Late Life Psychosis

Presenter: Dr. Milta Little
Disclosure Statement: I have nothing to disclose.

Objectives: By the end of the session, participants will be able to…

- Define psychosis
- Distinguish primary and secondary psychosis
- List the "Six D's" of psychotic disorders
- Identify the common medical causes of psychosis in older adults
- Discuss the potential risks and benefit for the use of antipsychotic medications

Expected Outcomes (Desired change in practice):

- Improve diagnostic reasoning for the causes of psychosis
- Increase confidence in the management of psychosis

Article for Review:

- Tampi RR, et al. Psychotic disorders in late life: a narrative review. Ther Adv Psychopharmacol 2019; 9:1-13

Additional Article:

- Reinhardt MM and Cohen CI. Late-Life Psychosis: Diagnosis and Treatment. Curr Psychiatry Rep 2015; 17:1-13

Outline for Rapid Fire session

1. Case presentation: Late Life Psychosis

   Ms. P is an 81 y/o cis-gender female was recently admitted to the secure memory unit of your long-term care facility after wandering out of her home where she lived with her daughter. She has a history of dementia (unknown type), CAD, HTN, CKD, macular degeneration, and recurrent UTIs. You receive a call from the unit charge nurse while rounding on a different unit asking you to evaluate Ms. P. She tells you that since admission, she has been accusing staff of stealing her belongings and poisoning the food. She will only eat what her daughter brings in sealed containers from the deli of the local grocer near her house. She will also on occasion become agitated because of the rodents she sees running around the building and shadows of people creeping into her room at night. She is particularly agitated today and has been trying to hit staff who approach her for care.

   What are your thoughts? What do you do next to evaluate Ms. P? How will you manage her psychosis?

2. Definition of psychosis – the presence of hallucinations, delusion, or a limited number of several abnormalities of behavior, such as gross excitement and overactivity, marked psychomotor retardation and catatonic behavior
   a. Primary – caused by a psychiatric disorder (schizophrenia, bipolar, schizoaffective)
   b. Secondary – due to a medical or neurological disorder

3. Main take home points
   a. Life-time risk of psychosis in older adults us up to 23% and occurs in 10-62% of NH residents
   b. Schizophrenia has a prevalence of 0.1-0.5% among older adults
   c. Older persons with MDD are more likely to have psychotic features and be resistant to treatment (usually mood-congruent delusions)
   d. Primary psychosis (e.g. late-onset or very late-onset schizophrenia) should be the *final* consideration after eliminating secondary causes
   e. Secondary psychosis accounts for 60% of late life psychosis
   f. A careful and thorough history is key. The following suggest secondary psychosis:
      i. Visual hallucinations independent of auditory hallucinations
      ii. No previous psychiatric or family history of psychotic disorder
      iii. Abnormal physical examination or known medical/neurologic condition or medication that could cause psychosis
      iv. Abrupt personality changes or abnormal cognition
      v. No signs are pathognomonic for either primary or secondary

4. The “Six-Ds”
    a. Delusional disorder and Schizophrenia-spectrum (primary)
    b. Depression and other affective disorders (primary)
    c. Dementia – 40% (secondary)

Table 2. Differences between psychosis of dementia and schizophrenia.[33,34,36,37]

Features	Psychosis of dementia	Schizophrenia
Prevalence	15–78% of patients	<1% of general population
Bizarre or complex delusions	Rare	Frequent
Misidentification	Frequent	Rare
Common form of hallucination	Visual	Auditory
Schneiderian First rank symptoms *ABCD:Auditory hallucinations, Broadcasting of thought, Controlled thought (delusions of control), Delusional perception*	Rare	Frequent
Past history of psychosis	Rare	Common
Eventual remission of psychosis	Frequent	Uncommon
Need for maintenance antipsychotic therapy	Uncommon	Common

    d. Delirium – 10% (secondary)
    e. Drugs/alcohol/toxins (secondary) – direct insult, intoxication, withdrawal
    f. Disease (MINE)

5. Common underlying medical causes – MINE

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

Metabolic	• Vitamin B_{12} deficiency • Folate deficiency • Electrolyte abnormalities ○Sodium ○Potassium ○Calcium ○Magnesium • Acute intermittent porphyria • Hepatic encephalopathy • Uremic encephalopathy • Other nutritional deficiencies • Anoxia/hypoxia • Hypercarbia
Infections	• Meningitides • Encephalitides (e.g., herpes, etc.) • Neurosyphilis • HIV/AIDS • Pneumonia
Neurological	• Parkinson's disease • Epilepsy ○Temporal lobe epilepsy ○Grand mal ○Non-convulsive status epilepticus • Subdural hematoma • Cerebrovascular events • Huntington's disease • Multiple sclerosis • Amyotrophic lateral sclerosis • Tumors ○Temporal lobe—auditory hallucinations ○Occipital lobe—visual hallucinations ○Limbic—delusions ○Hypothalamus—delusions • Limbic encephalitides • Autoimmune[reference] ○Paraneoplastic syndromes ○Systemic lupus erythematosis ○Vasculitides • Sleep disorders (narcolepsy) • Other genetic/heritable conditions ○Likely to have been diagnosed in childhood
Endocrine	• Hypo-/hyperthyroidism • Adrenal disease • Hypo-/hypoglycemia • Hypo-/hyperparathyroidism

