for VLOSLP increase by 11% every 5 years after age 60 [51]. Newer data suggest that the annual incidence for LOS between ages 45 and 64 years in the community is 0.3% [52].

Clinical Features—Several similarities exist between EOS and LOS, including the severity of global psychopathology and positive symptoms, levels of childhood maladjustment, family history of schizophrenia (10%–15% having a first-degree relative with schizophrenia), response to neuroleptics, and chronicity of course [3, 35]. Prospective studies indicate that both individuals with LOS and EOS have a 2–3 times greater mortality rate than various comparison groups, including the general United States population aged between 55 and 65 years [3]. Interestingly, both individuals with LOS and EOS share an elevated amount of minor physical anomalies compared to normal subjects, suggesting the possibility of early developmental aberrations [53]. Both groups have higher levels of corrected sensory deficits (e.g., wearing eyeglasses and/or hearing aides) compared with controls; however, they have similar levels of uncorrected sensory impairments as do age-matched individuals without schizophrenia [3].

Nonetheless, differences between individuals with EOS and LOS have also been observed in the literature. Phenomenological differences exist between the types of hallucinations and delusions that persons with LOS versus EOS experience. Individuals with LOS more commonly report visual, tactile, and olfactory hallucinations in addition to third-person running commentary and accusatory auditory hallucinations compared to those with EOS [49, 54, 55]. Individuals with LOS more frequently experience partition (the belief that people, objects or radiation can pass through what would normally constitute a barrier to such passage), phantom border, and persecutory delusions [49, 56]. According to most studies, individuals with LOS less commonly have severe negative symptoms or a formal thought disorder, and thus more commonly present with paranoid type schizophrenia [3, 35].

However, the most current findings from the research group at the University of California, San Diego (UCSD) synthesizing the data on middle-age and older adults with schizophrenia collected over the past 20 years challenge some of the accepted similarities and distinctions between individuals with EOS and LOS [57]. Contrasting previous studies, no statistically significant differences were found between the two groups' severity of negative symptoms nor in the proportion of individuals with illness paranoid subtype. More consonant with previous research, the LOS group had less severe positive symptoms and general psychopathology than did the EOS group and were prescribed lower doses of neuroleptics

than their EOS peers [57]. Sociodemographic differences were also observed between EOS and LOS patients. LOS patients were more likely to have been married at some point than persons with EOS [3, 57]. Women were consistently overrepresented in samples of LOS across multiple studies of LOS. Some investigators hypothesize that this gender difference may reflect psychosocial factors [49] whereas others theorize that this difference may be hormonally mediated [1].

Cognition and Function—As aforementioned, the Kraepelinian notion of *dementia praecox* fails to capture the stable cognitive trajectory associated with LOS over time [3, 31]. In a series of studies completed at UCSD, individuals with LOS were found to be less impaired than were those with EOS in terms of abstraction/flexibility of thinking and semantic memory [3]. Additionally, the newest analyses of the UCSD studies indicated that LOS patients have better processing speed and verbal memory than do EOS patients [57]. The San Diego studies also found that individuals with LOS exhibited better premorbid functioning in their adolescent and early adulthood years. Overall, the studies reveal that LOS is certainly not a dementing illness. Nor does EOS appear to be a dementing illness *per se* in the sense of progressing over time, but it appears possibly to cause more profound baseline cognitive deficits than LOS.

Neuroimaging—Similarly to imaging studies in EOS patients, non-specific structural abnormalities (e.g., higher ventricle-to-brain ratio) and focal structural changes (reductions in the superior temporal gyrus and left temporal lobe) have been seen in imaging studies of LOS patients [49, 58]. Interestingly, larger thalami have been found in imaging studies of LOS patients compared to EOS patients, suggesting the theoretical involvement of defective thalamic pruning in the etiology of LOS [3, 59]. Although some discrepancies exist in the literature, studies which carefully exclude individuals with organic cerebral illness do not indicate an increase in white matter hyperintensities or tumors in the brains of LOS patients [3, 60, 61].

