

A GUIDE TO THE MANAGEMENT OF PSYCHOTIC DISORDERS AND NEUROPSYCHIATRIC SYMPTOMS OF DEMENTIA IN OLDER ADULTS

From **THE AMERICAN GERIATRICS SOCIETY**

This guide was reviewed by a panel of AGS members representing geriatric medicine, geropsychiatry, and geriatric pharmacy. The guide was then reviewed and approved by the AGS Executive Committee in April 2011.

INTRODUCTION

This guide has been developed to assist healthcare providers in managing psychotic symptoms and disorders in older adults. It is based on two publications of the American Geriatrics Society (AGS) (www.americangeriatrics.org), the 2010 edition of *The Geriatrics Review Syllabus* and 2011 edition of *Geriatrics At Your Fingertips*.TM

We encourage readers to consult the publications listed in the [References Section](#) at the end of this guide for a more in-depth discussion of the information contained here, including evidence concerning the increased incidence of mortality in the use of antipsychotic medications in the treatment of behavioral and psychotic symptoms associated with dementia.

MANAGEMENT OF PSYCHOTIC DISORDERS IN OLDER ADULTS

KEY POINTS

- Psychotic symptoms are defined as either hallucinations or delusions. Hallucinations are perceptions without stimuli. Delusions are fixed, idiosyncratic, or false perceptions or beliefs with little if any basis in reality and are not the result of religious or cultural norms.
- Hallucinations can occur in any sensory modality (ie, visual, auditory, tactile, olfactory, gustatory). In late life, multimodal hallucinations are common.
- Delusions are unfounded ideas that can be suspicious (paranoid), grandiose, somatic, self-blaming, or hopeless. Delusions in late life are often paranoid or persecutory, such as a belief that one's safety is in jeopardy or that one's belongings are being stolen.
- When psychotic symptoms arise in the context of depression or bipolar affective disorder, the symptoms are often "mood congruent," eg, in depression, delusions that one is penniless or that one is already dead; in mania, grandiose delusions, elevated self-regard.
- Psychosis occurring for the first time in late life is often due to dementia or neurologic conditions such as Parkinson's disease or stroke, as opposed to a primary psychotic disorder, such as schizophrenia.

DIFFERENTIAL DIAGNOSIS

- Bipolar affective disorder
- Delirium: Hallucinations, particularly visual hallucinations, can be a symptom of delirium, even when it is mild. The onset of delirium is typically acute, and there is usually an identifiable metabolic, pharmacologic, or infectious cause. The mental status examination reveals multiple cognitive impairments and a diminished or waxing and waning level of consciousness.

- Dementia: Frontotemporal dementia can be confused with late-onset schizophrenia, as it can involve features of socially inappropriate, objectionable, and odd behaviors as well as premorbidly odd or "schizoid" personality features. Lewy body dementia usually presents with visual hallucinations in the context of autonomic instability, parkinsonism, and frequent falls.
- Medications/drugs: eg, antiparkinsonian agents, anticholinergics, benzodiazepines or alcohol (including withdrawal), stimulants, corticosteroids, cardiac medications (eg, digitalis), opioid analgesics
- Late-life delusional (paranoid) disorder
- Major depression: Delusions in major depressive disorder usually reflect self-deprecation, self-blame, hopelessness, or the conviction of ill health.
- Physical disorders: hypo- or hyperglycemia, hypo- or hyperthyroidism, sodium or potassium imbalance, Cushing's syndrome, Parkinson's disease, B₁₂ deficiency, sleep deprivation, AIDS
- Pain, untreated
- Schizophrenia
- Structural brain lesions: tumor or stroke
- Seizure disorder: eg, temporal lobe