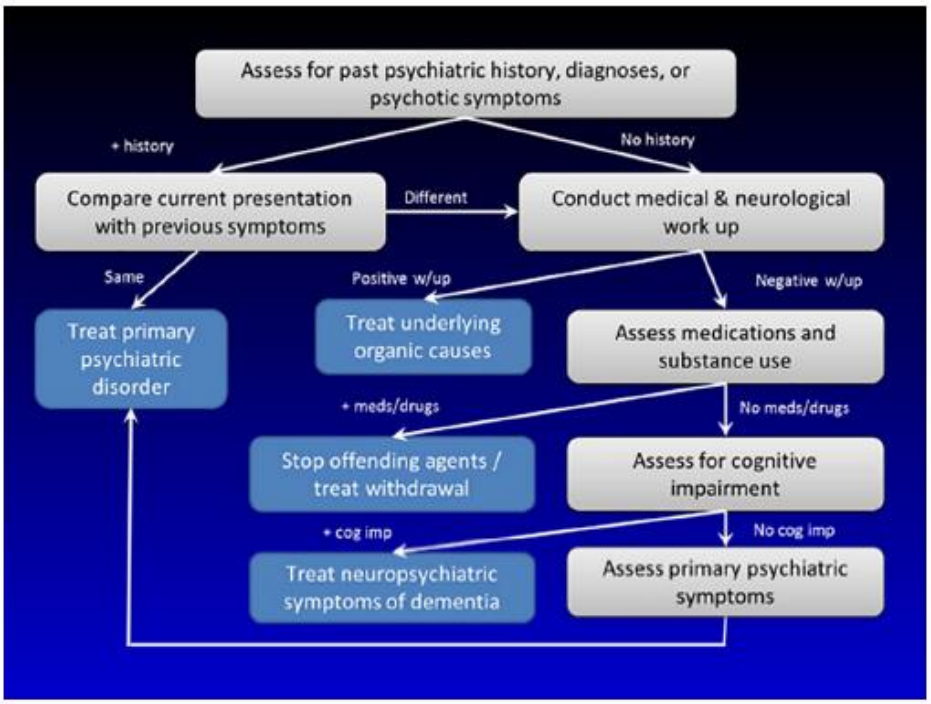

Figure 1. Pathway for identifying the etiologies for psychotic symptoms in late life.

6. Management of late-life psychosis
    a. Primary psychosis should consult with geriatric psychiatry specialist
    b. Non-pharmacological approaches are always first-line
        i. Alleviate unmet needs
        ii. Caregiver support/education, music therapy, cognitive stimulation therapy, multisensory stimulation, behavioral management, staff training/education
    c. ECT for severe depression with psychosis
    d. Medications
        i. Antipsychotics
            1. Risperidone and olanzapine typically considered first line
            2. Quetiapine and risperidone fewer metabolic effects
            3. Pimavanserin in PD only
            4. Clozapine for DLB with specialist assistance
        ii. Antidepressants – sertraline and citalopram
        iii. Acetylcholinesterase inhibitors and memantine in dementia

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Psychotic disorders in late life: a narrative review

Rajesh R. Tampi, Juan Young, Rakin Hoq, Kyle Resnick and Deena J. Tampi

***Abstract*:** Psychotic disorders are not uncommon in late life. These disorders often have varied etiologies, different clinical presentations, and are associated with significant morbidity and mortality among the older adult population. Psychotic disorders in late life develop due to the complex interaction between various biological, psychological, social, and environmental factors. Given the significant morbidity and mortality associated with psychotic disorders in late life, a comprehensive work-up should be conducted when they are encountered. The assessment should not only identify the potential etiologies for the psychotic disorders, but also recognize factors that predicts possible outcomes for these disorders. Treatment approaches for psychotic disorders in late life should include a combination of nonpharmacological management strategies with the judicious use of psychotropic medications. When antipsychotic medications are necessary, they should be used cautiously with the goal of optimizing outcomes with regular monitoring of their efficacy and adverse effects.

Keywords: delusional disorder, elderly, geriatric, late life, late-onset schizophrenia, psychotic disorders, schizoaffective disorder, schizophrenia, very late-onset schizophrenia-like psychosis

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Introduction

Although a formal definition of 'psychosis' is not stated in either the DSM-5 or the ICD classification systems, psychotic features include the presence of delusions, hallucinations, disorganized thinking (speech), grossly disorganized motor behavior (including catatonia), or negative symptoms.[1–3] When disorders are associated with psychotic features, they are termed psychotic disorders, for example, Schizophrenia Spectrum and Other Psychotic Disorders (DSM-5). The etiologies for psychosis in late life differs from psychosis in younger individuals, with a greater incidence of secondary causes for psychosis among older adults.[4] In addition, psychosis in late life is associated with higher rates of morbidity and mortality when compared with psychosis among younger adults.[5] Furthermore, the treatment of psychosis is complicated by the higher incidence of adverse effects when antipsychotic medications are prescribed to older adults when compared with younger adults.[6]

This paper intends to provide a comprehensive narrative review of the epidemiology, diagnostics, risks factors, and pathophysiology, as well as the treatment of psychotic disorders of late life. This review includes studies obtained through a literature search of the PubMed, MEDLINE, and Cochrane collaboration databases on 20 March 2019 using keywords related to each section about psychotic disorders in elderly patients (e.g. epidemiology of psychosis in late life, treatment of psychotic disorders in late life, psychosis in neurocognitive disorders, affective psychosis in late life, schizophrenia in late life, ICD-11 schizophrenia, etc.). The search was conducted by all authors, and if there were disagreements regarding the inclusion or exclusion of papers, a consensus was reached through discussion amongst all the authors. The authors included studies that they thought would be beneficial in educating practitioners about psychotic disorders in late life. The search was not restricted by the age of the participants. This review only included studies in human subjects published in English-language journals or those with official English translations. Studies that were included in this manuscript were not restricted by date of publication.