Very-Late-Onset Schizophrenia-Like Psychosis

In a prospective study comparing individuals with VLOSLP to a gender matched sample of individuals with earlier onset schizophrenia, the patients with VLOSLP were distinguished by higher rates of marriage, higher education levels, better responses to treatment with risperidone, and more pronounced cerebellar atrophy [5, 62]. A qualitative study examining the subjective experience of individuals with VLOSLP found four emerging themes: long-term experience of the self as different, loneliness, solitary coping style, and an attempt to find meaning in the manifestation of the psychosis. Overall, VLOSLP may be a neurodegenerative process in contrast to LOS that develops before age 60 which is theorized to be a neurodevelopmental process [1, 49]. However, more research is needed to substantiate these theories. The authors of a case report propose that a 100 year old woman meets the criteria for late onset schizophrenia, challenging our reluctance to diagnose schizophrenia when the symptoms emerge after age 60 [63]. Much research remains to be conducted to better characterize this syndrome currently labeled as VLOSLP.

Delusional Disorder

A dearth of literature exists about delusional disorder in older adults. Studies often do not distinguish between delusions in general, which can be present in a multitude of disorders, and delusional disorder more specifically. Further complicating the picture, the nosology of delusional disorder has shifted over time. Historically, delusional disorder has been referenced as paranoia, paranoid reaction, paraphrenia, paranoid psychosis, paranoid condition, paranoid psychosis, paranoid state, and paranoid disorder [64].

According to DSM-IV-TR, delusional disorder generally manifests in middle to late adulthood, with women presenting later than men. The prevalence is 0.03% and is somewhat higher in women [65]. De Portugal et al. [66] found a female-to-male ratio of 1.6:1, with men experiencing more severe symptoms and worse functional outcomes. Meanwhile, the incidence of delusional disorder is 15.6 per 100,000 [67].

Delusional disorder accounts for 1%–4% of inpatient psychiatric hospital admissions and is seen more frequently in lower socioeconomic status and immigrant populations [64]. In a study comparing patients with late-onset psychosis with somatic delusions to both controls and late-onset psychotic patients without somatic delusions, the majority of participants with somatic delusions met criteria for delusional disorder [68]. Additionally, those with somatic delusions were more commonly female, had been sick longer, had lower IQs, were often immigrants or first generation, poorly complied with psychotropic treatment, sought repeated medical evaluations, and presented with varied somatic delusions. Although admitted to hospitals less frequently, people with delusional disorder often have more severe psychopathology than individuals with schizophrenia [69]. Risk factors for delusional disorder for the general adult population include a family history of schizoid, avoidant, or paranoid personality disorder or schizophrenia [70]. Considering the symptomatic severity associated with delusional disorder, the related cost from extensive use of medical services, the decrease in patient quality of life, and the limited extant data on delusional disorder, there is an unambiguous need for increased research into the optimal identification of and treatment for older adults with delusional disorder. These efforts may entail training and interventions in primary care and other non-psychiatric settings.

Psychosis of Alzheimer's Disease

Epidemiology

In their extensive review of 55 studies on the psychosis of Alzheimer's disease (AD), Ropacki and Jeste [71] found the median prevalence of psychotic symptoms was 41.1%, the median prevalence of delusions was 36%, and the median prevalence of hallucinations was 18%. Prevalence was affected by setting, with higher rates of psychosis in inpatient settings than in outpatient settings. Prevalence rates of psychotic symptoms in 85 year-old individuals with AD have recently been found to be 36% [72]. One-year incidence rates for the development of psychosis in AD patients range from 20%–25%, whereas 2-year incidence rates range from 32.5% to 36.1% [73–75]. Incidence seemingly levels off after 3 years [71].

Clinical Features

Several differences distinguish the psychosis seen in AD from that in late-life schizophrenia. Visual hallucinations are more common than are auditory hallucinations in AD, contrasting the pattern seen in schizophrenia [71]. Schneiderian first-rank symptoms (e.g. auditory hallucinations commenting on actions, thought insertion, thought withdrawal) are exceedingly rare in AD [76].

The delusions seen in AD often have distinguishing characteristics from those in schizophrenia. The delusions are typically simple, non-bizarre, and paranoid [76]. They often relate to memory deficits, as exemplified by delusions of theft occurring after individuals with AD misplace items. Misidentification delusions, the false belief that close loved ones are not who they see they are, are frequent in the psychosis seen in AD. In fact, a recent study examining late-onset AD found that misidentification delusions were the most common psychotic symptom reported (23.4% had misidentification delusions, 21.1% had paranoid delusions, 3.1% had imposter delusions) [77].