RISK FACTORS FOR PSYCHOTIC SYMPTOMS IN OLDER ADULTS

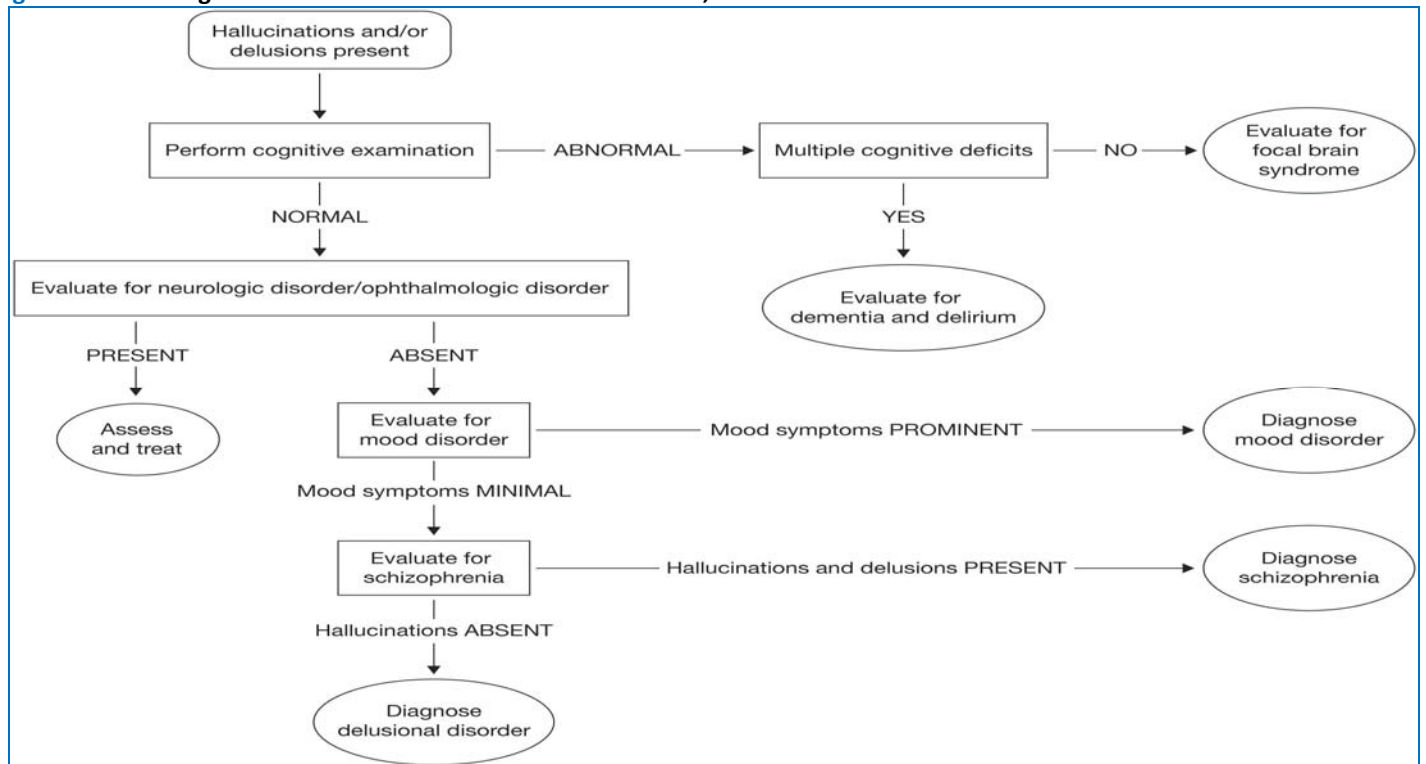
- Chronic bed rest
- Cognitive impairment
- Female gender
- Sensory impairment
- Social isolation

SCHIZOPHRENIA and SCHIZOPHRENIA-LIKE SYNDROMES

- Schizophrenia is characterized by positive symptoms (eg, hallucinations, delusions, and thought disorder) and negative symptoms (eg, social dilapidation and apathy).
- Approximately 85% of older adults with schizophrenia experienced onset of illness in early adult life. However, 10%–15% of cases of schizophrenia first come to clinical attention after age 45.
- Schizophrenia with onset between ages 40 to 60 is called "late-onset schizophrenia." Onset after age 60 is considered "very-late-onset schizophrenia-like psychosis."
- Late-onset schizophrenia-like conditions are characterized by prominent persecutory (paranoid) delusions and multimodal hallucinations manifesting as complaints, eg, items are being stolen or a neighbor is persistently banging on the walls or roof.

