

## Late-Life Psychosis: Diagnosis and Treatment

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**Abstract** Psychosis is one of the most common conditions in later life with a lifetime risk of 23 %. Despite its high prevalence, late-onset psychosis remains a diagnostic and treatment dilemma. There are no reliable pathognomonic signs to distinguish primary or secondary psychosis. Primary psychosis is a diagnosis of exclusion and the clinician must rule out secondary causes. Approximately 60 % of older patients with newly incident psychosis have a secondary psychosis. In this article, we review current, evidence-based diagnostic and treatment approaches for this heterogeneous condition, emphasizing a thorough evaluation for the “six d’s” of late-life psychosis (delirium, disease, drugs dementia, depression, delusions). Treatment is geared towards the specific cause of psychosis and tailored based on comorbid conditions. Frequently, environmental and psychosocial interventions are first-line treatments with the judicious use of pharmacotherapy as needed. There is an enormous gap between the prevalence of psychotic disorders in older adults and the availability of evidence-based treatment. The dramatic growth in the elderly population over the first half of this century creates a compelling need to address this gap.

**Keywords** Late-life psychosis · Geriatric psychosis · Psychosis · Geriatric · Elderly · Dementia · Neurocognitive disorders · Schizophrenia · Delirium · Primary psychotic disorders · Secondary psychotic disorders · Psychotic disorder due to another medical condition · Delusional disorder · Schizoaffective disorder · Major depressive disorder · Bipolar disorder · Substance/medication-induced psychotic disorder

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### Introduction



Ernst von Feuchtersleben has been credited with introducing the term “psychosis” in 1845 by combining the Greek “psyche” (life, soul, mind) and “osis” (an abnormal condition thereof), although Karl Friedrich Canstatt apparently used the term as early as 1841 [1]. In modern medical parlance, “psychosis,” according to the International Classification of Diseases, tenth revision (ICD-10), “simply indicates the presence of hallucinations, delusions, or a limited number of several abnormalities of behavior, such as gross excitement and overactivity, marked psychomotor retardation and catatonic behavior” [2]. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) aligns with the ICD-10, stating that psychotic disorders are defined by “abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms.” [3••]. However, in the appendix, the DSM-5 defines “psychotic features” as characterized by delusions, hallucinations, or formal thought disorder.

Late-life psychosis is strikingly prevalent in older adults, presenting in 5–15 % of elderly geropsychiatric inpatients, 10 to 62 % of nursing home patients, and as high as 27 % of community-dwelling psychiatric outpatients [4, 5]. The lifetime risk for psychotic symptoms in the elderly is up to 23 %, with dementia being the main contributing factor [4, 5]. Despite its widespread prevalence in older adults, late-onset psychosis frequently remains a diagnostic and treatment dilemma.



### Diagnosis and Treatment of Secondary Late-Life Psychoses

Psychoses can be either *primary* (caused by a psychiatric disorder) or *secondary* (due to a medical or neurological

disorder). About three fifths of psychotic disorders in later life are due to a secondary condition [4, 5]. The estimated prevalences of the conditions most commonly associated with late-life psychosis are listed in Table 1.

### History and Physical Examination

Accurate diagnosis of psychosis in the elderly is of critical importance, particularly given the presence of serious medical conditions that may masquerade as psychotic illness [6•, 7]. Because there are no pathognomonic signs to easily distinguish primary from secondary psychotic disorders, a primary psychotic disorder is the *final* consideration following the elimination of secondary causes of psychosis [3••]. A careful history and physical examination are the sine qua non of the workup of a psychotic disorder. Moreover, no diagnostic evaluation of late-life psychosis should be considered complete without collateral history.

A variety of risk factors associated with aging make older adults more prone to psychosis [8•]:

- Sensory deficits
- Social isolation
- Cognitive decline
- Medical comorbidities
- Polypharmacy
- Age-related changes in pharmacokinetics and pharmacodynamics
- Comorbid psychiatric illnesses such as dementia and delirium
- Age-related changes in cerebral structures such as frontotemporal cortices
- Neurochemical changes associated with aging

Clinical presentations that should raise suspicion of secondary causes of psychosis include [9] the following:

1. Unusual age of onset of the presenting psychiatric symptoms
2. An absence of family history of mental illness

3. An absence of past psychiatric history
4. Limited response to psychiatric treatment
5. Symptoms more severe than might be expected
6. Psychopathology developed following an abrupt personality change
7. Comorbid medical condition(s) with a known association with mental illness (psychosis)
8. Abnormalities of cognition, particularly memory and consciousness

There is no consensus approach for the initial diagnostic testing of psychotic illness in young or old adults [6•, 10]. Most clinicians conduct a complete blood count (CBC) and comprehensive metabolic panel (CMP) but also add thyroid-stimulating hormone (TSH), vitamin B<sub>12</sub>, folate, rapid plasma regain (RPR), and erythrocyte sedimentation rate (ESR). Autoimmune antibody screens, HIV testing, and toxicology may be done when indicated. Often, a head MRI or CT scan is done; EEG and polysomnography are done if indicated by history.

A useful way to think about the diagnosis of psychotic disorders is to use the “six d’s” approach, that distinguishes disorders based on the timeline of their presentation (see Table 1). In the sections that follow, we address each of the “d’s”.

### Delirium

Except for some minor rewording, the diagnosis of delirium in the DSM-5 has not changed from the DSM-IV-TR. It is a condition which often goes unrecognized and contributes to excess morbidity and mortality. A recent review by Inoue et al. noted a prevalence rate as high as 50 % among the hospitalized elderly in the intensive care unit [11••]. This same review and another recent meta-analysis by Witlox and coauthors [12] found that delirium had an appreciable impact on the relative risks of mortality, diagnosis of dementia, institutionalization, functional decline, and falls.

Perceptual disturbances are common during a delirium, with 40 to 70 % of elderly patients experiencing hallucinations

**Table 1** “Six d’s” of psychotic disorders [3•, 4, 123]

	Course	Proportion of all causes of psychoses	Type of psychoses
<b>Delirium</b>	Days to weeks	10 %	Secondary
Drugs, alcohol, toxins	Days to months	11 %	Secondary
<b>Disease</b>	Days to months	10 %	Secondary
Depression and other affective disorders	Weeks to months	33 % (depression) 5 % (bipolar)	Primary
<b>Dementia</b>	Months to years	40 %	Primary
Delusional disorder and schizophrenia-spectrum disorders	Months to decades	Delusions (2 %) Schizophrenia (1 %)	Primary

and 25 to 79 % experiencing delusions, depending on the subtype of delirium and the population being sampled [13•, 14, 15]. Psychosis is more common with patients experiencing the hyperactive variant of delirium; however, a recent study of oncology patients found prominent perceptual disturbances (50 %) and delusions (43 %) in hypoactive delirium [13•].

Factors that predispose to delirium include dementia, cognitive impairment, a previous history of delirium, a history of functional impairment, visual impairment, hearing impairment, comorbidities/severity of illness, depression, history of TIA/CVA, alcohol use disorders, and age >75 years [11•]. Importantly, a delirium episode is often the first sign of dementia. Rahkonen and colleagues [16] observed that dementia was diagnosed immediately after delirium symptoms had subsided in 27 % of patients and was present in 55 % of individuals on 2-year follow up.

The prompt diagnosis of the underlying etiology of delirium is essential. Validated screening tools for delirium such as the Confusion Assessment Method (CAM) and CAM-Severity (CAM-S) can be used [17, 18•]. EEG and neuroimaging need not be done routinely but should be ordered as indicated by the clinical features of a particular case. EEG has a typical pattern in delirium of diffuse slowing with increased theta and delta activity and poor organization of background activity, but this provides little insight into the underlying etiology [19]. Ordering an EEG may be most useful in difficult-to-evaluate cases, evaluating sudden deterioration in patients with dementia, and evaluating for non-convulsive status epilepticus or atypical partial complex seizures [11•].