Correspondence to:
Rajesh R. Tampi
Department of Psychiatry and Behavioral Sciences, Cleveland Clinic Akron General, Akron, OH 44307, USA

Section for Geriatric Psychiatry, Cleveland Clinic, Cleveland, OH 44195, USA

Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH 44195, USA
rajesh.tampi@gmail.com

Juan Young
Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA

Rakin Hoq
Kyle Resnick
NeoMed/Summa Psychiatry Residency Program, Akron, OH, USA

Deena J. Tampi
Diamond Healthcare, Richmond, VA, USA

Epidemiology

Understanding the possible etiologies for psychotic disorders in late life is important as they can have significant implications in both the presentation and treatment for these conditions. The initial primary distinction to be made is between primary psychotic disorders and secondary psychotic disorders.[7]

Primary psychotic disorders comprise illnesses where the psychotic symptoms appear as part of the core symptoms of the disorder, and include conditions like schizophrenia spectrum illnesses (which can be further subdivided in to categories of late-onset (LOS) and very-late onset schizophrenia-like psychosis (VLOS), as well as psychosis as a symptom of affective disorders like major depressive disorder or bipolar disorder. Secondary psychotic disorders include psychosis as a symptom of another disorder including neurocognitive disorders, delirium, illicit substance use, prescribed medications, or other medical and neurological disorders.[8,9] It is very important to identify the etiologies for psychosis among older adults as a majority of the cases (approximately 60%) of psychosis occur as a result of these disorders.[8,10,11]

Schizophrenia has a prevalence among older adults of approximately 0.1–0.5%,[12,13] which contrasts with the overall lifetime prevalence of schizophrenia at about 1%. The relatively lower prevalence of schizophrenia among older adults can be accounted for by the increased premature mortality (due to various causes) among individuals with this illness.[14,15] However, one should keep in mind that the cited prevalence of schizophrenia among older adults does not distinguish between younger adults with a diagnosis of schizophrenia who grew older versus incident cases of schizophrenia among older adults.

Schizophrenia can be further subdivided in to categories of early-onset (EOS, onset before age 40 years old), late-onset (LOS, onset at 40–60 years old), and very-late-onset schizophrenia-like psychosis (VLOS, onset after age 60).[4] Approximately 75–80% of cases of schizophrenia are of early onset by this definition, with 20–25% of cases being incident in late or very-late life.[16] The estimated incidence of schizophrenia after the age of 65 years is 7.5 per 100,000 person-years.[17] In the largest cohort study to date investigating epidemiology of VLOS, Stafford and colleagues found a crude incidence rate of VLOS to be 37.66 per 100,000 person-years at-risk.[18] They also found VLOS to have a preponderance of women (60%) with an accelerating incidence rate after age 80. There are notable differences in the symptomology and neuropsychiatric sequelae between EOS, LOS, and VLOS. It should be noted that risk of dementia has been shown to be increased in people with any history of schizophrenia.[19,20] In fact, a recent meta-analysis found a significantly greater risk of developing dementia [relative risk (RR) 2.29; 95% confidence interval (CI) 1.35–3.88] in individuals with schizophrenia.[21] Table 1 delineates the notable differences between each of these conditions.

A study by Meesters and colleagues estimated the 12-month prevalence of schizoaffective disorder among adults ⩾60 years to be at 0.14%.[24] Older adults with schizoaffective disorder appear to have greater severity of illness with worse outcomes, including greater treatment resistance and risk for suicide.[25] Older adults with schizophrenia and schizoaffective disorders have similar mortality rates, negative symptom burden, and clinical global impression of impairment.[26] In addition, older adults with schizophrenia or schizoaffective disorder are less likely to drive, are less likely to be married, and less likely to live independently compared with age-matched individuals with bipolar disorder. Also, individuals with the depressive-type of schizoaffective disorder more often had a history of suicide attempts and were more likely to be treated with an antidepressant medication compared with those with the bipolar-type illness.[26]

Data on delusional disorder among older adults is limited, but, typically, delusional disorder tends to occur in mid-to-late life (average age of onset being about 49 years old).[27] The estimated prevalence of delusional disorder among older adults is 0.03%.[28] From what is known about delusional disorder among older adults, it will typically cause social dysfunction, but otherwise these individuals appear to have normal cognitive, personal, and occupational functioning.[15]

Psychosis can also arise as a complication of affective disorders including both depression and bipolar disorder. The overall incidence of affective psychosis among older adults is estimated to be about 30.9 per 100,000 person-years.[17] However, it is important to consider that psychotic depression actually becomes more common in later life, with an estimated average age of onset of 51.2 years of age and delusions estimated to occur in as high as 45% of elderly patients admitted to hospitals for reasons related to

Table 1. Differences between EOS, LOS and VLOS.[4,20,22,23]