Also in contrast to the pattern with schizophrenia, a past history of psychosis is rare for AD patients with psychotic symptoms [78]. Hallucinations and delusions often appear to remit in the later stages of AD, but it is unclear if this pattern reflects an artifact secondary to patients being unable to communicate their psychotic symptoms in the later stages of their illness or a natural resolution of the symptoms; nonetheless the psychosis of AD does appear to have a more fluctuant course with remissions and recurrences than that seen in late-life schizophrenia [76].

Risk Factors and Associations

The association between psychosis in AD and several demographic variables is equivocal. In their review of the literature, Ropacki and Jeste [71] noted that five out of seven studies examining the relationship between psychosis with AD and ethnicity found an association with being African American. Meanwhile, family history of dementia, older age, and female gender are weakly associated with an increased risk for psychosis of AD [71, 79]. Psychosis of AD inconsistently relates to older age, duration of AD, and later age of onset of AD [71, 73].

Bassiony et al. [80] determined different associations and risk markers for the delusions and hallucinations of AD. Delusions and combined delusions and hallucinations in individuals with AD were associated with older age, increased depression, more aggression, and worse general health. In contrast, hallucinations in individuals with AD were associated with more severe dementia, being African American, less formal education, and gait impairment. Antihypertensive use was associated with delusions, whereas anxiolytic use was associated with hallucinations. However, these data are limited, as they were not analyzed with multiple regression analysis.

Newer data indicate that psychosis in AD may have genetic determinants. Psychosis with AD is thought to represent a distinct phenotype [81]. Sweet and colleagues found that psychosis aggregates with late-onset AD families, suggesting a possible genetic basis [77]. Apolipoprotein E4 (APO E4) genotype, dopamine and serotonin receptor gene polymorphisms, serotonin and dopamine transporter gene polymorphisms, as well as nicotinic acetylcholine receptor, interleukin-1 β gene promoter, catecholamine-O-methyltransferase (COMT), and (neuregulin-1) NRG1 genetic polymorphisms are being analyzed as possible correlates with psychosis of AD [72, 82]. The extant literature on APO E4 genotype and psychosis of AD is remarkably equivocal [72, 82], and data on other genes are quite premature, making it difficult to discern any clear genetic determinants of psychosis in AD at this time.

In summarizing the neuropathological, neurochemical, and neuroimaging correlates of psychosis in AD, Jeste and Finkel [76] reported that researchers have found an association between delusions in dementia and frontotemporal cortex dysfunction in addition to an association between psychosis in dementia and increased subcortical norepinephrine levels, greater cortical neurodegenerative changes, and decreased cortical and subcortical serotonin/5-HIAA levels. Lee and colleagues [83] describe a correlation between psychotic symptoms in AD and white matter changes in the frontal, left basal ganglia, and parieto-occipital brain regions. More specifically, the white matter changes are associated with delusional misidentification, but not hallucinations or paranoid delusions.

Clinical Sequelae

The clinical and psychosocial consequences of psychosis in AD and other dementias are profound. In distinction from AD without psychotic symptoms, psychosis with AD is associated with greater cognitive impairment and more rapid cognitive decline [73, 78, 84,

85]. Psychosis in dementia is linked to greater caregiver distress [86, 87], poorer quality of life [88], greater prevalence of extrapyramidal signs [89], decreased physical health [80], and increased mortality (specifically associated with hallucinations as opposed to delusions) [90, 91]. Psychosis of dementia has also been linked with other neuropsychiatric disturbances, such as anxiety, agitation and aggression [71, 92–95]. For example, 85% of patients with dementia who were selected to participate in a study based on their problematic behaviors had psychotic symptoms. Behavioral disturbances and agitation are often inciting factors for institutionalization in general. It is thus not surprising that psychosis of AD is a significant predictor of functional decline and institutionalization [88, 90, 96].

