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Geriatric Disorders (K Zdanys, Section Editor)

Treatment of Late-Life Psychosis

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Abstract

Purpose of review Psychosis in late life is a cause of significant distress, suffering, and decline in the quality of life for patients, caregivers, and family members. While psychotic symptoms in later life may be related to long-standing, chronic conditions, the new onset of delusions and hallucinations often presents a diagnostic dilemma to the clinician. This paper seeks to review the overall causes and conditions related to psychosis in later life and discuss available treatment options.
Recent findings The paucity of new research in the areas of psychosis in late-life and the near absences of clinical drug trials in this area is a source of great frustration to the practicing clinician. The need to abstract and modify drug dosing and treatment regimes for frail, elderly patients based on available data is typically required. The minimal availability of psychotherapy research in the area of psychosis in late life is troubling.
Summary Antipsychotic medications may be safely and effectively utilized for the treatment of psychosis in late life. Side effect monitoring is vital, and agents for the treatment of tardive dyskinesia may be required.

Introduction

Psychosis describes a state in which an individual's cognitive judgment and contact with reality are disturbed. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (*DSM-5*) includes diagnoses relevant to late

life: schizophrenia, delusional disorder, and the neurocognitive disorders such as dementia in which psychotic symptoms develop [1]. Typically, psychosis manifests as impaired perceptions and interpretation of reality, false beliefs, and disorganization of behavior, thinking, and speech. Psychosis in late life may present as a symptom of several disorders and conditions.

Schizophrenia

Schizophrenia is a disease characterized by delusions, hallucinations, disordered thinking, and emotional unresponsiveness. Generally, it is observed as an illness with onset in late adolescence or early adult life. In recent years, there has been a growing consensus among clinicians to use the term late-onset schizophrenia (LOS) to describe the onset of symptoms in mid-life (approximately 40 to 60 years old), and very-late-onset schizophrenia-like psychosis (VLOSLP) when the onset of symptoms occur after the age of 60 [2–4].

Among patients diagnosed with schizophrenia, the prevalence of LOS is approximately 0.15, while the prevalence of VLOSLP is about 0.05, making them rare diseases [3, 4]. However, with our aging population, which is rapidly increasing, these groups will represent a growing demographic in need of care.

Antipsychotics are the mainstay of treatment for those with schizophrenia (Table 1). Due to the adverse side effects associated with antipsychotics, prescribing such drugs should be done with caution, especially in the elderly. According to the Beers Criteria, antipsychotics are considered potentially inappropriate medications (PIMs) in elderly patients, and use should be avoided except for treating schizophrenia or bipolar disorder [5]. Similar to other medications, the elderly are generally more sensitive to the side effects associated with antipsychotics than their younger counterparts. Some of the most common side effects of antipsychotics include akathisia, dystonia, parkinsonism, tardive dyskinesia, metabolic syndrome, hypotension, sedation, and increase risk of falls [6, 7]. As a result of age-related pharmacodynamic changes, geriatric populations are at increased risk for medication side effects. Geriatric patients also tend to be on a number of other medications, making the risk of drug-drug interactions more likely.

Additionally, the black box warning on both first and second-generation antipsychotics warns of an increased risk of cerebrovascular adverse events including stroke when these medications are used in patients with dementia, as well as an increased risk of mortality [8]. It was found that those 70 years and older are 3.5 times more likely than younger individuals to be admitted to the hospital due to adverse drug reactions associated with the use of psychotropic medications [9]. Furthermore, the US Food and Drug Administration (FDA) suggested that the use of second-generation antipsychotics carries a 1.6- to 1.7-times higher incidence of mortality in elderly demented people than in the general population [8].

Given the FDA issued black box warning concerning the risks of first and second-generation antipsychotic, stating that “elderly patients with dementia-related psychosis treated with conventional or atypical antipsychotic drugs are

at an increased risk of death," it is no wonder providers are wary of prescribing such medications in this population [8]. However, it is important to keep in mind that the increased deaths found in the studies that informed this warning could not be ascribed to any specific cause. Further, examination of the specific causes of these deaths revealed that most were either due to heart-related events (e.g., heart failure, sudden death) or infections (community-acquired pneumonia) [8].