- A schizophrenia-like psychosis can be diagnosed only when cognitive disorder, mood disorder, or other explanatory medical conditions such as delirium or focal brain pathology have been excluded (see [Figure 1](#)).
- The schizophrenia-like psychoses of late life differ from schizophrenia beginning in early life in two ways:
 - Thought disorder (eg, speech in which a series of thoughts are not connected to one another in a logical fashion) is much less common in older adults. When illogical speech occurs in late life, delirium or dementia should be excluded.
 - Social deterioration and dilapidation is rare among older adults; personality is often intact in late-onset cases.
- Many individuals with schizophrenia experience fewer hallucinations and delusions as they age, others remain significantly functionally impaired by psychotic symptoms.
- Older adults with schizophrenia have an increased risk of suicidal behavior compared with that of their peers without mental illness.

Figure 1. Evaluating the Patient with Hallucinations or Delusions, or Both



Treatment and Management of Schizophrenia and Schizophrenia-like Syndromes

- Establish a trusting therapeutic relationship with the patient; focus on empathizing with the distress that symptoms cause rather than reality orientation.
- Encourage patients to maintain significant, supportive relationships.
- Alleviate underlying physical causes.
- Address identifiable psychosocial triggers.
- If psychotic symptoms are severe, frightening, or may affect safety, use antipsychotic medication (clinical experience and descriptive case studies suggest that antipsychotic medications are as effective in late-onset schizophrenia as in early-onset cases).
- Aripiprazole, olanzapine, quetiapine, risperidone are first choice because of fewer adverse events (tardive dyskinesia [TD] extremely high in older adults taking first-generation antipsychotics).
- All antipsychotics are associated with increased mortality in older adults.
- See [Table 1](#) for representative medications for treatment of schizophrenia or schizophrenia-like syndromes, [Table 2](#) for adverse events of second-generation antipsychotics, and [Table 3](#) for management of adverse events of antipsychotic medications.
- No studies are available to guide the duration of treatment with schizophrenia. Clinical experience suggests that patients who respond to antipsychotic medications should be continued on the minimal effective dosage for at least 6 mo. Patients with early-onset schizophrenia and chronic stable symptoms may be able to tolerate a gradual reduction in dosage of antipsychotic medication.
- For all patients who relapse on treatment or when the dosage is lowered, maintenance over a longer term (at least 1–2 yr) is recommended.

