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REVIEW

# Overview of late-onset psychoses

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ABSTRACT

**Background:** Several etiologies can underlie the development of late-onset psychosis, defined by first psychotic episode after age 40 years. Late-onset psychosis is distressing to patients and caregivers, often difficult to diagnose and treat effectively, and associated with increased morbidity and mortality.

**Methods:** The literature was reviewed with searches in Pubmed, MEDLINE, and the Cochrane library. Search terms included "psychosis," "delusions," hallucinations," "late onset," "secondary psychoses," "schizophrenia," bipolar disorder," "psychotic depression," "delirium," "dementia," "Alzheimer's," "Lewy body," "Parkinson's, "vascular dementia," and "frontotemporal dementia." This overview covers the epidemiology, clinical features, neurobiology, and therapeutics of late-onset psychoses.

**Results:** Late-onset schizophrenia, delusional disorder, and psychotic depression have unique clinical characteristics. The presentation of late-onset psychosis requires investigation for underlying etiologies of "secondary" psychosis, which include neurodegenerative, metabolic, infectious, inflammatory, nutritional, endocrine, and medication toxicity. In delirium, psychosis is common but controlled evidence is lacking to support psychotropic medication use. Delusions and hallucinations are common in Alzheimer's disease, and hallucinations are common in Parkinson's disease and Lewy body dementia. Psychosis in dementia is associated with increased agitation and a poor prognosis. Although commonly used, no medications are currently approved for treating psychosis in dementia patients in the USA and nonpharmacological interventions need consideration.

**Conclusion:** The plethora of possible causes of late-onset psychosis requires accurate diagnosis, estimation of prognosis, and cautious clinical management because older adults have greater susceptibility to the adverse effects of psychotropic medications, particularly antipsychotics. Research is warranted on developing and testing efficacious and safe treatments for late-onset psychotic disorders.

**Key words:** older adult, secondary psychosis, schizophrenia, delusional disorder, dementia, delirium

## Introduction

While there is no universally accepted definition of psychosis, Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) indicates that psychotic features include loss of touch with reality, delusions, hallucinations, disorganized thoughts, specific behaviors including catatonia, and negative symptoms such as decreased emotional expression, and avolition in schizophrenia (DSM-5). Onset of schizophrenia after age 40 years is considered as late-onset schizophrenia (Howard *et al.*, 2000). In this review, we identify psychotic disorders with age of onset after 40 years as late-onset psychosis. Late-onset psychotic disorders include late-onset schizophrenia, delusional disorder, psychotic depression, psychosis in Parkinson's disease (PD), psychosis during delirium, and psychosis in the major neurocognitive disorders or dementias—most commonly Alzheimer's disease (AD) and Lewy body disease (LBD) (DSM-5; Tampi and Jeste, 2022). "Secondary psychosis" includes neurodegenerative, metabolic, infectious, autoimmune, nutritional, and endocrine causes as well as stroke, prescription or illicit drug use and withdrawal, and medications that include sedatives in the intensive care unit or ICU and dopaminergic drugs for PD that can cause or contribute to late-onset psychosis (Keshavan and Kaneko, 2013).

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In older adults, the population prevalence of psychosis has not been studied systematically. One estimate of prevalence of psychosis in older adults is 1.7% with a lifetime incidence of 4.7% (Volkert *et al.*, 2013). These percentages do not include mild cases of psychosis that may be missed. Further, patients in nursing homes and hospitals where psychosis in patients with dementia and delirium is common are often not included in population surveys. A majority of older patients with late-onset psychosis have psychosis associated with other conditions, especially dementia, followed in frequency by delirium, psychotic depression, drug toxicity, and other medical disorders. Individuals who develop psychosis during dementia, delirium, and other predominantly late-onset disorders may outnumber those who have grown older with the longstanding illnesses of schizophrenia, bipolar disorder with psychosis, and other early-onset psychotic disorders (Tampi and Jeste, 2022). Isolated psychotic symptoms, particularly hallucinations, can develop for the first time in older adults.

A broad review of late-onset psychosis that focuses on both primary psychotic disorders and secondary psychoses that occur in older adults, including psychoses in dementia and delirium, is needed to inform clinicians who evaluate patients with late-onset psychotic disorders. In this evidence-based overview, we describe the prevalence, clinical presentation, diagnosis, prognosis, and clinical management for different types of late-onset psychosis in the older adult population. Potential etiologies and cognitive and functional deficits are discussed. The goal is to improve the understanding of the types of late-onset psychosis that present clinically in older adults and to provide suggestions for clinical practice.

## Methods

The literature was reviewed with searches in Pubmed, MEDLINE, and the Cochrane library. Search terms included "psychosis," "delusions," hallucinations," "late onset," "secondary psychoses," "schizophrenia," bipolar disorder," "psychotic depression," "delirium," "dementia," "Alzheimer's," "Lewy body," "vascular dementia," and "frontotemporal dementia." This overview covers the epidemiology, clinical features, neurobiology, and therapeutics of late-onset psychoses.