While there are numerous studies evaluating treatment options in younger adults with schizophrenia, there are only a few controlled, large-scale blinded trials of the effects of antipsychotic medication in geriatric populations suffering from the illness [10]. Therefore, clinicians often must utilize data from studies with younger adult populations, when treating elderly patients. Historically, the pharmacologic agents first used for the treatment of schizophrenia in the elderly were first generation antipsychotics (FGA). Second-generation antipsychotic (SGA) later replaced FGA as the first-line treatment for schizophrenia [10].

FGAs are often divided into low-potency and high-potency groups. Low-potency FGAs such as chlorpromazine and thioridazine have significant histaminergic and muscarinic activity, making them more likely to cause sedation, which can increase the risk of falls and weight gain. The high-potency FGAs such as haloperidol, fluphenazine, and perphenazine have low activity at histaminic and muscarinic receptors, but are more likely to cause extrapyramidal side effects (Table 1) [11•].

Chlorpromazine

The modern era of psychopharmacology began with the discovery of chlorpromazine in the 1950s. Chlorpromazine is now well-known as an agent for treating schizophrenia [12•]. Nevertheless, there are no randomized controlled trials looking at the effectiveness of chlorpromazine specifically in geriatric populations. However, a review that looked at all the relevant randomized controlled trials (RCTs) comparing varying doses of chlorpromazine in patients with schizophrenia found the drug to be effective in reducing positive symptoms such as hallucinations and delusions. However, the study also found that it was less effective in reducing negative symptoms like cognitive dysfunctions and altered mood. Chlorpromazine has a medium D2 dopaminergic receptor affinity, but also has a high affinity for the histamine H1 and muscarinic M1 receptors [13], making it a low/medium potency antipsychotic. As a result, it is associated with fewer extrapyramidal effects than other FGAs, but has other adverse effects like sialorrhea, sedation, tachycardia, EPS, and weight gain [10].

Haloperidol

Haloperidol is a first generation high potency antipsychotic that came after chlorpromazine, created in 1958. Despite its longevity, the lack of randomized controlled trials of haloperidol in schizophrenic geriatric populations means that providers must depend on the studies performed on middle aged

Table 1. First-generation antipsychotic (FGA) and second-generation antipsychotic (SGA) for the treatment of psychosis

Generic name	Brand name	Recommended geriatric dose range	Common side effects	Comments
SGA				
Aripiprazole	Abilify	2–20 mg/day	Akathisia, anxiety, insomnia,	Relative lower risk of EPS, TD, QTc prolongation, glucose dysregulation and weight gain Suggest given in the morning Available as LAI[a]
Asenapine	Saphris	5 mg/day to 10 mg bid	Orthostatic hypotension, oral hypoesthesia, leukopenia, elevated CK	Use is limited due to potential to cause orthostatic hypotension and rare anaphylactic shock
Clozapine	Clozaril	6.25–400 mg/day in divided doses	Leukopenia and agranulocytosis, glucose dysregulation, weight gain, constipation, salivary pooling	Not as well tolerated by elderly Use with benzodiazepines is associated with cardiorespiratory collapse Requires weekly CBC monitoring
Iloperidone	Fanapt	6–12 mg bid	Orthostatic hypotension, tachycardia, fatigue, dry mouth, nasal congestion	Limited use in elderly due to orthostatic hypotension Has a better profile with respect to EPS and akathisia than other atypical antipsychotics
Lurasidone	Latuda	40–80 mg/day	Somnolence, akathisia, agitation, nausea, insomnia and sedation	Low potential to cause orthostatic hypotension, QTc prolongation or metabolic effects *may improve cognition due to effects on 5-HT7 and 5-HT1A[a]
Olanzapine	Zyprexa	2.5–15 mg/day	Orthostatic hypotension, sedation, weight gain, glucose dysregulation, elevation of serum lipids, anticholinergic effects	Significant concern for metabolic side effects and orthostatic hypotension Available as LAI[a]
Paliperidone	Invega	3–12 mg/day	Orthostatic hypotension, syncope, prolonged QTc, increased serum prolactin	Use with caution in patients with known CVD. Hypotension is often dose related Available as LAI[a]
Pimavanserin[b]	Nuplazid	17–34 mg/day	QTc prolongation, Gait	