Table 1. Representative Medications for Treatment of Schizophrenia or Schizophrenia-like Syndromes			
Class, Medication	Dosage - Total mg/d (Frequency/d)	Formulations (in mg)	Comments (Metabolism)
Second-generation Antipsychotics			
*Aripiprazole	2-5 mg/d initially max 30 mg/d (1)	T: 2, 5, 10, 15, 20, 30 ODT: 10, 15 S: 1 mg/mL IM: 9.75 mg/1.3 mL	Wait 2 wk between dosage changes (CYP2D6, -3A4) (L)
Clozapine	25–150 mg/d (1)	T: 25, 100 ODT: 12.5, 25, 100	May be useful for parkinsonism and TD; significant risk of neutropenia and agranulocytosis; weekly CBCs x 6mo then bi-weekly (L)
*Olanzapine	2.5–10 mg/d (1)	T: 2.5, 5, 7.5, 10, 15, 20 ODT: 5, 10, 15, 20 IM: 5 mg/mL	Weight gain (L)
Paliperidone	3–12 mg/d (1)	T: ER 3, 6, 9	CrCl 51–80 mL/min, max 6 mg/d; CrCl ≤50 mL/min, max 3 mg/d; very limited geriatric data (K)
*Quetiapine	25–800 mg/d (1-2)	T: 25, 100, 200, 300 T: ER 50, 150, 200, 300, 400	Ophthalmic examination recommended q6mo (L, K)
*Risperidone	0.25–1 mg/d (1-2)	T: 0.25, 0.5, 1, 2, 3, 4 ODT: 0.5, 1, 2, 3, 4 S: 1 mg/mL IM long-acting: 25, 37.5, and 50 mg/2 mL	Dose-related EPS; IM not for acute treatment; do not exceed 6 mg (L, K)
Ziprasidone	20–80 mg/d (1-2)	C: 20, 40, 60, 80 IM: 20 mg/mL	May increase QTc; very limited geriatric data (L)
Low Potency First-generation Antipsychotics			
Thioridazine	25–200 mg/d (1-3)	T: 10, 15, 25, 50, 100, 150, 200 S: 30 mg/mL	Substantial anti-cholinergic effects, orthostasis, QTc prolongation, sedation, TD; for acute use only (L, K)
Intermediate Potency First-generation Antipsychotics			
Perphenazine	2–32 mg/d (1-2)	T: 2, 4, 8, 16	Risk of TD with long-term use (L, K)
High Potency First-generation Antipsychotics			
Haloperidol	0.5–2 mg/d (1-3) depot 25–200 mg IM q4wk	T: 0.5, 1, 2, 5, 10, 20 S: conc 2 mg/mL IM/IV: 5 mg/mL (lactate)	EPS, TD; for acute use only Depot form is for chronic use; monitor for TD and D/C if signs appear (L,K)
Fluphenazine	1-2.5 mg/d (max 5 mg/d) (1)	T: 1, 2.5, 5, 10 S: conc 5 mg/mL IM: 2.5 mg/mL (decanoate)	EPS, TD, akathisia (L, K)
* = preferred for treating older adults but does not imply low risk; mortality may be increased in patients with dementia			
T = tablet; ER = extended release; SR = sustained release; SL = sublingual; ODT = oral disintegrating tablet; C= capsule, caplet; S = liquid; IM = intramuscular; IV = intravenous; CrCl = creatinine clearance; TD = tardive dyskinesia; EPS = extrapyramidal symptoms			

Table 2. Adverse Events of Second-generation Antipsychotics							
	Aripiprazole	Clozapine	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Cardiovascular							
Level of Evidence	CR	CR	RCT	RCT	RCT	RCT	CR
Hypotension	?	0/+++	+	+	+++	+	?
QTc prolongation*	?	+	+	+	+	+	++
Endocrine/Metabolic							
Weight gain	?	+++	+++	++	++	++	?
Diabetes	?	+++	+++	++	++	++	?
Hypertriglyceridemia	0	+	+	?	0	?	0
Hyperprolactinemia	?	?	?	+++	?	+++	+
Gastrointestinal							
Nausea, vomiting, constipation	0	?	0	?	+	?	?
Neurologic							
Extrapyramidal symptoms	++	+	+	+++	+	+++	+
Seizures	?	+++	?	ND	?	ND	ND
Sedation	?	+++	+	+	+	+	?
Systemic							
Anticholinergic	0	+++	++	0	+	0	?
Neuroleptic malignant syndrome	ND	+	ND	ND	ND	+	ND
*QTc upper limit of normal = 44 millisec							
CR = case reports; RCT = randomized clinical trials; ND = no data							
? = uncertain effect							
0 = no effect							
+ = mild effect; ++ = moderate effect; +++ = severe effect; 0/+++ = no effect to severe effect in the case of drug interactions							

Table 3. Management of Adverse Events of Antipsychotic Medications		
Adverse Event	Treatment	Comment
Drug-induced parkinsonism	Reduce dosage or change drug or drug class	Often dose related; avoid anticholinergic agents
Akathisia (motor restlessness)	Consider adding β -blocker (eg, propranolol 20–40 mg/d) or low-dose benzodiazepine (eg, lorazepam 0.5 mg q12h)	Also seen with second-generation antipsychotics; more likely with traditional agents
Hypotension	Slow titration; reduce dosage; change drug class	More common with low-potency agents
Sedation	Reduce dosage; give at bedtime; change drug class	More common with low-potency agents
TD	Stop drug (if possible); consider second-generation antipsychotic (eg, aripiprazole, quetiapine) with lower potential for EPS	Increased risk in older adults; may be irreversible
<p>Note: Periodic (q4mo) reevaluation of antipsychotic dosage and ongoing need is important (see CMS guidance on unnecessary drugs in the nursing home: www.cms.hhs.gov/transmittals/downloads/R22SOMA.pdf).</p> <p>Older adults are particularly sensitive to adverse events of antipsychotic drugs. They are also at higher risk of developing tardive dyskinesia. Periodic use of an adverse-event scale such as the Abnormal Involuntary Movement Scale (AIMS) is highly recommended.</p>		