## Results

### Late-onset schizophrenia

Schizophrenia is a heterogeneous clinical syndrome characterized by psychosis that typically begins in late adolescence or early adulthood. The DSM-5 criteria also require functional impairment, but the ICD-11 guidelines do not (DSM-5; ICD-11) (Harrison *et al.*, 2021). The lifetime prevalence of schizophrenia in the general population is 1% and approximately 20% of older patients with schizophrenia have onset of illness after age 40 (Stafford *et al.*, 2018). Late-onset schizophrenia (LOS) with onset between 40 and 60 years of age differs from early-onset schizophrenia (EOS) in several ways. LOS is generally associated with lower severity of positive symptoms (i.e., delusions, hallucinations, disorganized speech and behavior) and lower antipsychotic dose requirement. In 2000, the International Late-Onset Schizophrenia Group proposed the terms LOS for cases with onset between 40 and 60 years of age and very-late-onset schizophrenia-like psychosis (VLOSLP) for those presenting with the first episode of psychosis after age 60 (Howard *et al.*, 2000). People who develop LOS typically have better premorbid functioning and a better prognosis than those with EOS. In LOS, persecutory delusions, delusions of reference, and third person and running-commentary auditory hallucinations are more common while disorganized thoughts are less frequent. In a sample of 854 older patients with schizophrenia, including 110 with LOS, patients with LOS had less severe psychotic symptoms, better functioning, and were on lower antipsychotic doses than patients with EOS (Vahia *et al.*, 2010). Women comprise a majority of patients with LOS and VLOSLP with the relative preponderance of women increasing with age (Reynolds *et al.*, 2022; Stafford *et al.*, 2018). The higher prevalence in women led to the estrogen hypothesis of schizophrenia – i.e., later onset of symptoms in postmenopausal women results from a loss of the previous protection conferred by estrogenic modulation of several neurotransmitters but attempts to identify specific polymorphisms of the estrogen receptors related to LOS have been inconclusive and estrogen therapies have not shown consistent results (Gonzalez-Rodriguez and Seeman, 2019). VLOSLP has some overlapping features with neurodegenerative disorders such as AD and PD with psychosis (Nilsson *et al.*, 2018).

Older patients with schizophrenia, both EOS and LOS, show considerable variability in their outcomes over the course of illness. Some patients experience worsening of psychosis, many have a stable course, and a minority demonstrate progressive improvement in symptoms with partial or full remission (Cohen and Reinhardt, 2020; Jeste *et al.*, 2011). A meta-analysis found that LOS patients demonstrated better cognitive performance than typical EOS patients in the domains of memory, executive function, and processing speed, but had more impairment in attention, verbal fluency and

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visuospatial construction, consistent with specific deficits related to the disorder rather than deficits solely due to aging-related decline (Rajji *et al.*, 2009). LOS is not a prodrome of AD because progressive cognitive worsening with an AD cognitive profile is uncommon (Rajji *et al.*, 2009). Functional impairments can be severe and disabling even in LOS. Patients with schizophrenia have an average 20% decrease in lifespan compared to the general population; accelerated aging, poor general health and healthcare, and other factors have been postulated to underlie this decrease (Nguyen *et al.*, 2018). There has been limited investigation of the genetics of LOS. The genetic variant in the dopamine D2 receptor (DRD2), rs2734839, is reported to be significantly associated with schizophrenia generally, but more with LOS (Voisey *et al.*, 2012).

## Schizophrenia and dementia

Studies of the links between primary psychosis and dementia have focused on schizophrenia, which increases the risk of all-cause dementia (Ribe *et al.*, 2015; Stroup *et al.*, 2021). In a national study from Denmark, schizophrenia increased the risk for all-cause dementia by 2.13-fold (Ribe *et al.*, 2015). A recent study that used data from the US Medicare program suggested an even higher risk (Stroup *et al.*, 2021). At 80 years, about 70% of schizophrenia individuals had a dementia diagnosis compared to 11% in the group without severe mental illness with diagnoses that included AD, senile dementia, and vascular dementia. Increased risk may have been due to some combination of early cognitive impairment, low cognitive reserve, metabolic syndrome, cardiovascular or cerebrovascular disease, neurodegenerative neuropathologic processes, and perhaps long-term use of antipsychotics (Jonas *et al.*, 2021; Stroup *et al.*, 2021). However, in these studies, early-onset patients were included and comprised the vast majority of patients with schizophrenia. In another study, postmortem examination of patients with LOS did not show histopathological changes consistent with AD as amyloid plaque burden was minimal (Casanova *et al.*, 2002). Current evidence suggests that LOS is not associated consistently with increased rates of dementia, although dementia is common in VLOSP (Howard *et al.*, 2000).

## Brain imaging in LOS

For the initial clinical presentation of late-onset psychosis, structural brain imaging with CT or MRI is important to rule out CNS causes such as tumor and stroke. Compared to EOS, LOS has been associated with lateral ventricular enlargement, larger thalamic volumes, decreased white matter integrity, and reduced cerebral blood flow in both postcentral gyri compared to EOS (Chen *et al.*, 2013; Tonkonogy and Geller, 1999; Wake *et al.*, 2016).

## Principles of antipsychotic prescribing in old age

Pharmacokinetic and pharmacodynamic changes that occur with aging lead to an increased sensitivity to antipsychotics in older individuals. Specifically, decreases in total body water and muscle mass combined with increase in the proportion of adipose tissue result in an increased volume of distribution and slower elimination of antipsychotic medications, while decreased hepatic protein synthesis results in greater amounts of "free" circulating drug (Uchida *et al.*, 2009). Also, increased permeability of the blood–brain barrier with aging can lead to higher brain concentrations of antipsychotic medications. Therefore, older adults are at a greater risk for antipsychotic-induced side effects such as extrapyramidal symptoms (EPS) and tardive dyskinesia (Uchida *et al.*, 2009). There is also an increased risk of falls, autonomic effects including anticholinergic symptoms of dry mouth and constipation, and sedation.