Table 1. (Continued)

Generic name	Brand name	Recommended geriatric dose range	Common side effects	Comments
		disturbance, constipation, peripheral edema	Not approved for dementia related psychosis unrelated to Parkinson disease Not advised in hepatic impairment	
Quetiapine	Seroquel	50–400 mg divided bid to tid	Orthostatic hypotension, somnolence, dizziness, glucose dysregulation, dyslipidemia	First line drug for treatment of acute mania in elderly
Risperidone	Risperdal	0.25–3 mg/day divided doses	Orthostatic hypotension, prolonged QTc, dysrhythmias, tachycardia	First line for treatment of mania in elderly Available as LAI[a]
Ziprasidone	Geodon	20–80 mg bid.	QTc prolongation, headache, nausea and akathisia	Concerns for cardiac toxicity
Cariprazine	Vraylar	1.5–3 mg/day	Sedation, EPS	Partial agonist at D2 and 5HT1A receptors
FGA				
		Fluphenazine (hypertension, labile blood pressure), EPS, TD, NMS, anticholinergic and agranulocytosis	Prolixin High potency typical antipsychotic similar to Haldol Available as LAI[a]	0.25–4 mg/day divided doses
Cardiovascular effects				
Haloperidol	Haldol	0.25–4 mg/day	EPS, TD, NMS, prolonged QTc, blood dyscrasias, liver dysfunction and anticholinergic effects	High potency antipsychotic. Used to control psychotic agitation in emergency situations and to treat delirium in medically compromised elderly Available as LAI[a]
		Perphenazine anticholinergic effects, retinal pigmentation and decreased visual acuity	Trilafon Similar efficacy to SGA, increased EPS risk	2–32 mg/day
Orthostasis, EPS, TD, NMS, blood dyscrasias, liver dysfunction and				

Note: ALL antipsychotics have warnings about hyperglycemia, cerebrovascular events, and increase in all-cause mortality when used in patients with dementia

[a]Antipsychotics available as long acting injectable (LAI)

[b]First FDA-approved antipsychotic for treatment of visual hallucinations in patients with Lewy body dementia

schizophrenic patients and patients with dementia. There are several randomized controlled trials assessing haloperidol's efficacy in treating the symptoms of schizophrenia in adult populations [14]. Haloperidol has been shown to decrease positive psychotic symptoms and ameliorate some negative symptoms [15], as demonstrated by improvement in the Positive and Negative Syndrome Scale (PANSS) negative subscale scores and the Montgomery–Åsberg Depression Rating Scale (MADRS) total score [14]. Haloperidol works primarily by blocking D2 dopaminergic receptors in the extrapyramidal system. Haloperidol has less anticholinergic side effects compared to chlorpromazine, making it less likely to cause adverse effects like sedation and tachycardia. However, the major disadvantage of haloperidol is the high incidence of EPS associated with its use.

Perphenazine

Perphenazine has been found to be as effective as several SGA (quetiapine, risperidone, ziprasidone) in treating the symptoms of schizophrenia [16]. Individuals treated with perphenazine showed significant improvement from baseline in the areas of the agitation, psychosis, and lability. In the clinical trials of perphenazine, there were some elderly participants. However, there were so few participants over the age of 65 that it was difficult to assess whether geriatric patients responded differently from their younger counterparts to the drug. As with all other antipsychotics, the recommendation is to "start low, and go slow". Perphenazine antagonizes at the α1- and α2-adrenergic receptors, D2 dopaminergic receptors, H1- and H2-histaminergic receptors, and muscarinic cholinergic receptors. Common side effects include EPS, orthostatic hypotension, sedation, and anticholinergic effects. As is a concern with any medication that causes hypotension and sedation, geriatric patients taking perphenazine are at potentially greater risk for falls and fall-related injuries. In addition, avoidance of perphenazine is recommended in geriatric patients with lower urinary tract symptoms (due to urinary retention), Parkinson's disease (worsening of the disease), and delirium and dementia (due to adverse CNS effects) [17].