Environmental and behavioral treatment strategies are best employed initially, with antipsychotic medications reserved only for severe agitation rather than as a standing medication [10]. If necessary, the best evidence suggests the use of oral or IM haloperidol or olanzapine for optimal patient outcomes and cost-effectiveness [20]. However, there is no FDA-approved pharmacologic treatment of delirium. Prevention and treatment strategies are covered extensively by guidelines (e.g., NICE, APA, and others) and recent review articles [11•, 21–24, 25•].

Disease

In DSM-5, all conditions attributable to other medical causes have been renamed from “[Condition] due to a general medical condition” to “[condition] due to another medical condition.” [3•]. The DSM-5 diagnosis of a psychotic disorder due to another medical condition requires the presence of delusions or hallucinations that are attributable through history, physical examination, or testing to another medical condition [3•]. The diagnosis is further specified according to the etiology and whether it is “with delusions” or “with hallucinations.” The prevalence is exclusive of delirium and

dementia. History and physical and neurological evaluations remain crucial to accurate diagnosis and treatment. While physical and neurological examinations are non-specific for primary psychoses, they may point to a secondary etiology of psychosis or conditions that may be exacerbating the primary disorder [26]. Table 2 lists potential medical etiologies of late-life psychoses. The acronym “MINE,” outlined in Table 2, is a useful mnemonic for recalling the principal medical etiologies. For an exhaustive reference on the diagnosis and potential causes of psychosis across the lifespan, we recommend the excellent book by Cardinal and Bullmore, *The Diagnosis of Psychosis* [27•].

**Table 2** Common medical causes of psychosis in older persons [8•, 19, 27•, 123, 124]

<b>Metabolic</b>	<ul style="list-style-type: none"> <li>• Vitamin B<sub>12</sub> deficiency</li> <li>• Folate deficiency</li> <li>• Electrolyte abnormalities                             <ul style="list-style-type: none"> <li>◦ Sodium</li> <li>◦ Potassium</li> <li>◦ Calcium</li> <li>◦ Magnesium</li> </ul> </li> <li>• Acute intermittent porphyria</li> <li>• Hepatic encephalopathy</li> <li>• Uremic encephalopathy</li> <li>• Other nutritional deficiencies</li> <li>• Anoxia/hypoxia</li> <li>• Hypercarbia</li> </ul>
<b>Infections</b>	<ul style="list-style-type: none"> <li>• Meningitides</li> <li>• Encephalitides (e.g., herpes, etc.)</li> <li>• Neurosyphilis</li> <li>• HIV/AIDS</li> <li>• Pneumonia</li> </ul>
<b>Neurological</b>	<ul style="list-style-type: none"> <li>• Parkinson’s disease</li> <li>• Epilepsy                             <ul style="list-style-type: none"> <li>◦ Temporal lobe epilepsy</li> <li>◦ Grand mal</li> <li>◦ Non-convulsive status epilepticus</li> </ul> </li> <li>• Subdural hematoma</li> <li>• Cerebrovascular events</li> <li>• Huntington’s disease</li> <li>• Multiple sclerosis</li> <li>• Amyotrophic lateral sclerosis</li> <li>• Tumors                             <ul style="list-style-type: none"> <li>◦ Temporal lobe—auditory hallucinations</li> <li>◦ Occipital lobe—visual hallucinations</li> <li>◦ Limbic—delusions</li> <li>◦ Hypothalamus—delusions</li> </ul> </li> <li>• Limbic encephalitides</li> <li>• Autoimmune<sup>reference</sup> <ul style="list-style-type: none"> <li>◦ Paraneoplastic syndromes</li> <li>◦ Systemic lupus erythematosus</li> <li>◦ Vasculitides</li> </ul> </li> <li>• Sleep disorders (narcolepsy)</li> <li>• Other genetic/heritable conditions                             <ul style="list-style-type: none"> <li>◦ Likely to have been diagnosed in childhood</li> </ul> </li> </ul>
<b>Endocrine</b>	<ul style="list-style-type: none"> <li>• Hypo-/hyperthyroidism</li> <li>• Adrenal disease</li> <li>• Hypo-/hypoglycemia</li> <li>• Hypo-/hyperparathyroidism</li> </ul>

The treatment of these conditions should be based on addressing the underlying medical condition. Behavioral and environmental strategies should be first-line treatments for these psychoses; however, short-term treatment with antipsychotic medications may be indicated due to symptom severity. This treatment should be time limited and dose limited and medication choice tailored to the needs of the specific patient.

According to general expert guidance on medication choice in the elderly, for patients with major metabolic conditions (diabetes, dyslipidemia, obesity), it is best to avoid clozapine, olanzapine, and conventional antipsychotic medications [28]. In the case of congestive heart failure or prolonged QTc, clozapine, ziprasidone, and conventional antipsychotics should be avoided [28]. Risperidone (first line) and quetiapine (second line) are the medications of choice in cases with comorbid obesity, cognitive impairment, diabetes, diabetic neuropathy, xerostomia, xerophthalmia, or dyslipidemia [28].

### Drugs, Alcohol, and Toxins

The problematic use of substances (illicit or prescribed) remains an under-recognized problem in the elderly [29]. While drug and alcohol use might continue to be less prevalent than in other age groups, the overall prevalence in the elderly is rising [30•, 31]. Recent predictive modeling estimates that the prevalence of substance use disorders in adults 50 and over (across genders, race groups, and age groups) will double from 2.8 million (average) in 2002–2006 to 5.7 million by 2020 [31]. This is attributable to the aging of the baby boomers who have a higher lifetime rate of alcohol and drug use than previous generational cohorts [31].

According to DSM-5, psychosis resulting from substance use is termed a substance/medication-induced psychotic disorder [3••]. Multiple substances have been associated with psychosis according to DSM-5. The diagnosis of a substance/medication-induced psychotic disorder is established by the presence of delusions and/or hallucinations and is attributable to substance intoxication or withdrawal through a plausible substance/medication mechanism [3••]. Screening for problematic drug and alcohol use is vital to accurate diagnosis in this population. The CAGE consists of only four questions but is a useful and validated tool for detecting alcohol misuse in elderly populations [32]. Urine toxicology should be conducted to evaluate for drug usage.

During intoxication, the following substances and substance classes are considered psychotogenic [3••]:

- Alcohol
- Cannabis
- Phencyclidine
- Other hallucinogens
- Inhalants

- Sedatives, hypnotics, or anxiolytics
- Stimulants (inclusive of amphetamine-type substances, cocaine, or other unspecified stimulants)
- Other/unknown substances

During withdrawal, the following substances/classes of substance have been implicated [3••]:

- Alcohol
- Sedatives, hypnotics, or anxiolytics
- Other/unknown substances

In theory, any medication that crosses the blood-brain barrier could induce psychotic symptoms; however, certain medications and classes of medications have been more commonly associated with psychosis [8••]:

- Antiparkinson drugs
- Anticholinergic drugs
- Cimetidine
- Digoxin
- Antiarrhythmic drugs
- Corticosteroids
- Interferon

There are no controlled studies on the treatment of substance/medication-induced psychotic disorders in the elderly. Whenever possible, the safe withdrawal (or dosage decrease) of the offending substance/medication should be initiated as first-line treatment. Psychosocial interventions should be encouraged such as motivational enhancement therapy, CBT, and support groups for substance cessation although many of these approaches are not validated in the elderly population [33••]. Of the pharmacologic approaches for substance cessation, naltrexone has the most evidence supporting its use in the elderly [33••].

### Dementia (Now: Neurocognitive Disorders)

Psychosis is found most commonly among persons with neurocognitive disorders. In the instances in which patients present with cognitive changes and psychotic illness, reversible causes of cognitive decline and associated psychosis must be addressed initially. Moreover, during the evaluation of a neurocognitive disorder with psychotic symptoms, careful attention must also be paid to the presence of sensory deficits, particularly visual impairment, that may contribute to the presence of psychotic symptoms [34•].