Randomized, double-blind, placebo-controlled clinical trials of antipsychotics in LOS are sparse. In VLOSLP, amisulpride showed moderate efficacy in a clinical trial (Howard *et al.*, 2018). In LOS and VLOSLP, the choice of antipsychotic medication is usually determined by the risks of specific side effects, e.g., neurological versus metabolic side effects. Second generation or "atypical" antipsychotics (e.g., risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, lurasidone) are generally associated with a lower risk for parkinsonism and tardive dyskinesia than first generation or "typical" antipsychotics (e.g., chlorpromazine, haloperidol, fluphenazine). Several atypical antipsychotics have elevated risk of metabolic side effects. A study using equipoise-stratified randomization compared four commonly prescribed atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) in 332 outpatients over 40 years old with psychotic symptoms related to different psychiatric diagnoses, especially schizophrenia and dementia, over 2 years of treatment (Jin *et al.*, 2013). Concerning findings included a high 1-year cumulative incidence of metabolic syndrome (36%), high rates of both serious and nonserious adverse events (50.8%), and no further symptom improvement in these patients, many of whom were already receiving long-term treatment. Over half of the study participants discontinued their assigned medication within 6 months, most often due to side effects (51.6%) or lack of efficacy (26%), suggesting that atypical

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antipsychotic medications may be helpful short-term but have limited efficacy and an increased risk of adverse effects over longer treatment periods in middle-aged and older adults with schizophrenia. Higher doses of commonly used antipsychotics (risperidone, olanzapine, and haloperidol) have been associated with higher risk of death than lower doses (Gerhard *et al.*, 2014). In a study of 29 older adults with schizophrenia (early and late onset) whose olanzapine or risperidone dose was reduced by up to 40%, there was no increase in relapse (Graff-Guerrero *et al.*, 2015). Clinically, using the lowest effective dose of antipsychotic medications is important to minimize adverse effects.

### Nonpharmacological interventions

Cognitive behavioral social skills training, a 36-session weekly group therapy program combining cognitive behavioral therapy, social skills training, and problem-solving training resulted in improved functioning in middle-aged and older patients with schizophrenia or schizoaffective disorder compared with a supportive therapy control (Granholm *et al.*, 2013). In another study of cognitive behavioral social skills training, older patients with schizophrenia who had the greatest executive dysfunction showed the most improvement in independent living skills compared to treatment-as-usual control patients (Rajji *et al.*, 2022). Functional adaptation and skills training, a 24-week functional skills course, was associated with improvement in functioning and decrease in utilization of emergency medical services in older adults with schizophrenia (Patterson *et al.*, 2006). Both these interventions, which included middle-aged and older adults with EOS and LOS, are considered evidence-based by the Substance Abuse and Mental Health Services Agency (SAMHSA) in the USA. These approaches need greater implementation in clinical practice. Nonpharmacological interventions have not been studied in delusional disorder and psychotic depression.

## Delusional disorder

Besides schizophrenia, DSM-5 specifies several psychotic disorders: delusional disorder, brief psychotic disorder, schizophreniform disorder, schizotypal (personality) disorder, schizoaffective disorder, substance/medication-induced psychotic disorder, and psychotic disorder due to another medical condition. Delusional disorder presents in middle to old age with prominent delusions but without hallucinations. Delusional disorder has an estimated prevalence of 0.03% in old age and a lifetime prevalence of approximately 0.2% (Tampi *et al.*, 2019). Women may be more commonly affected than men (Gonzalez-Rodrigues *et al.*, 2022). A diagnosis of delusional disorder requires ruling out other causes of delusions, including schizophrenia, delirium, neurocognitive disorders, substance-induced disorders, and mood disorders.

Studies of individual cases and others with small sample sizes suggest an association between incident delusional disorder and structural brain changes with cognitive deficits (Gonzales-Rodrigues *et al.*, 2022). There has been little systematic research on the genetics of delusional disorder. Apart from the direct consequences of delusions, everyday functioning usually is relatively intact (Munoz-Negro *et al.*, 2018). In delusional disorder, placebo-controlled medication trials have not been conducted. In clinical series, response rates to antipsychotics range from 20 to 39%, and full remission is rarely achieved (Nagendra and Snowdon, 2020).

## Psychotic depression

The estimated lifetime prevalence for psychotic depression is 0.35%, and like delusional disorder, the age of onset of psychotic depression averages around 50 years with no gender difference (Perälä *et al.*, 2007). Unipolar psychotic depression often has an onset in middle to old age, whereas early-onset psychotic depression is more frequent in bipolar disorder (Nelson and Charney, 1981). Delusions of guilt, worthlessness, nihilism, and somatic delusions are common in psychotic depression, but the subtlety of symptoms and patients' guardedness may lead to the diagnosis being missed. Delusions are far more common than hallucinations; hence the term delusional depression has been used synonymously with psychotic depression. Auditory hallucinations that are derogatory or belittling, which are mood-congruent with severe depression, can occur. Psychomotor retardation is common and there is greater severity, persistence, and recurrence of episodes than most other forms of depression. Completed suicide is more common in psychotic than nonpsychotic depression (Gournellis *et al.*, 2018). Patients with psychotic depression show more cognitive deficits in all domains, except for verbal fluency, compared to patients with nonpsychotic depression (Vermeulen *et al.*, 2019).

Psychotic depression may be associated with decreased gray matter volume, particularly in medial prefrontal cortex, but there are no consistent MRI changes associated with treatment response to electroconvulsive therapy (ECT) (Takamiya *et al.*, 2022). In a study that also included patients with schizophrenia and bipolar disorder, no specific genes were associated with psychotic depression (Luna *et al.*, 2022).