Currently, SGA medications are the most commonly used medications for schizophrenia in older patients. Specifically, risperidone, olanzapine, quetiapine, aripiprazole, and clozapine are the most often prescribed in the elderly. Mainly, this is due to their lower risk of both EPS and tardive dyskinesia. However, these medications also tend to have a poor metabolic profile (Table 1) [15, 18].

Risperidone

Risperidone is the most widely studied SGA in the elderly [15]. Risperidone is effective as a first-line antipsychotic agent and has also been demonstrated to be well tolerated at low doses with good clinical effect for the treatment of psychotic symptoms in the elderly [17]. Its activity is facilitated through a combination of D2 dopaminergic and 5-HT2 serotonin receptor antagonism. The most common side effects reported in elderly populations on the drug were extrapyramidal symptoms,

somnolence, and mild peripheral edema. The frequency of these adverse effects increased with dosage [19].

Olanzapine

Olanzapine is the next most studied antipsychotic in geriatrics populations. As a treatment for schizophrenia in the elderly, olanzapine has been found to be just as effective as risperidone, with the former having higher risk of diabetes, weight gain, and dyslipidemia [15]. Olanzapine exerts its antipsychotic effects, by antagonism at the D2 dopaminergic receptor, 5HT2A serotonin receptor, and at muscarinic receptors. Although not fully understood, the high likelihood of weight gain, dyslipidemia, and other metabolic side effects have been linked to olanzapine's actions at serotonin, dopamine, histamine, and muscarinic receptors (I). As a result of these adverse effects, olanzapine is not recommended as the first-line antipsychotic in patients with significant metabolic risk factors [19].

Quetiapine

There are no published controlled trials looking at quetiapine in the elderly for the treatment of schizophrenia. However, uncontrolled studies have shown it to be effective in treating the psychotic symptoms notable in schizophrenia [15, 19]. Quetiapine's efficacy in treating schizophrenia is mediated through a combination of D2 dopamine and 5HT2 serotonin antagonism. The drug higher selectivity for 5HT2 relative to D2 receptors is thought to contribute to its antipsychotic properties, while having fewer EPS. The most commonly reported adverse events were drowsiness, followed by unsteadiness, headache, postural hypotension, and weight gain. When comparing quetiapine with placebo, elderly patients who used quetiapine demonstrated higher rates of falls [20]. Interestingly, when compared with risperidone and olanzapine, quetiapine had significantly lower risk of mortality, lower rate of cerebrovascular events, increased rate of falls and injury, and less metabolic effects compared with olanzapine, but higher metabolic effects than risperidone [20].

Aripiprazole

Of the SGA mentioned so far, aripiprazole is least likely to cause EPS, sedation, weight gain, and cardiovascular side effects [15]. This is likely to its mechanism of action as a partial agonist at the D2 dopamine receptor, partial agonist at the 5-HT1A serotonin receptor, and antagonist profile at the 5-HT2A serotonin receptor [21]. However, with aripiprazole, there is an increased risk of akathisia. In geriatric populations, there are few studies that examine the safety profile and dosing strategies of using aripiprazole to treat schizophrenia. It has been re-

ported to be effective in improving both positive and negative symptoms of schizophrenia and caused fewer adverse effects [19, 22].