There have been extensive changes in the DSM-5 nomenclature [3••]. Previously called “dementias,” the neurocognitive disorders are classified according to neurocognitive domains and the characteristic deficits of these



domains within specific disorders. Deficits must be present in at least one of the following neurocognitive domains:

- Complex attention
- Executive function
- Learning and memory
- Language
- Perceptual motor
- Social cognition

The diagnosis has been subdivided into “major” and “mild” forms. The diagnostic criteria of a major neurocognitive disorder are based on a significant decline of cognitive function from the previous level of performance in one or more of the cognitive domains whereas mild neurocognitive disorder requires a less severe decline in at least one neurocognitive domain with no appreciable decline of function.

The prevalence of psychotic symptoms in Alzheimer’s disease ranges from 16 to 70 % (median 37 %) for delusions and 4 to 76 % (median 23 %) for hallucinations [35, 36, 37, 38]. The rates of psychoses vary by the stage of illness. It is found most commonly in the middle stages of the illness, with a 20 % rate in the early stages of Alzheimer’s disease and up to 50 % by the third or fourth years of illness (overall 30 to 50 %) [35, 36, 37, 38].

Visual hallucinations are the most common type of hallucination in Alzheimer’s disease patients, followed by auditory and, less commonly, other types (olfactory, tactile, gustatory) [36]. This differs from primary psychoses where auditory hallucinations are most common. The hallucinations experienced most commonly involve people from the past (e.g., deceased relatives), intruders, animals, and objects. The most frequent types of delusions experienced during the course of Alzheimer’s disease are false beliefs of theft, infidelity of one’s spouse, beliefs of abandonment, believing that their house is not their home, and persecution [36]. Delusions tend to decrease in later stages. Some symptoms, although appearing to be delusions or hallucinations, may be misidentifications due to cognitive deficits, e.g., mirror sign (mistakes self in mirror for someone else) and TV/magazine sign (belief that people on TV or in magazines are present and real) [36].

There is increasing evidence supporting a subtype of Alzheimer’s disease based on the presence of psychotic symptoms that has an association with dopamine receptor gene alleles, an increased density of plaques and tangles in the prosubiculum and frontal cortex, APOe genotypes, and differences in neurotransmitter concentrations [39, 40]. The anterior cingulum has recently been implicated in the presence of certain neuropsychiatric symptoms, particularly irritability, apathy, agitation, dysphoria, and nighttime behavioral disturbances [41, 42].

Psychosis associated with vascular dementia has been found to be epidemiologically similar with some

phenomenological differences. The Cache County study found the prevalence of hallucinations to be similar between Alzheimer’s disease and vascular dementia, while delusions were found to be more prevalent in Alzheimer’s disease versus vascular dementia (23 vs 8 %) [43].

Neurocognitive disorder with Lewy bodies (NCDLB) also known as dementia with Lewy bodies has three main classes of neuropsychiatric symptoms: visual hallucinations, misidentification syndromes, and delusions [44]. Most common are visual hallucinations with prevalence rates of 25 to 83 %, while delusions have reported rates between 13 and 75 % of patients [45]. Recent studies have reported 29 to 50 % rate of misidentification syndromes such as Capgras syndrome or phantom boarder syndrome in NCDLB [45–47]. The rate of misidentification syndromes was found to have a 4 % point prevalence and 22 % period prevalence for patients with Alzheimer’s disease, making this a useful clinical diagnostic indicator [47]. Approximately 43 % of patients with NCDLB have visual hallucinations in the earliest phases of the illness. Early visual hallucinations with or without clinically meaningful cognitive decline should always raise the suspicion of Lewy body disease [45].

Psychosis is also a common sequelae of Parkinson’s disease and neurocognitive disorder due to Parkinson’s disease. While the hallucinations of Parkinson’s disease (approximately 25 %) have been described as benign hallucinosis and remarkable for retained insight, the hallucinations of neurocognitive disorder due to Parkinson’s disease (previously Parkinson’s disease with dementia or PDD), seen in about 60 % of these patients, have been described as more complex and distressing, and present with a general loss of insight [48]. Visual hallucinations are more common than delusions in PDD patients [49]. As with the other neurocognitive disorders, these symptoms worsen prognosis, intensify caregiver distress, and increase the likelihood for institutionalization [50]. It is important to underscore the need to rule out extrinsic causes of hallucinations, i.e., antiparkinson’s medication/dopaminergic agents.

Given the multitude of studies that have described issues with the safety profiles of medications used to treat psychosis in the elderly, the consensus across the varied guidelines is a uniform recommendation for first-line non-pharmacological approaches [51, 52]. Every effort should be made to institute these treatments first, particularly in cases in which patients themselves are without subjective distress related to their psychotic symptoms. Moreover, it is important to alleviate “unmet needs” such as sensory deficits (e.g., hearing aids, glasses), social isolation of patients, environmental over- or under-stimulation, and so forth [51, 52].

Psychosocial strategies for dementia with the strongest evidence at present include alleviating caregiver burden (caregiver education, support systems), music therapy, cognitive stimulation therapy, Snoezelin therapy (multisensory stimulation), behavioral management (by professionals), and staff

training/education [51••, 52••]. Less convincing evidence exists for strategies such as reality orientation, caregiver-instituted behavioral management, validation therapy, reminiscence therapy, therapeutic activity programs, and physical environment stimulation strategies [51••, 52••].

When these first-line approaches have failed, and moderate or greater symptoms remain, pharmacologic approaches should be considered. This remains the consensus recommendation despite the associated risks of these approaches. The first step of a rational, evidence-based psychopharmacologic approach to psychotic symptoms in dementia should include the appropriate use of acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and memantine. Beyond their modest benefits for cognition, these medications have been shown to reduce behavioral symptoms (including psychosis) and possibly decrease the need for additional pharmacologic agents [53, 54, 55••].

When initial treatments fail, consideration should be given to the use of antipsychotic medications. Following the 2005 publication of a large meta-analysis noting an increased (OR 1.7) risk of mortality in patients with dementia with psychosis treated with atypical antipsychotic medications, the FDA issued a black box warning regarding the use of antipsychotic medications in this population [56]. It should be noted that the absolute increase in mortality is approximately 1 in 50 to 1 in 100 patients. Principal causes of mortality are cardiovascular, infectious, and cerebrovascular causes [56, 57]. There is controversy in the literature with some studies finding no increases in mortality, that the mortality risk may be associated with higher doses of medication, and that some medications may be safer, e.g., quetiapine has the lowest associated mortality rates [58, 59••]. Of note, data from the CATIE-AD trial have revealed an increased decline in cognition in those treated with atypical antipsychotics versus those treated with placebo [60••].

Perhaps due to a dearth of effective alternatives and the modest effectiveness of some of these medications, their carefully weighed use continues to be a part of expert guidelines [61–64]. The neuropsychiatric symptom domains which appear to improve differentially with antipsychotic treatment are anger, aggression, and paranoid ideation while functional abilities, care needs, and quality of life do not seem to improve [65].

Recommendations for antipsychotic treatment in the elderly include (ranging from starting dose to maximum target dose) [66, 67••] the following:

- Risperidone 0.25 to 1.5 mg daily
- Olanzapine 2.5 to 10 mg daily
- Quetiapine 12.5 to 200 mg daily
- Aripiprazole 2.5 to 12.5 mg daily

Antidepressant medications have shown promise, particularly sertraline and citalopram, for the treatment of behavioral

disturbances in neurocognitive disorders and are tolerated well when compared to antipsychotic medications and placebo [68••]. Carbamazepine has shown utility in small studies for the treatment of agitation in neurocognitive disorders, but potential adverse effects frequently outweigh benefits [69, 70]. Prazosin has one positive study for the treatment of agitation in neurocognitive disorders, but further research is needed [71].