Psychosis Associated with Other Dementias

Psychosis frequently complicates various other non-AD dementias. Three common disorders in that category are vascular dementia (VaD), Parkinson's Disease Dementia (PDD), and Lewy-Body Dementia (LBD). In their population based study of 85-year old individuals with dementia, Ostling and colleagues [72] found that a higher percentage of people with VaD had psychotic symptoms than did people with AD (54% versus 36% respectively). They also observed that delusions were nearly twice as common in VaD than in AD. No association was found between degree of dementia severity and presence of psychotic symptoms in VaD, contrasting the pattern found in AD wherein the probability of psychosis increases with worsening severity of AD up to a certain stage of illness. The manifestation of psychosis in VaD likely depends on the brain region(s) affected by the vascular insult(s), e.g. well-formed visual hallucinations in an occipital lobe infarct.

Psychosis commonly occurs in both PDD and LBD. The clinical characteristics of PDD and LBD are similar, but the timing of dementia onset relative to the onset of parkinsonism symptoms helps differentiate PDD from LBD. PDD is diagnosed when the dementia onset is 1 year or more after the onset of parkinsonism. In contrast, LBD is diagnosed when the dementia onset occurs within 1 year after the onset of motor symptoms of parkinsonism [97]. Patients with parkinsonism and psychosis (both LBD and PDD) can be categorized as experiencing "benign hallucinosis" or complex psychotic symptoms. "Benign hallucinosis", which often occurs in PD without dementia, implies non-troubling mild visual perceptual disturbances for which patients usually maintain insight and which often do not warrant treatment [98]. In contrast, people with PDD and LBD more often experience frightening complex psychotic symptoms for which they lack insight, which are associated with behavioral changes, and which often warrant treatment [98].

In a prospective study of 239 community-based patients with PD followed over 12 years [99], 60% had psychotic symptoms and the incidence rate of psychosis was 79.7 per 1000 person-years. Psychosis in PD is associated with increased odds of dementia, increased disability, older age at onset of PD, presence of REM sleep behavior disorder, and higher doses of dopaminergic treatment, suggesting that psychosis of PD indicates a more malignant course of the illness [99].

Proposed diagnostic criteria for psychosis in PD include having at least illusions, hallucinations, delusions, or a false sense of presence on a recurrent or continuous basis for one month with possible associated features of insight, dementia, and treatment for PD [100]. Visual hallucinations are the most frequent psychotic symptom present in PDD [101], occurring in nearly half of patients [102]. Delusions usually in the presence of comorbid hallucinations in PDD and are seen in up to 10% of patients [103, 104]. Similarly to AD, persistence of psychosis in PD and PDD is associated with caregiver distress, institutionalization, and functional impairment [98, 105].

Psychotic symptoms in LBD can be classified as hallucinations, delusions, or misidentifications [106]. As with PDD, visual hallucinations are the most frequent psychotic symptom in LBD and serve as one of the core diagnostic features [97]. Systematized delusions and hallucinations in other modalities occur less frequently than do visual hallucinations, but are not uncommon, and are thus supportive diagnostic features. Misidentifications in LBD range from simple misidentifications of people to “delusional misidentification syndromes”, such as Capgras syndrome and the ‘phantom boarder’ delusion [107, 108]. A recent study found that 78% of patients with LBD had hallucinations, 56% had misidentifications, and 25% had delusions [106]. Individuals with LBD have higher rates of hallucinations and delusions than do individuals with either PDD or PD without dementia [102]. Since the psychotic symptoms with LBD occur earlier in the course of the disease and are more frequent than in AD, they tend to cause more caregiver distress at the early stages of illness [109]. Interestingly, neural correlates to the psychotic symptoms in LBD have been discovered recently [110]. Visual hallucinations, delusions, and misidentifications respectively relate to dysfunction in the cortical occipital and parietal association areas, frontal cortex, and limbic-paralimbic areas.