Treatment with combined antipsychotic and antidepressant medications is the usual first-line

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strategy. In a randomized, double-blind, controlled trial (RCT) of 259 patients with psychotic depression, two-thirds of whom were older adults, a combination of olanzapine and sertraline was associated with a 41.9% remission rate compared to 23.9% remission rate on olanzapine plus placebo (Meyers *et al.*, 2010). ECT, however, shows the strongest efficacy in this disorder in all age groups, including old age, and complete remission can be achieved (Devanand and Krueger, 1994). Therefore, in patients showing partial or no response to combination pharmacotherapy, ECT is recommended.

## Bipolar disorder with psychosis

Bipolar disorder appears to have a trimodal age-of-onset distribution—early-onset with modal age of 17, mid-onset with modal age of 26, and late-onset with modal age of 46 years (Bolton *et al.*, 2021). Approximately 25% of people with bipolar disorder are older than 60 years (Sajatovic *et al.*, 2015). Older adults with bipolar disorder may experience psychotic symptoms in depressive or manic episodes (Bolton *et al.*, 2021). In older adults, new-onset bipolar disorder is not driven primarily by genetic predisposition, unlike early-onset bipolar disorder (Sajatovic *et al.*, 2015). The term "secondary mania" is used to describe mania that is related to medication toxicity, infections, and metabolic changes as well as brain pathology due to brain trauma and neurological illnesses such as stroke (Evans *et al.*, 1995). Secondary mania is more common in older than in younger adults. Psychotic symptoms in secondary mania are similar to those in early-onset bipolar disorder. Since lithium may lead to cognitive impairment in older patients with neurodegenerative disease, accurate diagnosis is important.

First-line therapy in older adults is comparable to treatment for younger adults with bipolar disorder, with the caveat that doses need to be lower because of increased age-related risk for neurological and metabolic side effects of lithium, anticonvulsants, and antipsychotics. Compared to younger adults, older adults require a lower dose of lithium to achieve a therapeutic plasma level, because of age-related decline in renal function and excretion of lithium (Malhi *et al.*, 2017; Dols and Beekman, 2018). A double-blind RCT of lithium and divalproex in older adults with mania, with and without psychosis, found no significant differences in efficacy between the two treatments (Young *et al.*, 2017). Clinically, lithium or anticonvulsants like valproate are effective treatments, particularly as maintenance treatments, with acute manic episodes often requiring the addition of antipsychotics. Most studies of bipolar disorder have been conducted in young to middle-aged adults. More research on the prevalence, etiology, treatment, and clinical course of late-onset bipolar disorder, with and without psychosis, is needed (Sajatovic *et al.*, 2015).

## Isolated hallucinations in older adults

Isolated auditory or visual hallucinations occur in 2–3% of older adults (Badcock *et al.*, 2017). A range of predisposing factors include decline in sensory or cognitive functioning, poor sleep, and psychosocial stressors that include social isolation, loneliness, and bereavement. There is no established treatment for idiopathic isolated hallucinations, and antipsychotics often are ineffective (Badcock *et al.*, 2017). In many cases, it is unclear if the hallucination is a result of abnormal functioning of the peripheral sensory pathways for hearing and vision that cannot be detected by testing, or due to abnormal brain physiology. In the presence of Parkinsonian features, however, the diagnosis of LBD leading to dementia needs to be considered. Few genetic, brain imaging, and treatment studies of this uncommon disorder have been conducted (Badcock *et al.*, 2017).

## Secondary psychoses

Secondary psychoses involve a specific etiology for psychosis that may or may not be reversible (Keshavan and Kaneko, 2013). Traumatic brain injury, autoimmune disorders, stroke, CNS malignancies including temporal lobe tumors, and CNS infections can be associated with psychotic features. Other causes of secondary psychosis that can occur throughout the life span include seizure disorders, endocrine disorders, metabolic disorders, and drug use. Illicit drug use can lead to specific psychotic symptoms based on the individual drug or combination of drugs, but these occur primarily in younger or middle-aged adults. Secondary psychoses are often characterized by visual hallucinations, disorientation/confusion, and a medical illness with onset of psychosis shortly after a new medical diagnosis or medication. Treatment involves addressing the cause of the secondary psychosis, which in some cases may be reversible. The remainder of this review focuses on common causes of secondary psychosis.

## Drug-induced toxicity and psychosis

Illicit drugs are primarily associated with psychosis in adolescents and young adults but occur occasionally in older adults who use them. Stimulants like amphetamines and cocaine, and psychotomimetic drugs like phencyclidine and ketamine, can induce psychosis (Keshavan and Kaneko, 2013). Withdrawal from alcohol and benzodiazepines can be

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associated with psychosis. Lysergic acid diethylamide and 3,4-methylenediozxy-N-methylamphetamine can lead to hallucinations during acute intoxication but these symptoms do not persist in the abstinent state. Opioids typically do not induce psychosis.

Prescription drugs can cause psychosis in older adults. Corticosteroids can induce depression, mania and psychosis, and medications with anticholinergic properties can be associated with psychosis as an acute delirium or a low-grade chronic delirium. Medications with anticholinergic properties include tricyclic antidepressants and older antiparkinsonian agents. There are case reports and clinical series of treatment with anticonvulsants, antiemetics, histamine antagonists, antimalarials, and antibiotics being associated with psychosis (Keshavan and Kaneko, 2013). The management of drug-induced psychosis consists of identifying and then tapering or discontinuing the drug that likely induced the psychosis.