Targeted treatment for patients suffering from Parkinson's disease (PD) or NCDLB and secondary psychosis must be initiated cautiously due to a much-heightened risk of extrapyramidal symptoms in these patients. It is critical to adjust antiparkinson's medications before initiating antipsychotic medications, starting with medications with the least effectiveness, as many of these medications may induce psychosis [72, 73••]. Typical antipsychotic medications should not be used in these patient populations. Clozapine has the most consistent evidence for efficacy in the PD population although its use has been limited by concerns about agranulocytosis, anticholinergic side effects, orthostatic hypotension, and the need for blood monitoring [72, 74]. Quetiapine has inconsistent evidence for its benefit in this population but is still used preferentially over clozapine because of the aforementioned concerns [72, 74]. Dosing ranges recommended for PD and NCDLB patients are [52••] the following:

- Clozapine 6.25 to 50 mg
- Quetiapine 12.5 to 150 mg

Donepezil and rivastigmine have shown some benefits for the treatment of psychosis in the PD population [72]. Recently, pimavanserin, a serotonin inverse agonist, successfully completed phase 3 trials and has been shown to have a greater decrease in Scale for Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD) scores compared to placebo [75••].

#### Diagnosis and Treatment of Primary Late-Life Psychoses

The diagnosis and treatment of primary late-life psychotic disorders should proceed only after the evaluation for secondary late-life psychotic disorders is complete. Clinicians should remember the pre-diagnostic probability in the elderly—three fifths of psychoses are secondary psychoses—and be willing to revisit their assessments as more information becomes available.

#### Depression and Other Affective Disorders with Psychotic Features

##### Major Depressive Disorder

Major depressive disorder (MDD) is common in the late life, with roughly 4 to 7% aggregate prevalence in adults 55 years

old and older [76, 77, 78]. Data from the National Comorbidity Survey Replication indicates a 12-month prevalence of 2.6% and a lifetime prevalence of 9.8% in adults 65 years and older [78]. When MDD was combined with minor depression and depression treatment status in adults 71 years and older, overall prevalence of clinically meaningful depressive symptoms rose to 11% [79]. In the DSM-5, the presence or absence of psychoses is indicated with a diagnostic specifier, “with psychotic features” that may be further detailed using the specifiers “with mood [congruent] psychotic features” or “with mood [incongruent] psychotic features [3••].

Older persons with MDD are more likely to have psychotic features and be resistant to treatment than their younger counterparts [80, 81]. Psychotic depression occurs in 20 to 45% of hospitalized elderly depressed patients and 15% of community-dwelling depressed persons. Rates of psychosis do not seem to differ between those elderly subjects with an early-onset (before age 60) and those with a late-onset (age 60 and above) depression. Delusions are the most common psychotic symptom in late-life depression with psychotic features, and they are most often mood congruent, e.g., delusions of guilt, delusions of deserved punishment for moral or personal inadequacies, delusions of nihilism, somatic delusions, and delusions of poverty. Auditory hallucinations are less common and not easily described by patients, e.g., vague derogatory voices [82].

A complete medical workup should be conducted, and alternative psychiatric diagnoses should be ruled out prior to this diagnosis. The differential diagnoses rely heavily on patient and collateral history. Hearing the voices of lost loved ones is very common in the bereaved elderly and in some cases has been reported to be a helpful phenomenon [83]. Once the diagnosis is established, treatment must be considered. In older adults, electroconvulsive therapy (ECT) may be most effective and limit the need for additional pharmacotherapy; however, research is necessary before a definitive statement can be made [84]. In particular, the greater the degree of frailty, the more likely ECT should be chosen as a first-line treatment [85].


When ECT is not possible, the best evidence for the pharmacologic treatment of the psychotically depressed elderly is combination therapy of an antidepressant and an antipsychotic medication. The only RCT that has been published on this topic noted the superiority of olanzapine plus sertraline in obtaining remission in the elderly [86]. Augmentation with psychotherapy and psychosocial treatments should be considered. Cognitive behavior therapy, problem solving therapy, interpersonal therapy, and supportive therapy are the most often cited, while CBT is the most studied and has the best evidence for its effectiveness [87].

### Bipolar Disorder

The prevalence of bipolar disorder in the elderly is estimated to be between 0.25 and 1% [88–90]. There are two peaks for

bipolar illness [91]. A majority of cases are diagnosed in the second to fifth decades of life, and a second peak occurs at age 65 and over [91]. In elderly inpatients with bipolar disorder, the mean prevalence of late-onset mania was 44% [91]. Those patients with late-onset bipolar disorder may represent a distinct subset of bipolar disorder [92, 93]. Studies of psychosis during late-life bipolar disorder are limited and conflicting, with one study finding increased depressive episodes with psychotic features and another finding no difference in the prevalence of psychosis between late-life patients and their younger counterparts [94, 95].

Because of the paucity of treatment studies in this age group, clinical interventions are extrapolated from those of non-elderly adult bipolar disorder. There is an on-going study of the treatment of acute mania, treatment of bipolar mania in older adults study (GERI-BD) examining the use of divalproex and lithium in the elderly [96]. To date, the GERI-BD study has revealed the positive effects of socialization on outcomes [97•]. It has also identified ethnicity (non-Hispanic Caucasian), symptom severity, and past psychopharmacologic treatments as factors increasing the likelihood of inpatient psychiatric treatment and a lack of associations between lifetime bipolar disorder and cognitive decline [98•, 99]. Another study examining age-group differences in bipolar disorder found a higher prevalence of disordered thought content in older adults versus a higher rate of aggression and irritability in younger adults [100•].

Sajatovic and Chen’s review of geriatric bipolar disorder provides an excellent summary of the treatment literature [101]. To target psychosis occurring in the context of acute mania, all the current atypical antipsychotic medications (except clozapine) are indicated for use. The olanzapine-fluoxetine combination has strong evidence for its use in mixed bipolar patients. 

### Delusional Disorder and Schizophrenia-Spectrum Illnesses

#### Schizophrenia

An important change in the DSM-5 from previous editions was the elimination of the subtypes of schizophrenia (paranoid, disorganized, undifferentiated, residual, and catatonic) due to their “limited diagnostic stability, low reliability, and poor validity” [3••]. Also eliminated were the symptoms that established the diagnosis of schizophrenia by their sole presence such as bizarre delusions and Schneiderian hallucinations. When establishing the diagnosis of schizophrenia, special attention should be paid to differentiating other DSM-5 disorders with psychotic features (major depression, bipolar disorder, schizoaffective disorder), delusional disorder, and personality disorders (schizoid and schizotypal personality disorders).

A review of studies of late-onset schizophrenia found that approximately 20 to 25 % of patients with schizophrenia were reported to have experienced the onset of the disorder after age 40, while the remaining four fifths of elderly patients with schizophrenia experienced early onset [102, 103]. Today, with greater numbers of schizophrenia patients surviving into old age, the prevalence estimates for schizophrenia in adults aged between 45 and 60 are approximately 0.6 to 1 % and 0.1 to 0.5 % in persons aged 65 plus [104–108]. By 2025, about one fourth of persons with schizophrenia will be age 55 and over [109].

Although neither the DSM-5 nor ICD-10 distinguishes by age of onset, the International Late-Onset Schizophrenia Group proposed that schizophrenia be termed “Late-Onset Schizophrenia” and “Very Late Onset Schizophrenia-Like Psychosis” for disorders that begin with an onset between age 40 and 60 and after the age of 60, respectively [110]. The former is considered similar to the early-onset disorder although there is greater preponderance of women. The very late disorder has features that suggest a neurodegenerative component including more brain abnormalities and neuropsychological deficits and is also distinguished from the other two types by many more females; greater prevalence of persecutory and partition delusions; higher rates of visual, tactile, and olfactory hallucinations; lower genetic load; more sensory abnormalities; and the absence of negative symptoms or formal thought disorder [110].

Jeste et al. have described an exaggerated “paradox of aging” among older adults with schizophrenia [111]. People with schizophrenia, when compared to the general population, have accelerated physical aging, including increased and earlier medical comorbidity and mortality; however, their cognitive aging rate remains normal following an initial, persistent occurrence of mild neurocognitive disorder [112]. Conversely, as these patients age, psychosocial function improves, psychosis decreases, relapse and hospitalization rates decrease, self-management improves, and they experience an improvement in their quality of well-being [112].