Treatment

Schizophrenia

Pharmacotherapy—Most of the studies of pharmacotherapy treatments for late-life schizophrenia focus on individuals with early-onset, rather than late-onset or very-late-onset schizophrenia-like psychosis. Although certain discrepancies exist, these studies overall support the efficacy of various atypical antipsychotics, including clozapine, risperidone, olanzapine, and aripiprazole, in the treatment of older adults with schizophrenia [111–113]. Use of low dose risperidone has relatively more positive data in controlled trials [114, 115]. Similar rates of efficacy for the treatment of older persons with chronic schizophrenia were found between risperidone (average dose 2mg) and olanzapine (average dose 10mg) in a RCT, but olanzapine was associated with greater metabolic side effects [116]. Jeste and colleagues [113] recommend that when employed, risperidone should be started at 0.25 to 0.5mg/day and increased no more than 0.5mg/day to a maximum dose of 3mg/day or less. Risperidone 1.25 to 3.5mg/day was the first-line recommendation according to expert consensus for the treatment of late-life schizophrenia, followed closely by quetiapine 100 to 300mg/day, olanzapine 7.5 to 15mg/day, and aripiprazole 15 to 30mg/day in a survey completed by 48 American experts in geriatric medicine and geriatric psychiatry [117]. A recent Cochrane review [118] concluded that there is no current evidence base specifically for antipsychotic drug treatment for older people with LOS or VLOSLP. Open studies of typical antipsychotics used for the treatment of LOS and VLOSLP indicated that 48%–61% of patients demonstrated full remission of psychotic symptoms [49].

When treating older adults with antipsychotic medications, it is imperative to consider various side effects. These include cardiovascular, sedative, anticholinergic, and metabolic effects, in addition to extrapyramidal symptoms (EPS), tardive dyskinesia (TD), hyperprolactinemia, agranulocytosis and neuroleptic malignant syndrome (NMS) [111]. Orthostatic hypotension commonly occurs in older adults treated with medications that block α -1 adrenoreceptors (e.g., conventional low-potency antipsychotics, risperidone, quetiapine, and clozapine) [111] and is associated with falls and hip fractures [119]. Meanwhile, the use of typical antipsychotics is limited by the dramatically increased risk of TD in older adults treated with typical antipsychotics. Jeste determined that the cumulative annual incidence of TD in older adults treated with low-dose typical antipsychotics was 26.1%, which is 5–6 times the rate of that observed in younger adults [120]. Atypical antipsychotics are associated with significantly lower rates of TD in older adults than are typical antipsychotics, as demonstrated by a prospective study comparing risperidone to

haloperidol [121]. However, adverse metabolic effects associated with atypical antipsychotics, including weight gain, dyslipidemia, and glucose intolerance/diabetes mellitus, are concerning. In an analysis of 45 cases of new onset diabetes and diabetic ketoacidosis associated with atypical antipsychotic use, Jin et al. [122] reported that 44% were related to clozapine while 42% were related to olanzapine. In light of their potential adverse metabolic consequences, close monitoring in older adults prescribed atypical antipsychotics remains important. Jin and colleagues [123] determined that the triglyceride-HDL ratio, waist circumference, and BMI were each independent risk markers for metabolic syndrome in antipsychotic-treated adults aged 40 and older. The underlying mechanisms of metabolic syndrome associated with atypical antipsychotic use are unknown, but hypothetically may involve alterations in ghrelin and adiponectin levels [124]. In summary, antipsychotics are useful in controlling the symptoms of late-life schizophrenia, but their use can be problematic in older adults due to their proclivity to cause side effects. As such, one should heed caution when using these medications in this population.

Psychosocial Interventions—Growing evidence supports the adjunctive use of psychosocial interventions to treat late-life schizophrenia. Pharmacologic treatments aim to reduce symptom burden. However, a reduction in psychotic symptoms does not necessarily translate into improved functioning [125]. In the arena of functional improvement, psychosocial interventions, used in conjunction with pharmacotherapy, show promise as an adjunctive treatment modality in older adults with schizophrenia. For example, Functional Adaptation Skills Training (FAST), a group-format manualized therapy that targets everyday life skills, improves the functional adaptation of older adults with schizophrenia [125, 126] and decreases their short-term use of emergency medical services [127]. Meanwhile, a pilot study of Programa de Entrenamiento para el Desarrollo de Aptitudes para Latinos (PEDAL) [A Training Program to Develop Skills for Latinos] [128], a culturally modified version of FAST for older Latinos with chronic psychosis, indicates that PEDAL helps improve the everyday living skills of older Latino patients with chronic psychotic disorders up to 6–12 months.

Cognitive-behavioral therapy (CBT) and social skills training (SST) are evidence-based adjunctive therapies to psychopharmacologic treatment in younger adults with schizophrenia [129]. Randomized controlled trials (RCTs) of the combination of CBT and SST, called cognitive behavioral social skills training (CBSST), for adults with late-life schizophrenia indicated that CBSST led to better skills acquisition and self-reported functioning than did participation in standard care [130], with benefits persisting at 1-year follow-up [131]. Participants' neuropsychological test results did not mediate the improvement in functioning observed with CBSST [132]. A decrease in personal sense of hopelessness may explain the efficacy of CBSST in older adults with schizophrenia, suggesting that hopelessness might be a promising target in CBT for late-life schizophrenia [133].