Features	EOS	LOS	VLOS
Age of onset	<40 years	40–60 years	>60 years
Female preponderance	No	Yes	Definitely
Negative symptoms	Definitely	May be	Less likely
Learning	Ok	Ok	Impaired
Retention	Ok	Ok	Impaired
Progressive cognitive deterioration	Yes	Yes	Yes (very high)
Brain structural abnormalities	No	No	Yes
Family history	Present	Present	Weak association
Early childhood maladjustments	Present	Present	Absent
Antipsychotic dosing	Higher	Lower	Lower
Risk of Tardive Dyskinesia	Present	Present	Very high

EOS, early onset schizophrenia; LOS, late onset schizophrenia; VLOS, very late onset schizophrenia like psychosis.

depression.[29] It has also been observed that, among older adults with psychotic depression, there was a higher prevalence of comorbid anxiety and somatic symptoms.[30]

The 1-year prevalence rate of bipolar disorders among older adults is 0.1%, which is lower than the prevalence rates among adults aged 18–44 years (1.4%) and 45–64 years (0.4%).[31] Much of the data reporting psychotic features in bipolar related illnesses among the elderly do not distinguish psychosis related to mania versus psychosis related to depression.[32] The mean frequency of psychotic features in bipolar disorder among the elderly that was pooled from a review of five studies was found to be 64%.[30] This frequency is actually similar to the frequency of psychotic symptoms seen among middle-aged adults with bipolar disorder, but older adults were noted to have more paranoia when compared with younger individuals.[32]

The overall pooled prevalence of psychotic symptoms among individuals with major neurocognitive disorders is estimated to be as high as 40%. In a literature review by Ropacki and Jeste, the investigators found a mean pooled prevalence of hallucinations or delusions among individuals with Alzheimer's disease (AD) to be 41.1%.[33] In the largest United States (US) population-based study to date, conducted by Leroi and colleagues, the investigators found the prevalence of hallucinations or delusions among individuals with vascular dementias to be about 15%.[34] In addition, in the same study, they delineated types of delusions, and found persecutory delusions to be the most common type of delusion in both AD and vascular neurocognitive disorders. They also found that visual hallucinations appeared to be more common than auditory hallucinations in both AD and vascular neurocognitive disorders. Among individuals with neurocognitive disorders with Lewy bodies, Nagahama and colleagues found the prevalence of visual and auditory hallucinations and delusions to be 78% and 25%, respectively.[35] Table 2 describes the differences between psychosis seen in individuals with dementia and schizophrenia.

The prevalence of any psychotic symptoms in delirium is estimated to be 42.7%, with a specific prevalence of visual hallucinations being 27%, auditory hallucinations 12.4%, tactile hallucinations 2.7%, and delusions 25.6%.[9] Older adults are at particular risk for developing psychosis secondary to drugs, toxins, and other underlying medical illnesses due to higher medical comorbidity, polypharmacy, and sensitivity to drug effect.[38] Due to the diversity of secondary causes of psychosis in older adults, it is difficult to elucidate epidemiologic statistics for all secondary psychoses (excluding the neurocognitive disorders as

Table 2. Differences between psychosis of dementia and schizophrenia.[33,34,36,37]

Features	Psychosis of dementia	Schizophrenia
Prevalence	15–78% of patients	<1% of general population
Bizarre or complex delusions	Rare	Frequent
Misidentification	Frequent	Rare
Common form of hallucination	Visual	Auditory
Schneiderian First rank symptoms *ABCD:Auditory hallucinations, Broadcasting of thought, Controlled thought (delusions of control), Delusional perception*	Rare	Frequent
Past history of psychosis	Rare	Common
Eventual remission of psychosis	Frequent	Uncommon
Need for maintenance antipsychotic therapy	Uncommon	Common

discussed earlier). Table 3 describes the differences between the presentation of delirium, AD, Lewy body dementia (LBD), and depression.

Risk factors and pathophysiology

Risk factors that are associated with developing psychotic disorders among older adults include cognitive decline, poor health status, visual impairment, and negative life events.[39] In addition, female gender appears to be a risk factor for developing late-onset schizophrenia and VLOS.[40] Furthermore, being from an immigrant population, greater abnormalities in brain structures, family history of schizophrenia or avoidant personality, paranoid or schizoid personality disorder, hearing loss, and being from a lower socioeconomic status are risk factors for VLOS.[4] Premorbid educational, occupational, and psychosocial functioning appears to be less impaired among late-onset than among early-onset individuals with schizophrenia.[11]

A recent study that compared the key risk factors among individuals with schizophrenia to identify trends according to the age of onset, comparing presentations prior to 26 years (youth onset), between 26 and 40 years (middle onset), and after 40 years of age (late onset) found that the older age of onset was associated with a weaker family history of schizophrenia, lower rates of substance use, better early psychosocial functioning, and higher educational achievement. In addition, female preponderance and comorbid physical health problems were notable among the late onset group compared with the other groups.[23] Furthermore, individuals in the later life schizophrenia group showed a relatively greater association with psychosocial factors proximal to the onset of psychosis, including unemployment.