## Delirium

In older adults, delirium and neurodegenerative disorders are common causes of secondary psychosis (Table 1). The DSM-5 criteria for delirium emphasize impaired attention and awareness, abrupt onset with fluctuating course, and at least one type of cognitive impairment (e.g., memory, language, orientation). The DSM-5 diagnostic criteria for delirium include a criterion for perceptual disturbance, which subsumes hallucinations.

There are multiple risk factors for delirium including age, alcohol and drug abuse, pre-existing cognitive compromises, medication toxicity, and surgery (Rengel *et al.*, 2021)). Delirium is associated with need for greater care, longer hospital stays, increased hospitalization costs, and increase in mortality (Inouye *et al.*, 2014). In intensive care units, rates of delirium have been reduced to about 16–33% from a high incidence of 80% in the early 2000s (Hayhurst *et al.*, 2016). We showed in a meta-analysis of 24 studies that delirium was associated with long-term cognitive decline with a Hedges G medium effect size of 0.45 (Goldberg *et al.*, 2020). The pathophysiology of delirium is not established but it may involve some combination of neuroinflammation, abnormalities in multiple neurotransmitters, and physiological effects of surgery/general anesthesia.

In an early study of 227 consecutively hospitalized patients diagnosed with delirium using DSM-IV criteria, the prevalence of psychotic symptoms was 42.7%, with 27% of patients having visual hallucinations, 12% having auditory hallucinations, 3% having tactile hallucinations, and 26% having delusions (Webster and Holroyd, 2000). Visual hallucinations, but not delusions or auditory hallucinations, were associated with more medical diagnoses and multiple etiologies. In another study using DSM-IV criteria and a delirium rating scale, psychotic symptoms were observed in 49% of the sample of over 200 patients (Paik *et al.*, 2018). Psychosis was associated with a significant increase in in-hospital mortality, the hyperactive delirium subtype, and unsurprisingly, antipsychotic use. A Cochrane review of nine studies found that antipsychotics did not reduce delirium severity compared to nonantipsychotic drugs or placebo, and antipsychotics also did not change the mortality rate (Wu *et al.*, 2019).

In summary, delirium is common in hospitalized older patients and the presence of psychosis is associated with poor prognosis. Besides reversing the cause of delirium when feasible, commonly used medication strategies that include antipsychotics are not supported by a robust evidence base. Individualized clinician decision-making, along with environmental strategies, is the norm.

## Major neurocognitive disorders

In the USA, AD comprises more than half of all cases of dementia, vascular dementia and Lewy body dementia (LBD) each contribute to 10–25% of cases of dementia, and frontotemporal dementia (FTD) comprises 2–10% of cases of dementia (Devanand *et al.*, 2022; Naasan *et al.*, 2021). Neuropathological studies indicate that overlap is common with more than one type of dementia identified in individual brains at autopsy (Devanand *et al.*, 2022).

The diagnostic criteria for psychosis in AD and related dementias require the presence of delusions or hallucinations, absence of delirium or a prior functional psychosis, and onset of psychosis after the clinical onset of dementia (Fischer *et al.*, 2020; Jeste and Finkel, 2000). Psychosis in dementia heralds a poor prognosis with greater cognitive decline and increased risk of institutionalization and death (Scarmeas *et al.*, 2005). Psychotic symptoms are often accompanied by agitation and aggression with markedly increased burden on caregivers and the healthcare system.

The prevalence of psychosis, defined by the presence of delusions or hallucinations, differs by clinically diagnosed subtype of dementia: 10–15% in behavioral variant of FTD (bvFTD) with a similar prevalence in vascular dementia, 30–50% in AD, and 30–70% in dementia with Lewy bodies (Tampi and Jeste, 2022). These estimates reflect prevalence over the entire disease course; prevalence for a specific timepoint or disease stage is lower because psychosis typically fluctuates over time in major neurocognitive disorders.

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**Table 1.** Characteristic features of common late-onset psychotic disorders

| Illness | Prevalence | Definition | Clinical features | Neurobiology | Therapeutics |
|---|---|---|---|---|---|
| Late-onset Schizophrenia (LOS) | 20% of older patients with schizophrenia have LOS; female preponderance | Onset after age 40, minimum 6-month symptom duration requirement as in early onset schizophrenia (EOS) | Compared to EOS, LOS shows better premorbid functioning, fewer positive symptoms, less cognitive impairment, and lower antipsychotic dose requirement | Dementia often diagnosed but it is not AD. Possible genetic variant in dopamine D2 receptor (DRD2), rs2734839 | Antipsychotics can be effective, doses needed are lower than in young adults; psychosocial interventions like CBT, social skills training may be effective. |
| Delusional disorder | 0.03% prevalence in older adults; possibly more common in women | Presence of at least one delusion for at least one month without bizarre behavior, not meet criteria for other psychotic disorders | Isolated delusions, no hallucinations. Everyday functioning is relatively intact. | Genetics are not known, limited data suggest brain atrophy with minimal cognitive deficits | No RCTs. Antipsychotics response rates of 20–39% in clinical series; full remission is rare |
| Psychotic depression | 0.35% lifetime prevalence; comprise 20–45% of hospitalized depressed patients and 3.6% of depressed outpatients | Presence of major depression with psychosis; prominent delusions, hallucinations are less common | Somatic, nihilistic, guilt, worthlessness delusions, usually mood congruent, are common. Severe depression and high psychic anxiety are common; suicide risk is high | Limited research, genetics unclear | Antipsychotic plus antidepressant is usual first-line treatment; ECT is efficacious with high remission rates |
| Late-onset bipolar disorder with psychosis | Modal age 46 years for late onset. 20% of all patients with bipolar disorder are >60 years old | Diagnostic symptom criteria are the same for early and late onset bipolar disorder | Secondary mania is common with etiologies of medication toxicity, infections, metabolic changes, brain trauma, stroke, dementia. Differential diagnosis: FTD. | Little systematic research restricted to late-onset bipolar disorder | Lithium and valproate show similar efficacy for mania in older adults; antipsychotics are needed in many patients |
| Delirium | Occurs in 25–35% of hospitalized patients, particularly post-surgery | Common features: disorientation, disturbances in attention, abrupt and fluctuating course, altered consciousness and arousal, thought disorganization. Hallucinations are common. | Risk factors: older age, alcohol and drug abuse, pre-existing cognitive deficits, medication toxicity, surgery | Neurobiology depends on etiology. Associated with long-term cognitive decline and increased mortality. | Antipsychotics and benzodiazepines are widely used but empirical research evidence is lacking. |
| Alzheimer's disease (AD) | 30–50% prevalence of psychotic symptoms during the clinical course | Delusions in 15–30%, hallucinations in 5–15% of patients. Psychotic features can fluctuate over time | Delusions of theft, infidelity, abandonment, and misidentification are common. Visual more common than auditory hallucinations. | Increased tau tangle pathology, reduced neurotransmitters including serotonin neurons, muscarinic cholinergic-dopaminergic imbalance, greater atrophy in medial temporal regions | No drug approved in the USA; few approvals for antipsychotics elsewhere; adverse effects including increased mortality. SSRI citalopram may be effective for agitation but not studied for psychosis |