### Schizoaffective Disorder

With the publication of DSM-5, the diagnosis of schizoaffective disorder was reformulated as a longitudinal condition, more in keeping with other major psychiatric disorders [3•]. The diagnosis now requires the presence of a major mood component during the “majority” of the lifetime duration of illness rather than only episodically as in DSM-IV-TR. The diagnosis is established once an uninterrupted period of illness includes a major mood episode concurrently with schizophrenia criteria. Delusions or hallucinations must occur in the absence of a mood episode for at least 2 weeks at any point during the course of the illness. The disorder is further classified into bipolar and depressed types.

The clinical features and risks of late-life schizoaffective disorder were first discussed in 1971 by Post, who noted their frequent treatment-refractory condition, risk of suicide, and severe illness [113]. A more recent retrospective chart review confirmed Post’s original findings, further noting an increased risk of suicide attempts in depressed versus bipolar-type patients greater than 60 years old [114•].

### Delusional Disorder

Delusional disorder, according to DSM-5, is diagnosed by the presence of one or more delusions for greater than 1 month [3•]. Diagnostic criteria for schizophrenia or schizoaffective disorder must not be met. Further classification is made by subtype of delusion, e.g., erotomanic, grandiose, jealous, persecutory, somatic, and mixed.

There is a paucity of literature regarding delusional disorders in the elderly. Studies indicate a prevalence of 0.03 % in the elderly, with women slightly more affected than men [115]. There are no clear neuroanatomical changes associated with delusional disorder. There is mixed evidence that hearing or visual abnormalities might play a role in the development of delusional disorder, with Maher observing that a subset of patients develops delusions in the context of sensory impairment [116].

### Treatment

There has been a paucity of studies devoted to the pharmacological treatment of older adults with schizophrenia. A Cochrane review of antipsychotic medications for elderly people (age 65+) with schizophrenia found only three RCTs involving 252 persons. One involved drugs that are no longer available. The other studies found no differences between risperidone and olanzapine and olanzapine and haloperidol [117].

Evidence-based treatment of late-onset schizophrenia is based primarily on findings of early-onset individuals who survived into later life. The most recent Cochrane review conducted in 2012 found no “good quality” data to support the use of antipsychotic medications in the late-onset or very late-onset schizophrenia [118]. One trial was found “acceptable,” a controlled study of risperidone and olanzapine, but did not provide enough usable data to make conclusions [118, 119].

On the other hand, there is considerable clinical experience using risperidone, olanzapine, aripiprazole, and clozapine for the treatment of late-life schizophrenia [28, 52•, 119]. Consensus guidelines currently recommended for schizophrenia in older adults are as follows [28]:

- First line: risperidone 1.25 to 3.5 mg/day
- Quetiapine 100 to 300 mg/day



- Olanzapine 7.5 to 15 mg/day
- Aripiprazole 15 to 30 mg/day

Starting dosages for late-onset persons should be at 25 % of the recommended adult dose and maintenance doses at 25–50 % of the adult dose. Often, effective doses for early onset can be 50–75 % of younger patients.

There are few specific treatment studies of late-life schizoaffective disorder, and most include this group with the treatment of late-life schizophrenia [118]. As noted above, a cautious approach is recommended with the smallest effective dosage of antipsychotic medication with adjunctive treatment based on their subtype of illness and according to the consensus guidelines for adults. Mood-stabilizing medications (lithium, divalproex, carbamazepine, lamotrigine) and antidepressants should be used judiciously and in the minimum effective dosages.

There are no available studies on the treatment of late-life delusional disorder. Expert consensus guidelines recommend the use of atypical antipsychotic medications as follows [28, 52••]:

- First line: risperidone 0.75–2.5 mg/day
- Olanzapine 5–10 mg/day
- Quetiapine 50–200 mg/day

The adage of geriatric psychiatry, “start low, go slow,” should be heeded when initiating antipsychotic treatment. Elders are prone to adverse effects including cardiovascular, metabolic, sedation, anticholinergic burden, extrapyramidal symptoms, tardive dyskinesia, orthostatic hypotension, metabolic changes, falls, hyperprolactinemia, agranulocytosis, and neuroleptic malignant syndrome [52••, 120]. To ensure their safety, patients should be monitored regularly with a complete blood count, comprehensive metabolic panel, lipid panel, hemoglobin A1C, electrocardiogram, orthostatic vital signs, abnormal involuntary movement scale, and weight checks.

Psychosocial treatments should be used adjunctively to pharmacologic treatment in the elderly to better target deficits in social and occupational functioning. Recent studies have found that Functional Adaptation Skills Training, cognitive behavior therapy, social skills training, cognitive behavioral social skills training, and cognitive training (cognitive remediation) are useful approaches for the treatment of patients with schizophrenia [121, 122].

## Conclusion

In summary, psychosis is among the most common experiences in later life with a lifetime risk of 23 % among older persons. Elderly patients with late-life-onset psychosis require

careful evaluation. There are no reliable pathognomonic signs to distinguish primary or secondary psychosis. Primary psychosis is a diagnosis of exclusion, and the clinician must rule out secondary causes. Roughly three out of five older patients with newly incident psychosis have secondary psychoses. Thus, every new-onset psychoses or appreciable change in symptoms necessitates a medical workup. It is useful to remember the “six d’s” of late-life psychosis (Table 1) in formulating a differential diagnosis and the acronym “MINE” to trigger a list of potential medical diagnoses associated with secondary psychosis (Table 2).

Treatment is geared towards the specific cause of psychosis and tailored based on comorbid conditions. Frequently, environmental and psychosocial interventions are first-line treatments in late-life psychoses. Caution should be exercised in all elderly patients when initiating pharmacotherapy for psychosis, particularly antipsychotic medications because of their association with increased morbidity and mortality. Each additional pharmacologic agent adds to the medication burden for elderly patients already at risk for adverse events because of polypharmacy.

Finally, there is a remarkable gap between the prevalence of psychotic disorders in older adults and the availability of evidence-based treatment. The dramatic growth in the elderly population over the first half of this century creates a compelling need to address this gap.

## Compliance with Ethics Guidelines

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Burgy M. The concept of psychosis: historical and phenomenological aspects. *Schizophr Bull.* 2008;34:1200–10.
2. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. 1992.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition. Arlington (VA): American Psychiatric Association. 2013. *The newly published and updated version of the Diagnostic and Statistical Manual of the American Psychiatric Association.*