One study found that the genetic variant in Dopamine D2 receptor (DRD2), rs2734839, was significantly associated with schizophrenia as well as late onset age.[41] Individuals who were carrying this genetic variation were more than twice as likely to have schizophrenia when compared with controls. Available evidence indicates that individuals with LOS appear to have larger thalamic volumes and abnormalities in white matter integrity when compared with individuals with EOS.[42–44] In addition, reduced cerebral blood flow has been noted in both postcentral gyri among individuals with LOS when compared with individuals with EOS, who had reduced blood flow to the precentral gyrus and inferior frontal gyrus.[45] One study found that older adults with delusional disorders had lateral ventricular volumes that were larger than those among older adults with schizophrenia and almost twice those of age-matched controls.[46]

Changes in dopaminergic, glutamatergic, and serotonergic systems associated with aging, including changes in the concentrations of these neurotransmitters, decline in serotonin receptors (5-HT2) and transporters (5-HTT), decreased dopamine and serotonin binding capacities, and reduced D1, D2, and D3 receptor densities are thought to be responsible extrapyramidal signs and symptoms including frequent falls, reduced

Table 3. Differences between delirium, AD, LBD, and depression.[9–11,37]

Characteristics	Delirium	AD	LBD	Depression
Presenting symptoms	Unfamiliarity with the environment with short term memory loss; "confusion"	Short term memory loss	Motor symptoms may appear before cognitive impairment; fluctuating cognition, visual hallucinations, and REM-sleep behavior disorder are part of core clinical features	Subjective complaints of poor memory and concentration
Onset	Sudden	Insidious	Insidious	Recent
Alertness	Fluctuating	Normal except in late phases	Fluctuating	Preserved
Duration	Hours to weeks	Months to years	Months to years	Variable
Orientation	Disorientation with onset	Disorientation occurs late in course	Fluctuating	Intact
Hallucinations	From onset	May occur late in course	From onset; visual hallucinations well-formed	Could occur in depression with psychotic features
Cognitive functioning	Fluctuating with alertness	Progressive deterioration	Progressive deterioration	Initially intact with efforts to perform cognitive tasks. May deteriorate without treatment progression
Mood	Fluctuate	Labile	Labile	Usually sad
Sundowning	Present	Present	Present	Absent, mood improve as day progress
Course	Usually reversible with treatment	Irreversible with progressive deterioration	Irreversible with progressive deterioration	Completely reversible

AD, Alzheimer's disease, LBD, Lewy Body dementia; REM, rapid eye movement.

cognitive flexibility, and sensitivity to psychotropic medications among older adults.[47]

Diagnosis

Diagnosing psychotic disorders among older adults can be difficult given the multitude of etiologies that can result in psychotic symptoms among these vulnerable individuals.[48] Differentiating between LOS and VLOS could be helpful in these guiding diagnostic efforts. Similar efforts have been made to categorize diagnosis of psychotic disorder in other age groups, including early-onset (psychotic symptoms present before the age of 17) and very early-onset (referring to psychotic symptoms present before the age of 12).[49] The initial diagnostic dilemma is to differentiate between the symptoms of psychosis due to a primary psychotic disorders versus psychotic symptoms that are secondary to medical/neurological disorders or due to the effect of medications or illicit drugs.[50] The World Health Organization recently has made efforts in the ICD-11 to address this challenge by renaming 'F2 Schizophrenia, schizotypal, and delusional disorders' to 'Schizophrenia spectrum and other primary psychotic disorders', to drive differentiation of these etiologies.[49]

A thorough history can help differentiate between primary and secondary causes psychosis in late life.[51] Acute or subacute onset of symptoms might suggest a secondary cause for the psychosis (e.g. delirium with an onset of days to weeks, or substance/medication-induced psychosis, with an onset of days to months). Neurocognitive disorders, on the other hand, may result in psychotic symptoms features that tend to have an insidious onset of symptoms that may take months to years

for the progressive development of symptoms. Primary psychotic disorders such as schizophrenia spectrum disorders or affective disorders with psychotic symptoms, or delusional disorders, may have onset varying from weeks (especially in the case of mood disorder) to decades. Older adults who are have a history of abuse or neglect may have paranoia towards others that may be justifiable or not pathological given their history.[52]

Two important principles that may help guide the diagnosis of psychosis in later life include:

(1) Assume until proven otherwise that new-onset of psychotic symptoms among older adults is secondary in nature, as approximately 60% of psychosis in late-life has a secondary cause.
(2) There are no pathognomonic findings for any given psychiatric illness in late life; hence, a broad differential diagnosis should be entertained.

In order to differentiate primary and secondary psychotic disorders, scrutiny of certain characteristics can be helpful. Secondary psychotic disorders tend to have atypical age of onset of symptoms.[39] If visual hallucinations are present independently of auditory hallucinations, suspect a secondary psychotic disorder. Psychotic symptoms in an individual with no previous psychiatric history or no family history may be suggestive of secondary cause for psychosis. Psychosis along with abnormalities in physical examinations also suggests a secondary psychotic disorder. Medical or neurological disorders with known psychiatric sequelae, or the presence of medication or illicit substances misuse, also suggests a secondary cause for psychotic symptoms among older adults.[53]