Cognitive training (CT), also referenced as cognitive remediation, aims to improve the neuropsychological functioning of individuals with schizophrenia. Reviews of the literature on CT conclude that this treatment modality helps improve the everyday functioning, symptoms, and cognitive performance of adults with schizophrenia, especially when combined with pharmacologic and psychosocial interventions [134, 135]. Additionally, employment can add meaning and quality to life and many middle-aged and older adults with schizophrenia, often to many people's surprise, desire to work or volunteer. Research shows that supported employment, based on the principle of 'place then train' is more successful than is conventional work rehabilitation, based on the principle of 'train then place' [136]. Supported employment is effective at helping middle-aged and older people with schizophrenia obtain competitive employment with respective improvement in their quality of life [137]. Overall, numerous evidence-based psychosocial interventions help

improve the quality of life and functional status of older adults with schizophrenia when used in conjunction with pharmacotherapy.

Treating the Psychosis of AD

Pharmacotherapy Interventions—Much of the evidenced-based research on the treatment of psychosis in dementia focuses on pharmacotherapy, despite a general consensus that trials of psychosocial interventions are preferred before initiating medications due to the general lack of favorable risk-benefit profiles for pharmacotherapy in psychosis of dementia [138]. As older adults are more susceptible to extrapyramidal side effects and tardive dyskinesia caused by typical antipsychotics [120], atypical antipsychotics have become widely used in the treatment of psychosis with AD over the past decade. Yet, the evidence to support their use is mixed [139]. The CATIE-AD trial is the largest non-industry sponsored study of the use of atypical antipsychotics to treat psychosis and/or agitation/aggression in individuals with dementia [139] and its primary outcome measure was one of effectiveness (versus efficacy)—time to medication discontinuation for any reason. The authors of CATIE-AD [140] found no significant difference between placebo, risperidone, quetiapine, and olanzapine for all-cause discontinuation rate, but found that less people taking risperidone and olanzapine discontinued due to lack of efficacy. However, several studies more clearly support the efficacy of low dose risperidone (1mg–2mg) and olanzapine (5mg–10mg) in treating AD with psychosis [92, 141–143]. It is difficult to generalize the findings from these studies, as most were conducted in nursing homes, many contained patients with forms of dementia other than AD, and the majority was not designed explicitly to examine psychotic symptoms [144]. Not all studies have found risperidone and olanzapine to be efficacious in this population. For example, Deberdt and colleagues [145] found no difference in efficacy between placebo, olanzapine, and risperidone, but did find that risperidone was associated with increased frequency of elevated prolactin levels (78% compared to 16.7% for olanzapine and 5% for placebo) and that olanzapine was associated with increased frequency of weight gain. Meanwhile, a review of the literature on aripiprazole for psychosis of AD indicates that only 1 out of 3 existing RCTs found that aripiprazole was significantly more efficacious for addressing psychosis of AD than placebo [112]. Similarly, the data on cholinesterase inhibitors for the treatment of psychosis of AD is mixed, and even less sound in its clinical trial design [71]. The efficacy of atypical antipsychotics may be no different from that of typical antipsychotics, as evidenced by similar effect sizes (about 18%) found in meta-analyses of atypical and typical antipsychotics [146, 147]. In the survey previously described, the expert's first-line recommendation for the treatment of agitated dementia with delusions was risperidone 0.5 to 2mg/day followed by olanzapine 5 to 7.5mg/day and quetiapine 50 to 150mg/day [117].