Clozapine

Clozapine is often described as the treatment of choice in treatment resistant schizophrenia [23]. It is effective in reducing and alleviating the positive symptoms of schizophrenia and can also effectively treat the negative symptoms of schizophrenia, such as flat affect, and isolation. As a treatment for schizophrenia, its mechanism of action is by antagonism at the D2 dopamine receptor and the 5-HT2A serotonin receptor [24]. It is also a treatment of choice in patients who suffer from both schizophrenia and dementia [21]. This is mostly due to its disinclination to induce EPS, particularly akathisia, tremor and typically does not result in dystonia or rigidity. However, the medication comes with several risks. The use of clozapine comes with the potentially fatal risk of agranulocytosis and requires routine laboratory work to assess a patient's blood counts. Additionally, clozapine has a poor metabolic profile, making it and olanzapine the antipsychotics most likely to cause weight gain [15]. Clozapine is also known to be very sedating, increasing one's risk for falls, a particular concern in the geriatric population. Clozapine also commonly causes hyper-salivation and constipation, a particular problem for older adults [25].

Prescribing for elderly patients is always challenging. However, prescribing for patients with LOS and VLOSLP can be even more difficult, as they are especially sensitive to antipsychotic drug side effects; however, the reason for this is poorly understood [26]. Clinicians agree that doses as low as 20% of those prescribed to individuals with LOS and 50% of those prescribed to individuals with LOS are adequate to relieve symptoms and reduce side effects in VLOSLP [27].

Extrapyramidal symptoms (EPS) as a result of antipsychotic use can occur with either short-term (dystonia, akathisia) or with long-term use of antipsychotics (tardive dyskinesia, tardive dystonia, and neuroleptic malignant syndrome [NMS]) [28, 29].

Dystonia is described as the sustained abnormal postures or muscle spasms that develop within 7 days of starting or increasing the dose of the antipsychotic medication or of reducing the medication used to treat (or prevent) acute extrapyramidal symptoms. Although acute dystonia is the only antipsychotic induced EPS side effect more common in young populations than the elderly, it may occur and should be treated appropriately [30]. Ideally, when dystonia occurs, it should be immediately treated with an intramuscular or intravenous anticholinergic or antihistaminergic agents (Table 2). Maintenance treatment of dystonia includes discontinuation of the offending agent, switching to a different antipsychotic (an SGA if possible) and adding an anticholinergic agent.

Anticholinergics typically used include benztropine, trihexyphenidyl, procyclidine, and biperiden [31]. Antihistamines, like diphenhydramine, have also been found to be effective in the treatment of dystonia. However, it is important that clinicians keep in mind that anticholinergics can cause cognitive impairment, while antihistamines will have a sedating effect (Table 2).

Table 2. Medications used to treat neurologic side effects of antipsychotics

Drug name	Mechanism of action	Dose	Used to treat	Notes
Amantadine	Dopaminergic agonists	Initially 100 mg PO daily; increase by 50–100 mg	Parkinsonism, antipsychotic drug-induced	
	hyperprolactinemia	Dosing based on creatinine clearance		
Benztropine	Muscarinic (M_1) acetylcholine receptor antagonist	Initially 0.5 mg PO/IM/IV once daily or q12hr; titrate dose in 0.5-mg increments every 5–6 days; not to exceed 4 mg/day	Dystonia	
Biperiden	Antagonist at acetylcholine receptor (M_1)	Initially 2 mg PO daily, increase by 2 mg, in divided doses Or 2 mg IM/IV repeated every 30 min until symptoms resolve, but not more than 4 consecutive doses (or 8 mg) per day	Dystonia	Narrow angle glaucoma and bowel obstruction are both
	contraindications	Bromocriptine	Dopaminergic agonists	Initially 0.5 mg PO Daily, or every 12 h; titrate dose in 0.5-mg increments every 5–6 days; not to exceed 4 mg/day
Parkinsonism, antipsychotic drug-induced	hyperprolactinemia			
Clonazepam	Benzodiazepine	Initially 0.125 mg PO Daily, may increase dose in increments of 0.125–0.5 mg/day	Akathisia	Monitor for over sedation, drowsiness and falls
Deutetrabenazine	Vesicular monoamine transporter 2 inhibitor	Initially 6 mg PO Daily, may increase dose in increments of 6 mg/day at weekly intervals; not to exceed 48 mg/day	Tardive Dyskinesia	Also used in the treatment of chorea in Huntington's disease
Diphenhydramine	Inverse agonist of the histamine (H_1) receptor	Initially 25 mg PO/IM/IV q6h for 24 h, increase by 25-50 mg	Dystonia	
Procyclidine	Blocking central cholinergic receptors	Initially 2.5 mg tid, increased gradually by 2.5–5 mg every 2–3 days if required	Drug-induced parkinsonism, Akathisia and Dystonia	