PSYCHOTIC DISORDER CAUSED BY A GENERAL MEDICAL CONDITION

Patients with Parkinson’s disease, stroke, and other brain disorders occasionally experience delusions and hallucinations without prominent cognitive impairment or other evidence of psychiatric disorder.

Parkinson’s Disease

- Psychotic symptoms may be secondary to a prescribed dopaminergic agent, but some patients experience visual hallucinations before any medications are started. Education and support should be offered to all patients with these symptoms. If the patients experience significant emotional distress or if the symptoms lead to dangerous or upsetting behavior, cautious use of an antipsychotic medication is appropriate (see [Table 1](#)).
- For patients with Parkinson’s disease and hallucinations, quetiapine 12.5–75 mg/d or olanzapine 2.5–5 mg/d may be beneficial. Some patients require clozapine 12.5–75 mg/d. However, patients taking clozapine must have a CBC done once a week for 6 mo and then biweekly thereafter because of the risk of granulocytopenia.

Lewy Body Dementia

- Dementia associated with Lewy bodies is increasingly recognized as an important cause of hallucinations in late life. The clinical scenario typically involves cognitive decline accompanied by motor features of parkinsonism. However, prominent visual hallucinations are a key part of the diagnosis. These hallucinations are often vivid and troubling.
- Dementia associated with Lewy bodies presents a challenge similar to that of psychosis in Parkinson’s disease, because antipsychotic medications worsen the parkinsonian symptoms. No trial data are available to guide medication choice, but there are case reports of significant improvement through the use of cholinesterase inhibitors, and one positive randomized placebo-controlled trial with rivastigmine (Grace, et al).
- If an antipsychotic medication must be used, then the treatment strategies outlined for Parkinson’s disease are appropriate if there is careful attention to the risk of extrapyramidal adverse events. Nonpharmacologic treatments include redirection, reassurance, and explanation.

SUBSTANCE-INDUCED PSYCHOTIC DISORDER

- Many classes of medications are associated with psychotic adverse events. Older adults are particularly vulnerable, especially those with CNS impairments.
- Psychotic symptoms have also been reported related to treatment with other medications including: antiarrhythmic agents, antineoplastic agents, antiviral agents, baclofen, β -blockers, cyclosporine, dopaminergic agents, interferon, opioids, and steroids. The appropriate

therapeutic management is to reduce the dosage of or to eliminate the associated medication.

MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS OF DEMENTIA

KEY POINTS

- The development of behavioral disturbances or neuropsychiatric symptoms (NPS) in dementia often precipitates early nursing-home placement and causes significant caregiver burden and distress.
- Behavioral symptoms in dementia require evaluation of the specific symptoms, the patient’s comfort, the care environment, the needs of the caregiver, and the degree of distress of all those involved in the life of the older adult with dementia.
- Delirium secondary to an underlying condition such as dehydration, urinary tract infection, medication toxicity, or pain is a common cause of abrupt behavioral disturbances in patients with dementia.
- Medication treatment of behavioral disturbances in dementia is of limited efficacy and should be used only after environmental and nonpharmacologic techniques have been implemented.
- No psychoactive medication prescribed to treat NPS of dementia should be continued indefinitely, and attempts at drug withdrawal should be made regularly (eg, every 3-6 months).
- Increased mortality has been identified with the use of both first- and second-generation agents. All antipsychotic agents now carry an FDA warning regarding increased all-cause mortality in patients with dementia.
- Despite these FDA warnings, antipsychotic medications may be needed for treatment of distressing delusions and hallucinations, and antidepressants may be helpful if symptoms of depression are evident. There is some evidence for considering mood stabilizers for symptoms such as impulsivity and aggression in patients who have significant behavioral disturbances.
- When using any antipsychotic medication for any patient, and particularly when using them for an off-label indication, it is prudent to include in the informed consent process a mention of the possible association of treatment with increased mortality among patients with dementia, in addition to the other potential adverse effects, such as cerebrovascular events or metabolic syndrome. It is also advisable to document the process of informing the family member and, if capable, the patient of the future risk of mortality, stroke, and metabolic syndrome weighed against the present risk posed by the psychosis.
- Treatment of psychiatric and behavioral disturbances in dementia is complex and may require several interventions as part of a comprehensive care plan.