4. Holroyd S, Laurie S. Correlates of psychotic symptoms among elderly outpatients. *Int J Geriatr Psychiatry*. 1999;14:379–84.
5. Webster J, Grossberg GT. Late-life onset of psychotic symptoms. *Am J Geriatr Psychiatry*. 1998;6(3):196–202.
6. Javadpour A, Sehatpour M, Mani A, Sahraian A. Assessing diagnosis and symptoms profiles of late-life psychosis. *J Gerontopsychol Geriatr Psychiatry*. 2013;26(4):205–9. *A study of 201 elderly people with psychosis indicating the heterogeneous etiologies of late-life psychosis*.
7. Freudenreich O. Differential diagnosis of psychotic symptoms: medical mimics. *Psychiatr Times*. 2010;27(12):56–61.
8. Brunelle S, Cole MG, Elie M. Risk factors for the late-onset psychoses: a systematic review of cohort studies. *Int J Geriatr Psychiatry*. 2012;27(3):240–52. *A recent systematic review of the risk factors for late-onset psychosis, indicating positive associations with history of psychotic symptoms, cognitive problems, poor health status, visual impairment, and negative life events. No association was found with female gender*.
9. Marsh CM. Psychiatric presentations of medical illness. *Psychiatr Clin N Am*. 1997;20(1):181–204.
10. Freudenreich O, Charles Schulz S, Goff DC. Initial medical work-up of first-episode psychosis: a conceptual review. *Early Interv Psychiatry*. 2009;3(1):10–8.
11. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911–22. *An up-to-date of review covering the state of delirium risk, diagnosis, prognosis, and treatment*.
12. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, Van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010;304(4):443–51.
13. Boettger S, Breitbart W. Phenomenology of the subtypes of delirium: phenomenological differences between hyperactive and hypoactive delirium. *Palliat Support Care*. 2011;9(02):129–35. *A study indicating a much higher prevalence of perceptual disturbances and delusions in hypoactive delirium than had previously been reported*.
14. Meagher DJ, Moran M, Raju B, Gibbons D, Donnelly S, Saunders J, et al. Phenomenology of delirium: assessment of 100 adult cases using standardised measures. *Br J Psychiatry*. 2007;190(2):135–41.
15. Webster R, Holroyd S. Prevalence of psychotic symptoms in delirium. *Psychosomatics*. 2000;41(6):519–22.
16. Rahkonen T, Luukkainen-Markkula R, Paanila S, Sivenius J, Sulkava R. Delirium episode as a sign of undetected dementia among community dwelling elderly subjects: a 2 year follow up study. *J Neurol Neurosurg Psychiatry*. 2000;69(4):519–21.
17. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113:941–8.
18. Inouye SK, Kosar CM, Tommet D, Schmitt EM, Puelle MR, Saczynski JS, et al. The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts. *Ann Intern Med*. 2014;160(8):526–33. *Results from the development and validation of a new severity measure for delirium (CAM-S), showing that as severity scores increased, length of stay, nursing home admissions, and mortality also increased*.
19. Jacobson S, Jerrier H. EEG in delirium. *Semin Clin Neuropsychiatry*. 2000;5:86–92.
20. Desai AK, Grossberg GT. Differential diagnosis of psychotic disorders in the elderly. In: Cohen CI, editor. *Schizophrenia into later life*. Washington: American Psychiatric Publishing; 2003.
21. National Institute for Health and Care Excellence. Dementia. CG103. London: National Institute for Health and Care Excellence. 2010.
22. Trzepacz, P., Breitbart, W., Franklin, J., Levenson, J., Martini, D. R., & Wang, P. Practice guideline for the treatment of patients with delirium. *American Journal of Psychiatry*, 1999;156.
23. Cook, I. Guideline watch: practice guideline for the treatment of patients with delirium. *APA Practice Guidelines*. American Psychiatric Publishing, Inc. 2010.
24. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing*. 2006;35(4):350–64.
25. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing*. 2011;40(1):23–9. *A systematic review of medications associated with delirium; revealing statistically significant increased risk for: opioids, benzodiazepines, dihydropyridines, and possibly antihistamines; no increased risk was found with digoxin and neuroleptics. Uncertain change of risk status was found H2 antagonists, tricyclic antidepressants, antiparkinson medications, steroids, non-steroidal anti-inflammatory drugs and antimuscarinics. Conclusions are limited by the relatively small number of included studies (14), having eliminated 18,753 other studies uncovered by their search method*.
26. Johnstone EC, Cooling NJ, Frith CD, et al. Phenomenology of organic and functional psychoses and the overlap between them. *Br J Psychiatry*. 1988;153:770–6.
27. Cardinal RN, Bullmore ET. The diagnosis of psychosis. New York: Cambridge University Press; 2011. *A comprehensive textbook on the diagnosis of psychosis across the life span. Provides an extensive differential diagnosis of potential conditions associated with secondary psychosis*.
28. Alexopoulos GS, Streim JE, Carpenter D. Expert consensus guidelines for using antipsychotic agents in older patients. *J Clin Psychiatry*. 2004;65:5–99.
29. Atkinson RM. Aging and alcohol use disorders: diagnostic issues in the elderly. *Int Psychogeriatr*. 1990;2(1):55–72.
30. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: summary of national findings. NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville (MD): Substance Abuse and Mental Health Services Administration. 2013. *The most recent national survey on drug use and health*.
31. Han B, Gfroerer JC, Colliver JD, Penne MA. Substance use disorder among older adults in the United States in 2020. *Addiction*. 2009;104:88–96.
32. Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse. *Wis Med J*. 1995;94:135–40.
33. Kuerbis AN, Sacco P. A review of existing treatments for substance abuse among the elderly and recommendations for future directions. *Subst Abus*. 2013;7:13–37. *A review of the current literature on late-life substance abuse and treatments. Continued study is urgently needed and the review notes that like their younger counterparts, treatment response is heterogeneous*.
34. Brunelle S, Cole MG, Elie M. Risk factors for the late-onset psychoses: a systematic review of cohort studies. *Int J Geriatr Psychiatry*. 2012;27(3):240–52. *A systematic review of cohort studies, revealing limitations of all studies included but some evidence that a history of psychotic symptoms, cognitive problems, poor physical health, visual impairment, and negative life events are risk factors for late-onset psychosis*.
35. Paulsen JS et al. Incidence of and risk factors for hallucinations and delusions in patients with probable AD. *Neurology*. 2000;54(10):1965–71.
36. 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*. 2005;162:2022–30.
37. Ostling S, Gustafson D, Blennow K, Borjesson-Hanson A, Waern M. Psychotic symptoms in a population-based sample of 85-year-old individuals with dementia. *J Geriatr Psychiatry Neurol*.