In addition to their mixed efficacy, atypical antipsychotics use is complicated by their side effect profile and respective FDA black-box warnings. The FDA first issued a warning about atypical antipsychotics in 2003 entitled 'Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia'. An avalanche of similar warnings for various atypical antipsychotics including olanzapine and aripiprazole ensued, followed by warnings for an increased risk of mortality in patients receiving atypical antipsychotics. A meta-analysis of the data [146] indicated that the overall rates of cerebrovascular events (CVAEs) in patients treated with atypical antipsychotics was 1.9% versus 0.9% in placebo treated individuals, with a respective odds ratio of 2.1. Meanwhile, another meta-analysis [148] determined that the risk of mortality in patients receiving atypical antipsychotics was 3.5% compared to 2.3% in the placebo group, yielding an odds ratio of 1.5. Limitations in the data used to formulate the black box warnings abound. The studies were designed to determine efficacy, not CVAEs or mortality; the category of CVAEs was not operationally defined; substantial information regarding the specifics of the deaths was not available; and no clear

differences between the risks of atypical and typical antipsychotics have been discerned [139]. Yet, the known side effects, including metabolic symptoms, are alarming. In lieu of these adverse events and the lack of solid evidenced-based research regarding the treatment of psychosis in AD, Meeks and Jeste [149] conclude “When treatment becomes necessary, atypical antipsychotics are one of several off-label treatment options but, if chosen, should be used judiciously in the context of shared-decision making, close monitoring, and minimization of dose/treatment duration”. When antipsychotics are utilized, the treatment should be individualized. Low doses should be used over short periods of time with the eventual goal of discontinuation when possible.

Treatment Considerations for the psychosis of PDD and LBD—Special pharmacologic treatment decisions need to be considered with the psychosis of PDD and LBD. Worsening parkinsonism with the use of antipsychotics merits careful attention, especially since sensitivity to antipsychotic medications is one of the suggestive diagnostic features of LBD [97] and dopaminergic blockade can worsen parkinsonian symptoms in both conditions. For the psychosis of PDD, RCTs indicate that low dose clozapine (25 to 150mg) is efficacious without worsening parkinsonism symptoms, although clozapine is challenging to use in older adults because of its risk for agranulocytosis (necessitating frequent lab draws) and its potent anti-cholinergic properties [101, 150, 151]. Quetiapine is anecdotally the first-line treatment for psychosis in PD, but interestingly, RCTs comparing it to placebo do not strongly support its efficacy [152, 153]. Quetiapine was found to be just as effective as clozapine in one study [154] and its use has been supported by open-label trials [98]. Although not commonly considered for treating the psychosis associated with PD, small doses of Risperidone (0.25 to 1.25mg per day) have been shown to improve hallucinations without worsening Parkinsonism in a limited number of patients [155]. In a meta-analysis of studies on the treatment of psychosis in PD [156], only clozapine was clearly recommended as an evidence-based treatment. Nevertheless, clozapine is often not chosen first clinically because of the possibility for serious adverse events and the required close monitoring. Some evidence suggests that cholinesterase inhibitors may have antipsychotic properties in PD [98].

For the psychosis of LBD, cholinesterase inhibitors are the recommended first-line treatment considering their possible cognitive symptom benefit and relative lack of toxicity compared with antipsychotic medications [98]. In addition to worsening Parkinsonism, neuroleptic use in LBD patients has been associated with life-threatening adverse events in approximately half of exposed individuals [157]. In a very recent randomized control trial of citalopram and risperidone for the treatment of neuropsychiatric symptoms in LBD, both citalopram and risperidone were poorly tolerated and lacked clear efficacy [158]. As with PDD, when antipsychotics are used in LBD, quetiapine is often a first-line therapy, despite the overwhelming lack of supportive empirical evidence.

Psychosocial Interventions—In light of the black-box warnings and the conflicting efficacy data on the use of antipsychotics to address psychosis of dementia, psychosocial interventions are of particular interest. Yet, there is a clear dearth of literature guiding clinicians on the systematic use of psychosocial interventions [159, 160]. Ayalom and colleagues [161] organized nonpharmacologic interventions for dementia into 3 categories, which each assume a different etiology for the presenting neuropsychiatric symptoms. These include learning and behavioral (eg, a patient’s screaming behaviors become reinforced as they attract desired attention), unmet needs (eg, repetitive vocalizations serve as auditory stimulation), and environmental vulnerability and reduced stress-threshold (eg, too much noise results in agitation).