The goal is reduction rather than elimination of the distressing behavior. In refractory cases, a specialist, such as a geriatric psychiatrist, geriatrician, or neurologist with specific expertise in the pharmacologic treatment of the neuropsychiatric symptoms of Alzheimer’s disease, should be consulted.

- May cause acceleration of decline if untreated
- Recreational programs and activity therapies have shown positive results
- See [Table 4](#) for medications most commonly used to treat depressive features of behavioral disturbances in dementia; first-line agents are SSRIs, preferred for more favorable adverse-event profiles.

COMMON NEUROPSYCHIATRIC SYMPTOMS ASSOCIATED WITH DEMENTIA

Psychotic Symptoms (delusions, hallucinations)

- Seen in about 20% of Alzheimer’s disease (AD) patients
- Delusions may be paranoid (eg, people stealing things, spouse unfaithful)
- Hallucinations (~11% of patients) are more commonly visual
- See [Table 1](#) for antipsychotic medications for the treatment of psychosis in dementia.

Depressive Symptoms

- Seen in up to 40% of AD patients; may precede onset of AD
- Signs include sadness, loss of interest in usual activities, anxiety, and irritability
- Suspect if patient stops eating or withdraws

Apathy

- High prevalence and persistence throughout course of AD
- Causes more impairment in Activities of Daily Living than expected for cognitive status
- High overlap with depressive symptoms but lacks depressive mood, guilt, and hopelessness

Manic-like Behavioral Syndromes

- Characterized by pressured speech, disinhibition, elevated or irritable mood, intrusiveness, hyperactivity, impulsivity, reduced sleep
- Frequent co-occurrence with confusional states
- See [Table 5](#) for mood stabilizers for behavioral disturbances in dementia with manic-like feature

Table 4. Medications to Treat Depressive Features of Behavioral Disturbances in Dementia

Medication	Daily Geriatric Dosage	Uses	Precautions
Selective serotonin-reuptake inhibitors (SSRIs)			
Citalopram	10–40 mg	Depression, anxiety (Off-label for anxiety)	Adverse events among all SSRIs: EPS, hyponatremia, GI upset, nausea, increased risk of upper GI bleeding, suicide (early in treatment), insomnia
Escitalopram	5–20 mg	Depression, anxiety	
Fluoxetine	10–40 mg	Depression, anxiety	Long half-life, greater inhibition of the CYP-450 system, may cause more insomnia than other SSRIs
Paroxetine	10–40 mg	Depression, anxiety	Greater inhibition of CYP-450 system, some anticholinergic effects, increased risk of withdrawal symptoms (dizziness, nausea, insomnia, anxiety)
Sertraline	25–100 mg	Depression, anxiety	Hypomania
Serotonin norepinephrine-reuptake inhibitors (SNRIs)			
Desvenlafaxine	50 mg	Depression	Nausea, hypertension, dry mouth, headaches, dizziness
Duloxetine	20–60 mg	Depression, diabetic neuropathy	Nausea, dry mouth, dizziness, hypertension, reduce dosage if CrCl 30-60 mL/min, contraindicated if CrCl <30mL/min
Venlafaxine	25–150 mg	Useful in severe depression, anxiety	Hypertension and increased QTc may be a problem, EPS, withdrawal symptoms, hyponatremia, insomnia
Tricyclic antidepressants (TCAs)			
Desipramine	10–100 mg	Useful in severe depression, anxiety; high degree of efficacy; therapeutic serum level > 115ng/mL	Anticholinergic effects, hypotension, sedation, cardiac arrhythmias (conduction delays)
Nortriptyline	10–75 mg	High efficacy for depression if adverse events are tolerable; therapeutic serum range 50–150 ng/mL	Anticholinergic effects, hypotension, sedation, cardiac arrhythmias (conduction delays)