Clinicians should also gather collateral history through interviewing family members and discussing salient features of cases with other providers. In addition, conducting thorough physical examinations and cognitive assessments will help differentiate the various etiologies for the psychotic symptoms. Brain imaging such as magnetic resonance imaging (MRI) or computerized tomography (CT) scans can rule out structural brain abnormalities in the brain that could manifest psychotic symptoms. CT scans are faster to acquire than MRIs and would be more beneficial when examining anxious or claustrophobic individuals. In contrast, MRIs are more likely to be utilized in patients with focal neurological findings suggestive of an organic cause for psychotic symptoms, and when higher detail of soft tissue is required.[54] Regular screening with imaging in first-episode psychosis patients is generally not recommended as a recent meta-analysis has indicated minimal diagnostic yield and clinical usefulness.[55] Common laboratory studies including complete blood count (CBC), complete metabolic panel (CMP), thyroid stimulating hormone (TSH), vitamin B12, folate level, rapid plasma reagin (RPR), erythrocyte sedimentation rate (ESR), urine toxicology and autoimmune panels, and HIV panels can identify causes for the psychotic symptoms among older adults.[56] Neuropsychological testing can help differentiate the etiologies and the extent of psychotic symptoms among older individuals.[57] Figure 1 describes the pathway for identifying the etiologies for psychotic symptoms in late life.

Treatment

Initial treatment of psychosis in late life often requires the elimination of possible causes of secondary psychotic symptoms, including offending medications or organic causes for these symptoms. Thus, the treatment of neurological disorders, delirium, and substance intoxication/withdrawals contributing to, or exacerbating, psychosis would be the first step in improving secondary psychotic symptoms. If psychotic symptoms are due to a primary psychiatric disorder, then pharmacological treatment becomes essential when these symptoms do not respond to nonpharmacological treatment strategies.[58] In addition, pharmacotherapy is necessary when the safety and well-being of the older individual or of others is being compromised. However, antipsychotic medications should be prescribed cautiously as their long-term use among older adults may result in significant negative health outcomes.[59,60]

Contemporary guidelines recommend the short-term use of antipsychotics to alleviate problematic symptoms to avoid long-term and nonreversible side effects.[6] Notably, while typical antipsychotics may exhibit a smaller metabolic side effect burden compared with atypical drugs, they do exhibit an increased risk of tardive dyskinesia.[61] In contrast, atypical antipsychotics often have the opposite side effect profile with metabolic adverse effects classically being more prominent while exhibiting a decreased risk of tardive dyskinesia as a result of more variable D2 receptor blockade. Thus, there should always be a risk vs. benefits analysis when

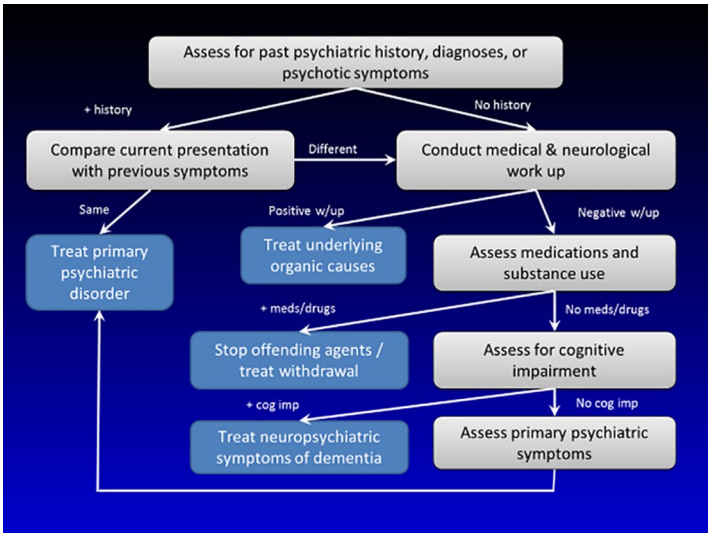

Figure 1. Pathway for identifying the etiologies for psychotic symptoms in late life.

employing psychotropics including a thorough evaluation of a patient's physical state and medical comorbidities prior to initiation of treatment.[6,62] In addition, lower dose initiation (1/2 the starting dose for adults) and gradual dose titration to the optimal dose may reduce the incidence of adverse effects.[63] Furthermore, older adults may require liquid preparations of psychotropic medications if they are unable to swallow tablets or capsules.[64]

There is a dearth of high-quality pharmacotherapy studies among individuals with LOS and VLOS. During our literature review, we only found two prospective/population based studies,[65,66] [Level 3 evidence according to the Centre for Evidence-Based Medicine (CEBM)],[67] two randomized controlled trials (RCTs) (Level 2 evidence),[68,69] and one expert consensus guideline (Level 5 evidence).[70] A Cochrane review also found only one study that they could include in their review.[71]

More recently, Howard and colleagues published an RCT investigating the effect of low-dose amisulpride (a D2/D3 receptor blocker) at 100 mg daily in patients diagnosed with VLOS.[68] The investigators found a significant improvement in the Brief Psychiatric Rating Scale (BPRS) in the amisulpride group compared with placebo, although it should be noted that the authors found no improvement in the secondary outcomes measuring patient-rated health-related quality of life, possibly reflecting the poor insight patients have regarding their psychotic symptoms.