- 2011;24(1):3–8. *A large population based study (n=495) of Swedish adults aged 85 and over diagnosed with dementia showing a prevalence of psychotic symptoms ranging from 36% (Alzheimer's Disease) and 54% (vascular dementia). Increasing prevalence of psychosis was noted to correlate with increasing severity of dementia.*
38. Bassiony MM, Steinberg MS, Warren A, et al. Delusions and hallucinations in Alzheimer's disease: prevalence and clinical correlates. *Int J Geriatr Psychiatry.* 2000;15:99–107.
  39. Broadway J, Mintzer J. The many faces of psychosis in the elderly. *Curr Opin Psychiatry.* 2007;20:551–8.
  40. Panza F, Frisardi V, Seripa D, D'Onofrio G, Santamato A, Masullo C, et al. Apolipoprotein E genotypes and neuropsychiatric symptoms and syndromes in late-onset Alzheimer's disease. *Ageing Res Rev.* 2012;11(1):87–103. *A review of the current literature regarding a putative association between apolipoprotein-E genotypes and neuropsychiatric symptoms.*
  41. Tighe SK, Oishi K, Mori S, Smith GS, Albert M, Lyketsos CG, et al. Diffusion tensor imaging of neuropsychiatric symptoms in mild cognitive impairment and Alzheimer's dementia. *J Neuropsychiatry Clin Neurosci.* 2012;24(4):484–8. *A study using diffusion tensor imaging to measure functional anisotropy (FA) in AD and MCI. Low anterior cingulate FA was associated with increased odds of irritability in mild AD and MCI participants.*
  42. Balthazar MLF, Pereira FRS, Lopes TM, da Silva EL, Coan AC, Campos BM, et al. Neuropsychiatric symptoms in Alzheimer's disease are related to functional connectivity alterations in the salience network. *Hum Brain Mapp.* 2014;35:1237–46. *A brain network connectivity study of (n=20) AD patients showing a correlation between increased connectivity in anterior cingulate cortex and right insula areas of the SN and hyperactivity syndrome.*
  43. Leroi I, Voulgari A, Breitner JC, Lyketsos CG. The epidemiology of psychosis in dementia. *Am J Geriatr Psychiatry.* 2003;11(1):83–91.
  44. Nagahama Y, Okina T, Suzuki N, Matsuda M, Fukao K, Murai T. Classification of psychotic symptoms in dementia with Lewy bodies. *Am J Geriatr Psychiatry.* 2007;15(11):961–7.
  45. Ballard C, Holmes C, McKeith I, Neill D, O'Brien J, Cairns N, et al. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. *Am J Psychiatr.* 1999;156(7):1039–45.
  46. Ballard CG, Saad K, Patel A, Gahir M, Solis M, Coope B, et al. The prevalence and phenomenology of psychotic symptoms in dementia sufferers. *Int J Geriatr Psychiatry.* 1995;10(6):477–85.
  47. Ballard CG et al. A prospective study of dementia with Lewy bodies. *Age Ageing.* 1998;27(5):631–6.
  48. Forsaa EB, Larsen JP, Wentzel-Larsen T, et al. A 12-year population-based study of psychosis in Parkinson disease. *Arch Neurol.* 2010;67:996–1001.
  49. Aarsland D, Larsen JP, Tandberg E, et al. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc.* 2000;48:938–42.
  50. Marsh L, Williams JR, Rocco M, et al. Psychiatric comorbidities in patients with Parkinson disease and psychosis. *Neurology.* 2004;63:293–300.
  51. Wang LY, Borisovskaya A, Maxwell AL, Pascualy M. Common psychiatric problems in cognitively impaired older patients. *Clin Geriatr Med.* 2014;30(3):443–67. *A thorough review of the myriad of psychiatric disorders and neuropsychiatric symptoms facing adults with neurocognitive disorders and their treatment.*
  52. Iglewicz A, Meeks TW, Jeste DV. New wine in old bottle: late-life psychosis. *Psychiatr Clin N Am.* 2011;34(2):295–318. *A comprehensive review of late-life schizophrenia and psychosis in the context of neurocognitive disorders.*
  53. Gauthier S, Wirth Y, Mobius HJ. Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. *Int J Geriatr Psychiatry.* 2005;20(5):459–64.
  54. Rodda J, Morgan S, Walker Z. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. *Int Psychogeriatr.* 2009;21(5):813–24.
  55. Lachaine J, Beauchemin C, Crochard A, et al. The impact of memantine and cholinesterase inhibitor initiation for Alzheimer disease on the use of antipsychotic agents: analysis using the Regie de l'Assurance Maladie du Quebec database. *Can J Psychiatry.* 2013;58(4):195–200. *A study of AD patients in the Quebec provincial health system noting a decreased initiation of antipsychotic medication following memantine prescription but not acetylcholinesterase inhibitors.*
  56. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA.* 2005;294(15):1934–43.
  57. 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.* 2006;14(3):191–210.
  58. Rossom RC, Rector TS, Lederle FA, Dysken MW. Are all commonly prescribed antipsychotics associated with greater mortality in elderly male veterans with dementia? *J Am Geriatr Soc.* 2010;58(6):1027–34.
  59. Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. *Br Med J.* 2012;344:e977. *A large, population based study of nursing home patients (n=75,445), >65 years old, newly started on antipsychotic medication, indicating an increase risk of mortality for haloperidol in this population (compared to risperidone) and a relative decreased risk of mortality with the use of quetiapine.*
  60. Vigen CL, Mack WJ, Keefe RS, Sano M, Sultzer DL, Stroup TS, et al. Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. *Am J Psychiatry.* 2011;168(8):831–9. *A publication from the CATIE-AD trial indicating a more pronounced decline in cognitive function in patients treated with antipsychotic medications than those treated with placebo.*
  61. Ballard C., Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst Rev.* (1): 2006
  62. Rabins PV, Blacker D, et al. APA work group on Alzheimer's disease and other dementias. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry.* 2007;164 Suppl 12:5–56.
  63. Lyketsos CG, Colenda CC, Beck C, et al. Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer disease. *Am J Geriatr Psychiatry.* 2006;14(7):561–72.
  64. National Institute for Health and Care Excellence. Dementia. CG42. London: National Institute for Health and Care Excellence. 2006
  65. Sultzer DL, Davis SM, Tariot PN, Dagerman KS, Lebowitz BD, Lyketsos CG, et al. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase I outcomes from the CATIE-AD effectiveness trial. *Am J Psychiatry.* 2008;165(7):844–54.



66. Meeks TW, Jeste DV. Beyond the black box: what is the role for antipsychotics in dementia? *Curr Psychiatry*. 2008;7(6):50–65.
67. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA*. 2011;306(12):1359–69. *A systematic review of off-label atypical antipsychotic use showing a small but significant improvement in global behavioral scores in dementia patients.*
68. Seitz DP, Adunuri N, Gill SS, Gruneir A, Herrmann N, Rochon P. Antidepressants for agitation and psychosis in dementia. *Cochrane Database Syst Rev*. 2011;16(2):CD008191. *The most current Cochrane review of the use of antidepressants in the treatment of agitation and psychosis in dementia. Indicates an association between reduction of agitation and treatment with sertraline and citalopram. Further controlled studies are needed to verify this association.*
69. Tariot PN, Erb R, Leibovici A, et al. Carbamazepine treatment of agitation in nursing home patients with dementia: a preliminary study. *J Am Geriatr Soc*. 1994;42(11):1160–6.
70. Tariot PN, Erb R, Podgorski CA, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry*. 1998;155(1):54–61.
71. Wang LY, Shofer JB, Rohde K, Hart KL, Hoff DJ, McFall YH, et al. Prazosin for the treatment of behavioral symptoms in patients with Alzheimer disease with agitation and aggression. *Am J Geriatr Psychiatry*. 2009;17(9):744–51.
72. Diederich NJ, Fénelon G, Stebbins G, Goetz CG. Hallucinations in Parkinson disease. *Nat Rev Neurol*. 2009;5(6):331–42.
73. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. *JAMA*. 2014;311(16):1670–83. *A recent, well-sourced review of the current state of the pharmacologic treatment of Parkinson's Disease.*
74. Miyasaki JM, Shannon K, Voon V, et al. Quality standards subcommittee of the American Academy of Neurology. 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*. 2006;66(7):996–1002.
75. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet*. 2014;383(9916):533–40. *Published, positive results from phase 3 RCT for a novel treatment (Pimavanserin) for psychosis in Parkinson's disease.*
76. Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML. High occurrence of mood and anxiety disorders among older adults: the national comorbidity survey replication. *Arch Gen Psychiatry*. 2010;67(5):489.
77. Luppia M, Sikorski C, Luck T, et al. Age- and gender-specific prevalence of depression in latest-life—systematic review and meta-analysis. *J Affect Disord*. 2012;136(3):212–21. *A systematic review of 24 studies regarding the prevalence of late-life depression. This systematic review showed a pooled prevalence of DSM-IV MDD of 7.2% in adults > 55 years old and pooled prevalence of depressive disorders in the same age group of 17.1%.*
78. Kessler RC, Birmbaum H, Bromet E, Hwang I, Sampson N, Shahly V. Age differences in major depression: results from the national comorbidity survey replication (NCS-R). *Psychol Med*. 2010;40(2):225–37.
79. Steffens DC, Fisher GG, Langa KM, et al. Prevalence of depression among older Americans: the Aging Demographics and Memory Study. *Int Psychogeriatr*. 2009;21(5):879–88.
80. Brodaty H, Luscombe G, Parker G, et al. Increased rate of psychosis and psychomotor change in depression with age. *Psychol Med*. 1997;27(5):1205–13.
81. Blazer, D., Steffens, D., & Koenig, H. Mood disorders. In *The American Psychiatric Publishing textbook of geriatric psychiatry, 4th Edition*. American Psychiatric Publishing, Inc. 2009.
82. Meyers BS, Klimstra SA, Gabriele M, et al. Continuation treatment of delusional depression in older adults. *Am J Geriatr Psychiatry*. 2001;9(4):415–22.
83. Grimby A. Bereavement among elderly people: grief reactions, post-bereavement hallucinations and quality of life. *Acta Psychiatr Scand*. 1993;87:72–80.
84. Van der Wurff FB, Stek ML, Hoogendijk WL, et al. Electroconvulsive therapy for the depressed elderly. *Cochrane Database Syst Rev*. 2003;2:CD003593.
85. Andreescu C, Mulsant BH, Rothschild AJ, et al. Pharmacotherapy of major depression with psychotic features: what is the evidence? *Psychiatr Ann*. 2006;36:31–8.
86. Meyers BS, Flint AJ, Rothschild AJ, et al. A double-blind randomized controlled trial of olanzapine plus sertraline vs olanzapine plus placebo for psychotic depression: the study of pharmacotherapy of psychotic depression (STOP-PD). *Arch Gen Psychiatry*. 2009;66:838–47.
87. Wilson KC, Mottram PG, Vassilas CA, et al. Psychotherapeutic treatments for older depressed people. *Cochrane Database Syst Rev*. 2008;1:CD004853.
88. Unutzer J, Simon G, Pabiniak C, et al. The treated prevalence of bipolar disorder in a large staff-model HMO. *Psychiatr Serv*. 1998;49(8):1072–8.
89. Hirschfeld RM, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. *J Clin Psychiatry*. 2003;64(1):53–9.
90. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593–602.
91. Sajatovic M, Blow FC, Ignacio RV, et al. New-onset bipolar disorder in later life. *Am J Geriatr Psychiatry*. 2005;13(4):282–9.
92. Leboyer M, Henry C, Paillere-Martinot ML, et al. Age at onset in bipolar affective disorders: a review. *Bipolar Disord*. 2005;7(2):111–8.
93. Hamshere ML, Gordon-Smith K, Forty L, Jones L, Caesar S, Fraser C, et al. Age-at-onset in bipolar-I disorder: mixture analysis of 1369 cases identifies three distinct clinical sub-groups. *J Affect Disord*. 2009;116(1–2):23–9.
94. Kessing LV. Diagnostic subtypes of bipolar disorder in older versus younger adults. *Bipolar Disord*. 2006;8(1):56–64.
95. Van Gerpen MW, Johnson JE, Winstead DK. Mania in the geriatric patient population: a review of the literature. *Am J Geriatr Psychiatry*. 1999;7(3):188–202.
96. Young RC, Schulberg HC, Gildengers AG, Sajatovic M, Mulsant BH, Gyulai L, et al. Conceptual and methodological issues in designing a randomized, controlled treatment trial for geriatric bipolar disorder: GERI-BD. *Bipolar Disord*. 2010;12(1):56–67.
97. Beyer JL, Greenberg RL, Marino P, Bruce ML, Al Jurdi RK, Sajatovic M, et al. Social support in late life mania: GERI-BD. *Int J Geriatr Psychiatry*. 2014. doi:10.1002/gps.4093. *An analysis of the NIMH GERI-BD database (n= 100) illustrating the importance of close social interactions on limiting time to treatment during illness episodes. Non-family interactions were less important in this study.*
98. Al Jurdi RK, Schulberg HC, Greenberg RL, Kunik ME, Gildengers A, Sajatovic M, et al. Characteristics associated with inpatient versus outpatient status in older adults with bipolar disorder. *J Geriatr Psychiatry Neurol*. 2012;25(1):62–8. *An exploratory study of initial participants in the ongoing GERI-BD RCT study of geriatric bipolar patients. It showed an association between ethnicity (non-Hispanic Caucasian), history of treatment with a first generation antipsychotic medication, and the presence of psychotic symptoms and inpatient treatment status.*