Table 2. (Continued)

Drug name	Mechanism of action	Dose	Used to treat	Notes
Propranolol	Beta-Blocker	Initially 10 mg PO Daily or BID, increase as tolerated	Akathisia	Hypotension
Trihexyphenidyl	Exact mechanism unknown, but blocks efferent impulses in parasympathetically innervated structures	Initially, 1 mg daily, increased to 5–15 mg daily in 3–4 divided doses.	Drug-induced parkinsonism, Akathisia and Dystonia	

Akathisia, characterized by a feeling of inner restlessness and a compelling need to be in constant motion, is a well-known side effect of antipsychotic medications. The short-term use of benzodiazepines for managing akathisia has been shown to be effective [26, 29], while some studies have found the beta blocker, propranolol, to be more beneficial [27]. Long-term treatment should include decreasing the antipsychotic dose, switching to a second-generation antipsychotic, or adding an anticholinergic agent (Table 2). Of course, in elderly patients, benzodiazepines and anticholinergic agents should be used with caution, with the prescribing clinician weighing the risks and benefits.

Neuroleptic malignant syndrome (NMS), although rare, is a life-threatening reaction to the use of antipsychotics. It is characterized by fever, muscular rigidity, autonomic dysfunction, and altered mental status. Treatment includes discontinuing the antipsychotic, supportive care to maintain hydration and management of fever and other renal or cardiovascular signs and symptoms which is most safely achieved in a hospital setting [28].

Tardive dyskinesia (TD) is a syndrome that develops after the long-term use of neuroleptic drugs. TD is characterized by repetitive, involuntary movements, such as grimacing, tongue fasciculations, and blinking. The first step in treatment of TD is prevention. When treating with antipsychotics, clinicians should use the lowest effective doses of antipsychotics possible and while monitoring the patient for side effects. Deutetrabenazine is a new FDA-approved medication for the treatment of TD and chorea associated with Huntington's disease [32]. Its mechanism of action is believed to be related to its effect as a reversible monoamine inhibitor (Table 2). Long-term treatment of tardive includes an antipsychotics medication dose reduction and switching to a different medication [32]. However, tardive symptoms may persist after the antipsychotic is discontinued. It has also been recommended that vitamin E supplementation be considered as an additional treatment option in patients with newly diagnosed tardive dyskinesia [33].

Delusional disorders

A delusion is a fixed, false belief that is held with unusual conviction despite superior evidence and without being a part of a person's cultural or religious views. DSM-5 defines delusional disorder as the presence of at least one

delusion for at least 1 month [1]. Delusional disorder has been associated with poorer treatment response though it is not completely clear whether this is related to poorer response to medication, poor compliance with medication and follow-up, or both. Structural neuropathology has been implied as a reason for poor treatment response in late onset delusional disorder [34].

One randomized controlled trial compared the effectiveness of cognitive behavioral therapy (CBT) versus supportive psychotherapy for the treatment of delusional disorder. While positive outcomes were found with both therapies, the small sample size limits any generalizable recommendations [35].

Antipsychotics are likely moderately effective and the best currently available pharmacological option [36]. The use of long-acting injectables (LAI) might be helpful in aiding with medication compliance. A small longitudinal study found comparable outcomes in patients with delusional disorder treated with the long-acting injectable antipsychotics paliperidone or risperidone versus those treated with their oral equivalents. Those treated with LAI should a somewhat better improvement in negative symptoms [37].