There exists some data regarding the treatment of EOS in late-life using risperidone and olanzapine (Level 3 evidence),[65] although there is little evidence to support the use of clozapine in treatment-resistance geriatric patients due to the drug's significant side effect profile.[72] Paliperidone was also shown to demonstrate some efficacy compared with placebo in the treatment of elderly patients with schizophrenia (Level 2 evidence).[69] Recommended dosing is based on expert consensus. For example, risperidone dosage recommendations suggest administering 1.25 to 3.5 mg/day as the first-line agent. Alternatively, quetiapine may be dosed at 100–300 mg/day, olanzapine at 7.5–15 mg/day, and aripiprazole at 15–30 mg/day (Level 5 evidence).[70] Lastly, a recent population-based study (Level 3 evidence) investigating the effect of optimized dose adjustments of amisulpride for psychosis symptoms (i.e. delusions) in elderly patients with AD suggests that the 50 mg/day of amisulpride is the minimally clinically effective dose in that target population.[66] One caveat the authors reported though was that, in patients >75 years of age, 50 mg/day was also the maximally tolerated dose.[73]

Psychosis symptoms and agitation due to LBD are difficult to treat due to the possibility of worsening Parkinsonian symptoms with antipsychotic administration. In addition, there is a paucity of data concerning the safety and efficacy of antipsychotics in LBD.[74] However, studies indicate some utility for Clozapine in treating LBD-related psychosis (Level 2 evidence).[75–77] This is due to

Clozapine's greater serotonergic affinity and selective binding of D1 mesolimbic receptors while sparing striatal D2 receptors implicated in the deterioration of motor functions.[78] However, clinicians should remain mindful of Clozapine's significant side effect profile, which includes orthostatic hypotension, sedation, and agranulocytosis.[78] In contrast, studies and reviews investigating the efficacy and tolerability of other antipsychotics have reported mixed results. One systematic review investigating the efficacy of quetiapine in patients with LBD found only one open-label trial that was able to report a significant reduction in psychotic symptoms when patients were prescribed quetiapine at tolerable doses (Level 3 evidence).[79] Alternatively, one RCT investigating the efficacy of Olanzapine administration in LBD patients found that individuals treated with 5 mg daily dosages demonstrated improvements in hallucinations and delusions compared with the placebo group (Level 2 evidence).[80] Higher doses were not found be more effective than placebo. Caution should be exercised when prescribing neuroleptics in patients with LBD due to their potential to cause rigidity, neuroleptic malignant syndrome, and death as a consequence of the underlying disruption of dopaminergic neurotransmission.[81] If risks of neuroleptic administration outweigh any potential benefits they may produce, another option would be the use of a benzodiazepine such as clonazepam, which has the added benefit of treating the rapid eye movement (REM) sleep behavior disorder commonly found in LBD patients.[82] The 5HT2A receptor inverse agonist, Pimavanserin, has demonstrated efficacy in improving psychosis symptoms in Parkinson's disease,[83] but no trials or studies have yet to be conducted in LBD populations.

Despite being the drugs of choice in treating psychotic symptoms and severe agitation associated with dementia and delirium states, there are controversies regarding the use of antipsychotics among older adults who present with these symptoms.[84,85] This is due to the Food and Drug Administration (FDA) black box warning indicating an association between the administration of antipsychotics in geriatric patients and increased mortality risk.[62] Studies have also shown an increased risk of cerebrovascular events, metabolic side effects, and pneumonia with the prescribing of antipsychotics in older adults compared with same-age cohorts not being prescribed these drugs.[62,86] More recently, a systematic review and meta-analysis of the prevention and treatment of delirium with antipsychotics in adult surgical and medical patients suggests that antipsychotics may be more limited in their efficacy in treating delirium than once thought (Level 1 evidence).[87] Thus, careful consideration should be conducted before initiating medications that may produce serious harmful effects relative to the moderately beneficial effects they could potentially generate.[85]

Although there is an impetus to discontinue antipsychotics as soon as safely possible due to reports of increased risk of cerebrovascular adverse events and intolerable side effects in geriatric patients,[88,89] there is limited data regarding the discontinuation of antipsychotic medications in older adults diagnosed with chronic schizophrenia (Level 2 evidence).[90] As a result, it is imperative to attempt discontinuation of antipsychotics only in older patients who do not respond to these classes of medications or if they have demonstrated long-standing clinical remission. If discontinuation is not possible due to persistent psychotic symptoms, decreasing the dose of medications to the lowest effective dosage should be done to minimize risk of adverse events.

There is a paucity of studies investigating the treatment of psychosis symptoms using electroconvulsive therapy (ECT) in the geriatric population. However, one selective review reports that prospective trials of ECT in psychotic elderly patients (Level 3 evidence) have indicated that bilateral ECT is a safe and effective treatment for older patients with schizophrenia[91]; it was also found to be synergistic with concurrent antipsychotic therapy. The authors also noted that the best evidence for ECT treatment is its utilization in patients presenting with aggression, catatonia, and in other cases that require rapid response such as acute suicidality or an acute onset of illness.

Alternatively, the combination of pharmacotherapy and psychosocial modalities are the most likely to alleviate psychotic symptoms with the least risk of severe side effects associated with pharmacological therapy alone. Although the number of studies investigating these psychosocial modalities are limited, there is existing high quality data (Level 2 evidence) indicating some benefit from cognitive behavioral social skills training (CBSST), Functional Adaptation Skills Training (FAST), supported employment, social skills training, and preventative healthcare programs.[92–97] CBSST, for example, utilizes group

therapy to promote cognitive and behavioral coping skills, problem solving skills, and improved social functioning in order to compensate for neurocognitive deficits.[92] In contrast, FAST interventions focus more on improving daily living skills in middle-aged and older adults diagnosed with a psychotic disorder who live in the community. These interventions have been reported to help improve patient organization, arranging transportation, social skills, managing finances, and medication management.[94] In addition, combined skills training along with preventative health care and health management could be employed to promote social functioning and independent living skills.[95] Studies have also indicated that individuals with schizophrenia who received supported employment experienced better work outcomes and achieved superior quality of life measures compared with conventional vocational rehabilitation programs.[98,99] Hence, psychosocial treatment modalities have the potential to improve many aspects of life and daily living among older adults with psychotic symptoms. Their implementation in any treatment plan is likely to produce benefits if utilized in appropriate situations based on the needs of individual.