**Table 1.** Continued

| Illness | Prevalence | Definition | Clinical features | Neurobiology | Therapeutics |
|---|---|---|---|---|---|
| Lewy body dementia (LBD) | 10–20% of dementia cases. In LBD, 30–80% have psychosis, 40–60% have hallucinations, 25% have delusions | Progressive memory loss, visual hallucinations, parkinsonism, cognitive fluctuations, REM sleep behavior disorder | Well-formed visual hallucinations, passage hallucinations, presence phenomena, pareidolias can occur. | Visual hallucinations correlate with lower PET glucose metabolism and weaker metabolic connectivity in the parietal-occipital cortex. Decreased dopamine transporter on PET scan | Highly sensitive to antipsychotics with risk of severe EPS and falls. Low dose olanzapine and quetiapine may be useful for psychosis. |
| Parkinson's disease (PD) | Prevalence 1% in people >60 years. 60% of patients with PD develop psychotic symptoms | Resting tremor, rigidity, bradykinesia. Visual hallucinations are the most common psychotic symptom | Stereotyped and nonfrightening visual hallucinations are common; delusions are less common, usually paranoid and nonbizarre | In PD, dopaminergic neurons degenerate in substantia nigra. Hallucinations are associated with REM sleep behavior disorder, indicating possible LBD in the neocortex. | Dopaminergic therapeutic drugs, e.g., L-DOPA carbidopa, used to treat Parkinson's may induce psychosis. Treatment of motor symptoms versus psychosis requires balance. Low dose quetiapine may be beneficial. |
| Frontotemporal dementia (FTD) | 5% of cases of dementia; psychosis occurs in 15–20% of patients with FTD | FTD includes several, specific genetically defined subtypes. Delusions, hallucinations can occur but are not prominent | Somatic delusions, bizarre delusions, visual hallucinations can occur. | Pathologically, TAR DNA-binding protein-43 (TDP-43) is often present in FTD and related disorders. | RCTs of psychosis in FTD are lacking; low dose antipsychotics are used infrequently. |

EOS: early onset schizophrenia. CBT: cognitive behavioral therapy. RCT: randomized clinical trial. ECT: electroconvulsive therapy. REM: rapid eye movement. PET: positron emission tomography. EPS: extrapyramidal signs.

### Alzheimer's disease (AD)

Psychosis occurs in 30–50% of patients with AD during their disease course. Delusions occur in approximately 15–30% of patients with mild to moderate AD without any increase in prevalence with disease severity (Devanand *et al.*, 1997; Lyketsos *et al.*, 2002). Delusions of theft are common and typically directed at the spouse or other caregivers; delusions of persecution, infidelity, and abandonment also occur. Phantom boarder syndrome, which is the belief that someone else is staying in the home, is less common but can be disruptive to the patient and the caregiver. Misidentification due to cognitive worsening can manifest as a delusion, including the belief that one's house is not one's home or that a family member is an imposter (Capgras syndrome). Hallucinations occur in 5–15% of patients in the mild to moderate stage, may not be well-defined, and manifest in any sensory modality with visual and auditory hallucinations being the most common. Agitation is commonly comorbid with psychosis.

Neurodegeneration in most types of dementia, particularly AD and LBD, is associated with degeneration of the major neurotransmitter pathways, including dopaminergic pathways. There may be a therapeutic window of D2/D3 receptor occupancy to treat psychosis in AD (Reeves *et al.*, 2017). Serotonin (5-HT) is reduced in the ventral temporal cortex and prosubiculum in AD with psychosis compared to AD without psychosis, which may be related to lower cell counts in the dorsal raphe nucleus in AD with psychosis (Creese *et al.*, 2014). There may be an altered monoamine-cholinergic balance in both AD and LBD patients with psychosis (Perry *et al.*, 1990). Increased neocortical neurofibrillary tangle density has been reported in AD with psychosis (Farber *et al.*, 2000). In AD psychosis, PET studies have been limited while MRI studies show associations of delusions with increased frontotemporal, hippocampal, and parahippocampal atrophy (Lee *et al.*, 2019). The risk for psychosis in AD may be familial with an estimated heritability of 61%, which compares with 50–60% for AD more broadly (Hollingworth *et al.*, 2012).