Since the serotonin system has also been shown to contribute to psychosis [38], serotonergic dysfunction in the pathogenesis of delusional disorder has also been postulated [36]. It has been speculated that SGA, due to their effects on the serotonergic system by blockade of 5HT2 receptors [38], their favorable side effect profiles in comparison to FGA, might be a useful alternative for treatment. However, there is no evidence proving their superiority over FGA [39].

A few case reports looking at antidepressants (selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA)) have been published with overall high response rates to these medications [36]. Though multiple factors may have influenced this result, future research to assess their treatment efficacy alone and in conjunction with antipsychotics would be enlightening. Additionally, N-methyl-D-aspartate (NMDA) or gamma aminobutyric acid (GABA) agents have also been considered due to their plausible utility in treating cognitive dimension (negative) symptoms [36].

Charles Bonnet syndrome

Charles Bonnet syndrome (CBS) is generally defined as consistent or periodic visual hallucinations that occur in individuals with visual impairment and intact cognition [40]. It refers to hallucinations resulting from damage to the visual pathway [41]. CBS is more common with increased age and estimated to occur in 10–40% of patients with visual impairment [42] .

Patient education is critical and the best treatment is to improve vision, whether by corrective devices or surgery [40–42]. Antipsychotics such as olanzapine and risperidone have been shown effective. Donepezil has been shown to be modestly effective as well [42]. CBS also has been shown to respond to antiepileptic drugs, including levetiracetam and clonazepam [42, 43]. Anecdotal evidence has suggested that SSRIs and SNRIs might be a well-tolerated treatment [44, 45].

A similar syndrome of musical hallucinations has been found in a subgroup of patients with impaired hearing. Treatment recommendations are also anecdotal and have included the following: SGA, namely quetiapine and olanzapine

in low doses, Donepezil (doses of 5 mg) Gabapentin (at 100 mg); all showing results within first week. Response to carbamazepine, lamotrigine and ECT has also been reported [46].

Dementia

Dementia is a complex illness characterized by gradual changes in cognition, behavior, and mood. Alzheimer's dementia (AD) is the most common form of dementia. Fifty percent to seventy percent of all individuals with dementia are diagnosed with dementia due to Alzheimer's. Other causes of dementia include dementias due to Lewy body disease, Parkinson's disease dementia, vascular dementia, and frontotemporal dementia.

Neuropsychiatric symptoms are a hallmark of dementia, affecting almost all individuals with dementia over the course of the illness. These symptoms cause substantial distress to the patient and caregivers and are a common cause of early institutionalization. There are four distinct clusters of neuropsychiatric symptoms: aggressiveness (agitation and irritability), apathy and eating problems (apathy and appetite/eating disturbance), psychosis (delusions and hallucinations), and emotion/disinhibition (depression, euphoria, and disinhibition) [47].

Studies have shown prevalence of delusions in AD ranging from 9 to 59% with an overall pooled prevalence of 31% and a prevalence of hallucinations ranging between 6 and 41% with pooled prevalence of 16% [48]. Psychotic symptoms were common in patients with AD with a significant association between delusions and age. Delusional patients were older than those without psychotic symptoms. Some studies also reported hallucinations associated with younger age [49]. In a study looking at 124 patients with dementia, 67% had psychotic symptoms which occurred two to six times a week, and these persisted for 12 weeks among 32% and recurred in 50% within 12 months [50, 51•]. Unlike Lewy body and Parkinson's dementia, hallucinations occur less frequently than delusions in AD. Hallucinations in AD are often visual and less commonly auditory, tactile, or olfactory [50, 52]. Persecutory delusions occur earlier in AD than misidentification delusions and both increase with dementia severity.

Treatment

The treatment of psychosis in dementia is largely symptomatic as there are currently no disease-modifying drugs. Specific challenges must be considered when using medications in the elderly population, including altered metabolism, increased sensitivity to side effects, and possible exacerbation of certain symptoms.