Treatment of individuals with late life psychotic disorders should always be individualized, with careful attention to comorbidities. In addition, the use of evidence-based nonpharmacological treatments in combination with pharmacological strategies can optimize outcomes in these cases. Nonpharmacological treatments for psychotic disorders in late life have the highest quality of evidence when investigating their efficacy and include cognitive skills training, functional adaptation skills training, social rehabilitation, supported employment, and work rehabilitation. For more resistant and severe psychotic presentations, or in cases where there is need for emergency treatment, the use of psychotropics is indicated. When using antipsychotic medications in older adults, their use should be optimized, wherein the efficacy of these medications is maximized and adverse-effect profile is minimized, and they should be employed only for an appropriate period of time. However, it should be noted that data for the use of pharmacological agents in late-life psychotic disorders is limited, with this review finding only two RCTs investigating antipsychotic efficacy. The highest level of evidence supports the utilization of amisulpride and paliperidone for psychosis in elderly patients, although there is some evidence for the use of olanzapine and risperidone in this population. The use of clozapine should be restricted due to its significant side effect profile.

Conclusion

Psychotic disorders in late life represent a diverse group of illnesses with varied etiologies. In addition, they often have different clinical presentations and outcomes when compared with younger adults. In a majority of cases, psychosis in late life occurs due to underlying medical illnesses, or medications or illicit drug effects. It is important for secondary causes of psychosis to be identified and treated in order to reduce suffering among vulnerable older adults. Although differentiating between primary and secondary causes of psychosis can be challenging, it can be accomplished by obtaining a thorough history, by completing a focused physical examination, by using neuropsychological assessments, and by the appropriate use of laboratory data.

In producing this report, we were constrained by the relative scarcity of well-powered studies to conduct a systematic review, which is why we elected to produce a narrative review. This review is intended to provide an overall diagnostic and treatment guideline for clinicians to utilize in their everyday practice. As most studies investigating pharmacological treatments for psychotic disorders in late life were commonly low in power, future studies should endeavor to recruit larger cohorts to further examine the potential benefits and adverse events of prolonged psychotropic treatment. In addition, as Howard and colleagues have indicated in their report,[68] further study of patient insight into psychotic disorders in late life would be beneficial in improving health outcomes by enhancing our understanding of patient perception of the disorder and developing methods to improve treatment compliance.

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ORCID iD

Rajesh R Tampi https://orcid.org/0000-0002-3770-4074

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GERIATRIC DISORDERS (W MCDONALD, SECTION EDITOR)

Late-Life Psychosis: Diagnosis and Treatment

Michael M. Reinhardt · Carl I. Cohen

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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

This article is part of the Topical Collection on *Geriatric Disorders*

M. M. Reinhardt (✉) · C. I. Cohen
Department of Psychiatry and Behavioral Sciences, Division of Geriatric Psychiatry, SUNY Downstate Medical Center, 450 Clarkson Ave, Box 1203, Brooklyn, NY 11203, USA
e-mail: Michael.reinhardt@downstate.edu

C. I. Cohen
e-mail: carl.cohen@downstate.edu

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_{12}, 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
Delirium	Days to weeks	10 %	Secondary
Drugs, alcohol, toxins	Days to months	11 %	Secondary
Disease	Days to months	10 %	Secondary
Depression and other affective disorders	Weeks to months	33 % (depression) 5 % (bipolar)	Primary
Dementia	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]

Metabolic	• Vitamin B_{12} deficiency • Folate deficiency • Electrolyte abnormalities ○Sodium ○Potassium ○Calcium ○Magnesium • Acute intermittent porphyria • Hepatic encephalopathy • Uremic encephalopathy • Other nutritional deficiencies • Anoxia/hypoxia • Hypercarbia
Infections	• Meningitides • Encephalitides (e.g., herpes, etc.) • Neurosyphilis • HIV/AIDS • Pneumonia
Neurological	• Parkinson's disease • Epilepsy ○Temporal lobe epilepsy ○Grand mal ○Non-convulsive status epilepticus • Subdural hematoma • Cerebrovascular events • Huntington's disease • Multiple sclerosis • Amyotrophic lateral sclerosis • Tumors ○Temporal lobe—auditory hallucinations ○Occipital lobe—visual hallucinations ○Limbic—delusions ○Hypothalamus—delusions • Limbic encephalitides • Autoimmune[reference] ○Paraneoplastic syndromes ○Systemic lupus erythematosis ○Vasculitides • Sleep disorders (narcolepsy) • Other genetic/heritable conditions ○Likely to have been diagnosed in childhood
Endocrine	• Hypo-/hyperthyroidism • Adrenal disease • Hypo-/hypoglycemia • Hypo-/hyperparathyroidism

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 decreases 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 show 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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