Behavioral interventions that include caregiver education are recommended as first-line treatment based on small to medium effect sizes in single-blind trials of agitation in dementia (Tampi and Jeste, 2022). Psychosis, which often accompanies agitation, has not been the primary outcome in these behavioral trials.

Pharmacological treatments currently are not approved for psychosis in patients with dementia in the USA, and only a few countries have approved the use of atypical antipsychotics in limited circumstances in patients with dementia. Nevertheless, many patients are treated off-label with antipsychotics; placebo-controlled RCTs of these medications have shown inconsistent efficacy with small effect sizes. Among the atypical antipsychotics, risperidone in the dose range of 0.5–2 mg daily has the strongest evidence for efficacy with a small to medium effect size (Katz *et al.*, 2007). Antipsychotic use in patients with dementia is associated with increased risk of mortality with an odds ratio of 1.6 that led the FDA to issue a boxed warning in 2005 (Schneider *et al.*, 2005). Antipsychotic use in older patients with dementia and psychosis is also associated with other adverse reactions including EPS, autonomic side effects, and cognitive impairment. Both RCTs and electronic health record studies show that the risk of adverse effects and mortality increases markedly for higher compared to lower doses for all commonly used antipsychotics (Gerhard *et al.*, 2014; Huybrechts *et al.*, 2012). In the large NIMH-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE-AD) trial, which compared olanzapine, quetiapine, and risperidone to placebo for psychosis, aggression, and agitation in AD, the benefits of antipsychotic treatment on symptoms were offset by adverse effects (Schneider *et al.*, 2006).

The advent of atypical antipsychotics led to a decrease in tardive dyskinesia in older adults, though EPS remain a concern with increased risk of falls. Recently, the FDA in the USA has approved two medications for treatment of tardive dyskinesia – viz., valbenazine and deutetrabenazine (McEvoy, 2019). Standardized measures to assess behavioral symptoms in neurocognitive disorders, such as the Neuropsychiatric Inventory, can help to monitor the effects of treatment. Antipsychotic discontinuation in patients with dementia in nursing homes, which is required by the Centers for Medicare and Medicaid Services in the USA "unless clinically contraindicated", is associated with an increased rate of relapse; this risk of relapse needs to be balanced against the increased likelihood of adverse effects with long-term antipsychotic treatment (Devanand *et al.*, 2012). Although very few countries have approved the use of antipsychotics to treat psychosis in patients with dementia, based on the available evidence, antipsychotics may be used in individuals with psychosis associated with dementia when the symptoms are severe or refractory and when non-pharmacological treatments have not produced benefit or are not safe or feasible to employ. Furthermore, antipsychotics should be used at the lowest effective dosage and for the shortest possible time, with close monitoring of risk factors and adverse effects (Tampi and Jeste, 2022).

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### Lewy body dementia (LBD)

LBD symptoms include progressive memory loss, visual hallucinations, parkinsonism, cognitive fluctuations, and rapid eye movement sleep behavior disorder. LBD is associated with psychosis in 30–80% of patients during the disease course. Hallucinations are more common in LBD than AD. Visual hallucinations are one of the criteria for making the diagnosis of LBD but not all patients with LBD manifest this symptom (McKeith *et al.*, 2017). Hallucinations in LBD range from incompletely formed passage hallucinations (perception in the peripheral visual field that a person or animal is passing by) to presence phenomena (someone is present even though no one is there) (Outeiro *et al.*, 2019). Pareidolias, which are complex visual illusions involving ambiguous forms that are perceived as meaningful objects, are analogous to visual hallucinations in LBD.

In clinically diagnosed patients with LBD, SPECT, or PET scan shows decreased dopamine transporter as in PD, and CSF biomarkers for AD may be positive in LBD (Outeiro *et al.*, 2019). In patients with dementia who manifest psychosis during life, AD alone, LBD alone, and comorbid AD with LBD are all commonly identified in autopsied brains (Devanand *et al.*, 2022).

Patients with LBD are more sensitive to antipsychotic medications and at high risk for severe adverse reactions including EPS and anticholinergic and hypotensive effects. In small clinical trials, low doses of olanzapine and quetiapine showed limited efficacy in the treatment of psychosis in LBD (Cummings *et al.*, 2002; Culo *et al.*, 2010).

### Cognition and mechanisms of psychosis in AD and LBD

The cognitive profile of psychosis in AD and LBD may be a more severe variant of a modal neurocognitive profile in which episodic memory disturbances are most prominent, along with slowing in speed of processing and impairments in semantic, naming, and executive abilities, as well as visual processing/visual construction impairments. These impairments reflect the progression of neurodegeneration but are not specific to psychosis.

In a series of 1808 brain autopsies from the National Alzheimer's Coordinating Center (NACC) database in the USA, we found an association between greater severity of psychotic symptoms and greater evidence of pathology in AD (Devanand *et al.*, 2022). Increase in alpha-synuclein pathology, which indicates LBD, from midbrain to limbic and then neocortical areas was strongly associated with the presence and severity of psychosis. Neocortical Lewy bodies are prominent in parietal and occipital cortex but interestingly, not primary visual cortex. There are, however, severe impairments in visual and visual spatial identification in such patients, and these deficits may promote visual hallucinations or pareidolias. In PET studies of LBD psychosis, misidentification syndromes were associated with insula, prefrontal, and hippocampal hypoperfusion, perhaps consistent with a loss of interoceptive or mnemonic confirmation of identity, along with a failure in monitoring reality. Visual hallucinations in LBD correlate with lower glucose metabolism and weaker metabolic connectivity in the parietal-occipital cortex, but stronger connectivity in the insula and prefrontal cortex (Ffytche *et al.*, 2017). In AD, both the extra-striatal dorsal and ventral visual streams for visual processing are heavily compromised and could result in bottom-up-driven visual hallucinations. In particular, the fusiform face area and parahippocampal 'place' area appear to be involved. Visual hallucinations are more frequent than auditory hallucinations in AD and LBD in contrast to predominantly auditory hallucinations in schizophrenia, suggesting different underlying mechanisms.