99. Gildengers AG, Mulsant BH, Al Jurdi RK, Beyer JL, Greenberg RL, Gyulai L, et al. The relationship of bipolar disorder lifetime duration and vascular burden to cognition in older adults. *Bipolar Disord.* 2010;12(8):851–8.
100. Safer DJ, Magno Zito J, Safer AM. Age-grouped differences in bipolar mania. *Compr Psychiatry.* 2012;53(8):1110–7. *An age-group comparison study showing a higher prevalence of disordered thought content in older adults versus a higher rate of aggression and irritability in younger adults.*
101. Sajatovic M, Chen P. Geriatric Bipolar Disorder. *Psychiatr Clin N Am.* 2011;34(2):319–33.
102. Jeste DV, Lanouette NM, Vahia IV. Schizophrenia and paranoid disorders. In: Blazer DG, Steffens DC, editors. *Textbook of geriatric psychiatry.* 4th ed. Washington: American Psychiatric Press; 2009. p. 317–31.
103. Harris MJ, Jeste DV. Late-onset schizophrenia: an overview. *Schizophr Bull.* 1988;14:39–45.
104. Keith SJ, Regier DA, Rae DS. Schizophrenic disorders. In: Robins LN, Regier DA, editors. *Psychiatric disorders in America: the epidemiologic catchment area study.* New York: Free Press; 1991. p. 33–52.
105. Copeland JRM, Davidson IA, Dewey ME, Gilmore C, Larkin BA, McWilliam C, et al. Alzheimer's disease, other dementias, depression and pseudodementia: prevalence, incidence and three-year outcome in Liverpool. *Br J Psychiatry.* 1992;161:230–9.
106. Kua EHA. Community study of mental disorders in elderly Singaporean Chinese using the GMS-AGECAT package. *Aust NZ J Psychiatry.* 1992;26:502–6.
107. Copeland JR, Dewey ME, Scott A, Gilmore C, Larkin BA, Cleave N, et al. Schizophrenia and delusional disorder in older age: community prevalence, incidence, comorbidity, and outcome. *Schizophr Bull.* 1998;24(1):153–61.
108. Castle DJ, Murray RM. The epidemiology of late-onset schizophrenia. *Schizophr Bull.* 1993;19(4):691–700.
109. Cohen CI, Vahia I, Reyes P, Diwan S, Bankole AO, Palekar N, et al. Schizophrenia in later life: clinical symptoms and well-being. *Psychiatr Serv.* 2008;59:232–4.
110. Howard R, Rabins PV, Seeman MV, Jeste DV. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. *Am J Psychiatr.* 2000;157(2):172–8.
111. Jeste DV, Wolkowitz OM, Palmer BW. Divergent trajectories of physical, cognitive, and psychosocial aging in schizophrenia. *Schizophrenia bulletin.* 2011;37(3):451–455. *An recent article pointing toward the aging paradox of individuals aging with schizophrenia: accelerated aging, increased medical comorbidity and mortality with stable cognitive aging, while psychosocial function, well-being, self-management, and recurrence rates tend to improve with age.*
112. Post F. Schizo-affective symptomatology in late life. *Br J Psychiatry.* 1971;118(545):437–45.
113. Baran XY, Young RC. Bipolar and depressive types of schizoaffective disorder in old age. *Am J Geriatr Psychiatry.* 2006;14(4):382–3.
114. Meesters PD, de Haan L, Comijs HC, Stek ML, Smeets-Janssen MMJ, Weeda MR, et al. Schizophrenia spectrum disorders in later life: prevalence and distribution of age at onset and sex in a Dutch catchment area. *Am J Geriatr Psychiatry.* 2012;20(1):18–28. *Dutch prevalence study of late-life psychotic disorders, including delusional disorder, evidencing a 0.03% prevalence of this disorder.*
115. Maher B. Delusional thinking and cognitive disorders. *Integr Physiol Behav Sci.* 2005;40:136–46.
116. Marriott R.G., Neil W., Waddingham S. Antipsychotic medication for elderly people with schizophrenia. *Cochrane Database Syst Rev.* 2006;25.
117. Essali A, Ali G. Antipsychotic drug treatment for elderly people with late-onset schizophrenia. *Cochrane Database Syst Rev.* 2012;2:CD004162.
118. Jeste DV, Barak Y, Madhusoodanan S, Grossman F, Gharabawi G. International multisite double-blind trial of the atypical antipsychotics risperidone and olanzapine in 175 elderly patients with chronic schizophrenia. *Am J Geriatr Psychiatry.* 2003;11(6):638–47.
119. Sable JA, Jeste DV. Antipsychotic treatment for late-life schizophrenia. *Curr Psychiatry Rep.* 2002;4:299–306.
120. Huang X, Zhong Z, Zhang J. The effects of risperidone and olanzapine on the glucose metabolism and lipid metabolism in elderly patients with schizophrenia. *J Clin Psychosom Dis.* 2007;13(1):1–3.
121. Patterson TL, McKibbin C, Mautsach 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.* 2006;86:291–9.
122. 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.* 2007;68:730–7.
123. Manepalli JN, Gebretsadik M, Hook J, Grossberg GT. Differential diagnosis of the older patient with psychotic symptoms. *Prim Psychiatry.* 2007;14(8):55–62.
124. Richards CF, Gurr DE. Psychosis. *Emerg Med Clin North Am.* 2000;18(2):253–62.