Pharmacologic treatment

There is no FDA-approved medication for treatment of psychosis in dementia patient. Off-label use atypical antipsychotics such as risperidone, olanzapine quetiapine, and aripiprazole have replaced conventional antipsychotics such as

haloperidol in treatment of psychosis in dementia which come with black box warning of increased risk of death as previously discussed [53]. They are associated with many adverse effects such as somnolence, cognitive decline, movement disorders, and increased risk of falls and strokes [54]. American Psychiatric Association (APA) guidelines recommend that antipsychotics be used only when symptoms of psychosis and agitation are severe and dangerous or cause significant distress to the patient [55]. Other recommendations include monitoring response to nonpharmacological interventions prior to nonemergency use of antipsychotic, medications being initiated at lowest dose and titrated to minimum effective dose, tapering, and discontinuing medication if no clinical response within a 4-week trial of an adequate dose and finally, tapering or discontinuing the medication in patients who have demonstrated stability of symptoms within 4 months of initiation.

Patients with Lewy body dementia (LBD) and Parkinson's disease dementia (PDD) may react adversely to both FGA and SGA through the mechanism of dopamine modulation. Of note are motor symptoms, which typically worsen [56]. A lack of response to antipsychotics may also be seen, particularly in the case of visual hallucinations. For visual hallucinations, alternate treatment strategies can be utilized including optimizing vision, psychoeducation, and cognitive behavioral therapy [57, 58]. Low doses of clozapine may be considered with careful monitoring.

Recently, a 5-HT2A receptor antagonist/inverse agonist, pimavanserin, became the first FDA-approved medication for the treatment of visual hallucinations in Parkinson's disease. Future studies will help to further establish its role in a comprehensive treatment plan.

Antidepressants

Studies have demonstrated antidepressants citalopram and escitalopram to be favorable treatment options in the management of dementia-related agitation. These studies have also determined escitalopram to be significantly more effective [14–17]. Other studies have compared the efficacy of escitalopram and risperidone in elderly psychotic patients with AD and found both medications equally effective; however, the risperidone group experienced severe EPS [59].

Cholinesterase inhibitors

Studies show that donepezil improves neuropsychiatric symptoms in AD [60–62]. A study of 86 patients with AD treated with donepezil found that delusions, agitation, disinhibition, anxiety, and irritability all significantly improved for patients [63]. Another study of 140 patients compared donepezil with placebo in patients with dementia with Lewy bodies (DLB) and found Neuropsychiatric Inventory score (NPI) sub scores for hallucinations and cognitive fluctuations, for delusions, apathy and depression were significantly improved with donepezil compared to placebo [64]. Cholinesterase inhibitors do not show benefit in treatment of frontotemporal dementia and may cause a decline in behavior and cognition [65, 66].

Medications available to treat dementia-related psychosis are limited; therefore, it is important that providers utilize pharmacological as well as nonpharmacological interventions. Behavioral therapy, as an adjunct to medication, has been found to be effective in addressing some distressing symptoms

found in dementia. For example, the addition of an exercise intervention to psychopharmacological interventions significantly improved neuropsychiatric symptoms when compared to psychopharmacological interventions alone [67]. In addition to accurate assessment of symptoms, it is important to take note of the environments in which they occur. Actively identifying symptom precipitants can help to reduce the burden on patients and their caregivers. Some forms of nonpharmacologic interventions include patient and caregiver counseling and offering coping strategies. The environment also plays a crucial role, so making sure the patient's surroundings are safe and accessible is crucial.

Conclusion

Psychotic symptoms in late life are associated with a number of conditions with many contributory factors. The distress and disability related to psychosis in late life are high and contribute to excess morbidity and mortality. Treatments for late-life psychosis focus primarily on the use of antipsychotic medications to treat the distressing hallucinations and delusions that are often prominent. SGA agents are likely better tolerated, but the limited controlled trials of these agents in older adults require the clinician to extrapolate data from younger populations. Studies of newer agents including pimavanserin show some promise for select populations including those with Parkinson's associated psychosis. Side effect monitoring and need for ongoing dose adjustments must be considered in older adults. Unmet needs for studies in the area of social support, caregiver burden, psychotherapy of late life psychosis, and family education are overt and raise the issue of research priorities in improving quality of life for older adults with psychosis.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

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

References and Recommended Reading

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