### Psychosis in FTD

There are several subtypes of FTD, most of which have specific underlying genetic abnormalities. In patients with FTD, the neuropathological diagnosis is termed frontotemporal lobar degeneration (FTLD). Description of the genetics of the large number of genetic subtypes in FTD is beyond the scope of this review. Delusions and hallucinations are less common in FTD and vascular dementia compared to AD and DLB. In an autopsy study, hallucinations were uncommon in patients with FTD but delusions, including paranoid and somatic delusions, occurred in up to one-third of patients with the TDP-43 subtype but was rare in the tau-subtype of FTD (Naasan *et al.*, 2021). In the NACC consortium postmortem series of 1808 brains with dementia diagnoses, psychotic symptoms were present in 22% of FTLD cases with a higher prevalence in AD and LBD (Devanand *et al.*, 2022). There have been no clinical trials to treat psychosis in FTD and antipsychotics are rarely used clinically in this condition.

### Vascular dementia

Vascular dementia may be a consequence of a large stroke, multiple lacunes and infarcts, or extensive microvascular pathology. While psychosis has been described in vascular dementia, it is less common than in AD or LBD and psychosis in these patients

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may be related to comorbid AD or LBD. Patients with vascular dementia and mixed dementia (vascular dementia with AD) have been included in antipsychotic trials that focused on patients with AD. These trials showed no differences in efficacy between AD and mixed dementia (Mühlbauer *et al.*, 2021).

### PD psychosis

PD is a disease of the basal ganglia resulting in abnormalities in motor function, and psychosis can develop during the illness. During the course of illness, psychotic symptoms occur in 60% of patients with PD, often because of treatment with excessive doses of dopaminergic medications, including the widely used L-DOPA Carbidopa combination that targets the basal ganglia dopamine deficit (Ffytche *et al.*, 2017). Lowering the doses of these drugs to reduce psychotic symptoms usually worsens rigidity and tremor, leading to difficulty in balancing efficacy against side effects of dopaminergic anti-Parkinsonian drugs. Hallucinations are prominent in PD psychosis. Some drug-naïve patients, however, may experience "minor" hallucinations and correlations between the dose of the dopamine agonist and hallucinations are not strong (Lenka *et al.*, 2019). Hallucinations have been associated with rapid eye movement (REM) sleep behavior disorder in PD, indicating possible LBD in the neocortex. Quetiapine in low doses is used clinically to treat psychosis in PD but controlled evidence of its efficacy is lacking. Pimavanserin has been approved for the treatment of psychosis in PD in the USA.

Table 1 describes the key commonalties and distinctions among late-onset psychotic disorders in older adults. In the table, we have included common disorders reviewed in this paper that need consideration in the differential diagnosis of new-onset psychosis in older adults.

## Conclusions and future directions

Late-onset psychotic disorders are the manifestations of a variety of etiologies. Careful history and examination with laboratory investigations may be necessary to rule out possible reversible causes that include complications of medical illnesses and medication toxicity. Some late-onset psychotic disorders have overlapping clinical features with psychoses of earlier onset, e.g., schizophrenia, delusional disorder, psychotic depression, and bipolar disorder, but have unique characteristics as well. Psychosis often develops in delirium, dementia, and PD. Genetic predisposition demonstrated for early-onset psychotic disorders is generally uncommon in late-onset psychoses.

Pharmacokinetic and pharmacodynamic changes that occur with aging lead to an increased sensitivity to the adverse effects of various medications, especially antipsychotics. These include EPS, tardive dyskinesia, orthostatic hypotension, cognitive impairment, falls, and anticholinergic effects that impair cognitive functioning. Higher doses of antipsychotics are associated with increased mortality in older adults, particularly in those with dementia. Lower doses, typically a quarter of the dose prescribed in young adults, are recommended to reduce adverse effects and mortality risk. In older adults with psychotic depression and bipolar disorder, it is advisable to use low doses of antipsychotics, anticonvulsants, and lithium. Hallucinations, predominantly visual hallucinations, and delusions occur in nearly half of patients who develop delirium for which evidence for the efficacy of psychotropic medications is lacking. Delusions and hallucinations are common in AD, LBD, and related dementias. In subtypes of dementia, hallucinations are more often visual than auditory. Psychosis in dementia is associated with increased agitation, and these complications increase the risk of hospitalization, institutionalization, and death. Antipsychotics, though widely used, have not been approved to treat psychosis in dementia in the USA and most other countries, and have been shown to be associated with increased mortality.

More systematic research is needed into the neurobiology and optimal therapeutic strategies for LOS, delusional disorder, psychotic depression, bipolar disorder, and isolated hallucinations in older adults. While research on psychosis in dementia subtypes is expanding, there remains a pressing need for better understanding of the underlying neurobiology of psychosis and evidence-based pharmacological and nonpharmacological therapeutic strategies for these disorders, which are increasing in prevalence with the aging of the population and represent a growing and largely unmet public health need.

## Conflict of interest

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