In their systematic review of the evidenced-based literature on non-pharmacologic interventions, Ayalon and colleagues [161] found only 3 RCTs meeting the strict inclusion criteria outlined by the American Psychological Association, all of which examined caregiving interventions. The results of these studies were inconclusive. Livingston et al. [159] also reviewed non-pharmacologic treatments for the neuropsychiatric symptoms of dementia and similarly found a paucity of high-quality studies. Of the 162 reviewed studies, they found that behavioral management and caregiver psycho-education techniques were efficacious over several months, whereas music therapy and sensory stimulation were only useful during the session, but lacked enduring efficacy. In contrast, repetitive exercise, reality orientation therapy, Montessori activities, and validation therapy did not improve the neuropsychiatric symptoms of dementia, at least based on the criteria utilized in the studies. Of course, as wisely quoted, absence of evidence is not evidence of absence [of efficacy] [139, 159].

Despite the dearth of evidence-based research into psychosocial interventions for dementia, lessons gleaned from clinical experience and the extant clinical research suggest clinicians first identify and address the potential underlying triggers for the psychosis and/or problematic behaviors. Physical symptoms (e.g. pain, urinary infections, or constipation), environmental triggers, and under- or over-stimulation can all serve as inciting factors [138, 161]. Underlying medical etiology and delirium always need to be considered when evaluating psychosis in people with dementia [160]. Cohen-Mansfield [160] cautions clinicians against assuming that individuals with dementia are experiencing psychosis when their behavior may actually be reflecting misinterpretations of reality based on memory deficits, sensory impairments, inappropriate sensory stimulation, or underlying medical causes. Overall, the approach should be individualized and patient-centered.

Future Research Directions

With the exponential aging of the population, the numbers of older individuals experiencing psychosis will likewise expand. As outlined in this article, late-life psychosis is associated with decreased quality of life, caregiver distress, institutionalization, and increased healthcare costs. Existing pharmacotherapy for late-life psychosis is far from ideal in light of its risky side effect profile, especially for the psychosis of dementia. Existing psychosocial therapies for psychosis of dementia are promising, but more evidence-based data on these therapies are needed to merit widespread implementation. There is thus a call for research into novel safe, well-tolerated, and efficacious pharmacotherapies for psychosis in late life. There is also a call for research into psychosocial interventions, especially for dementias since the high quality empirical evidence base is notably sparse. Recent research challenges the Kraepelinian notion of *dementia praecox* and should help dispel some of the stigma associated with the long-term prognosis of schizophrenia. Efforts to educate the public and health care providers in order to dispel myths about aging with schizophrenia would be worthwhile causes. Similarly, intergenerational dialogues between younger individuals with new-onset schizophrenia and older individuals who have aged with schizophrenia in the community may be fruitful. A prophylactic model is also warranted. The consistent finding that the best predictor of the long-term consequences of schizophrenia is the severity of symptoms in the first two years of illness should inspire continued research into early interventions for schizophrenia. Finally, clinicians who are providing pharmacotherapy to older adults with schizophrenia need better education about existing adjunctive evidence-based psychosocial interventions and how to integrate and implement these treatments. By building on the existing and future research, and ensuring we provide individualized, patient-centered care grounded in common sense principles, we can optimize the care of older adults with psychosis.

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Table 1

Comparison of Clinical Characteristics Among Various Diagnoses of Late-life Psychosis [1]

	EOS	LOS	VLOSLP	PoD
Schizophrenia family history	↑	↑	Ø	Ø
Dementia-like cognitive decline	Ø	Ø	↑	↑↑
Magnitude of necessary neuroleptic dose	↑↑	↑	↑	↑/Ø
Conclusive/specific brain MRI abnormalities	Ø	Ø	↑	↑/Ø
Female preponderance	Ø	↑	↑↑	Ø
Negative symptoms	↑↑	↑	Ø	Ø
Overall magnitude of cognitive impairment	↑	↑	↑↑	↑↑↑
Presence of minor physical anomalies	↑	↑	Ø	Ø
Preponderance of paranoid subtype	↑	↑↑	↑↑?	N/A
Thought disorder	↑/↑↑	↑	Ø	Ø
Prominence of visual (vs auditory) hallucinations	↑/Ø	↑	↑?	↑↑
Complex (>simple) delusions	↑↑	↑	↑?	↑/Ø

EOS = Early-onset schizophrenia; LOS = Late-onset schizophrenia; PoD = Psychosis of dementia; VLOSLP = Very late-onset schizophrenia-like psychosis

↑ = moderately present

↑↑ = strongly present

Ø = not present