Table 4. Medications to Treat Depressive Features of Behavioral Disturbances in Dementia (continued)

Medication	Daily Geriatric Dosage	Uses	Precautions
<i>Other</i>			
Bupropion	75–225 mg	More activating, lack of cardiac and sexual side effects	Irritability, insomnia, can lower seizure threshold
Mirtazapine	7.5–30 mg	Useful for depression with insomnia and weight loss	Sedation, hypotension, may increase appetite
Trazodone	25–150 mg	When sedation is desirable	Sedation, falls, hypotension

Table 5. Mood Stabilizers for Behavioral Disturbances in Dementia with Manic-like Features

Medication	Geriatric Dosage	Adverse Events	Comments
Carbamazepine ^{OL*}	200–1,000 mg/d (therapeutic level 4–12 mcg/mL)	Nausea, fatigue, ataxia, blurred vision, hyponatremia	Poor tolerability in older adults; must monitor CBC, liver function tests, electrolytes every 2 weeks for first 2 mo, then every 3 mo
Lamotrigine ^{OL}	25–200 mg/d	Skin rash, rare cases of Stevens-Johnson syndrome, dizziness, sedation, neutropenia, anemia	Increased adverse events and interactions when used with divalproex, slow-dose titration required
Lithium ^{OL*}	150–1,000 mg/d (therapeutic level 0.5–0.8 mEq/L)	Nausea, vomiting, tremor, confusion, leukocytosis, gait ataxia	Poor tolerability in older adults; toxicity at low serum concentrations; monitor thyroid and renal function
Divalproex sodium ^{OL*}	250–2,000 mg/d (therapeutic level 40–100 mcg/mL)	Nausea, GI upset, ataxia, sedation, hyponatremia	Requires monitoring of CBC, platelets, liver function tests at baseline and every 6 mo, and after each dose increase; better tolerated than other mood stabilizers in older adults

*Approved by FDA for treatment of bipolar disorder, OL = Off-label

Agitation or Aggression

- Seen in up to 80% of patients with Alzheimer’s disease
- A leading cause of nursing-home admission
- Identify and examine context of behavior (is it harmful to patient or others?) and environmental triggers (eg, overstimulation, unfamiliar surroundings, frustrating interactions).
- Determine whether delusions or hallucinations are interfering with function.
- Exclude underlying physical discomfort (eg, pain or hunger).
- Always consider nonpharmacologic strategies first:
 - Advise caregiver(s) to:
 - Use scheduled toileting and prompted toileting for incontinence.
 - Offer graded assistance (as little help as possible to perform ADLs), role modeling, cueing, and positive reinforcement to increase independence.
 - Avoid adversarial debates; try to redirect conversation instead.
 - Maintain a calm demeanor.
 - Use services of caregiver support groups.
 - For problem behaviors:
 - Music during meals, bathing
 - Walking or light exercise
 - Simulate family presence with video or audio tapes
 - Pet therapy
 - Speak at patient’s comprehension level
 - Bright light, “white” noise (ie, low-level, background noise).
- For intermittent disruptive behaviors (once per week or less), identifying antecedents of the behavior and avoiding triggers is often most useful. Behavior modification using positive reinforcement of desirable behavior has been shown to be effective, and also helps caregiver focus on times when behavior is not a problem.
- Physical restraint in any form should be avoided if at all possible. If restraining measures are necessary, careful supportive care should be provided to the patient. Over time, it is usually possible to reduce or eliminate the amount of restraint.
- Select pharmacologic agent on the basis of symptoms (see [Table 6](#)).
 - Cognitive enhancers may slow deterioration, and agitation may worsen if they are discontinued.
 - Low dosages of antipsychotic medications have a limited role but may be necessary at times. **Note:** this use is “off label;” use in AD patients has a BLACK BOX warning because the risk of death was higher with drug treatment than with placebo in clinical trials. Risk-benefit must be discussed with patients, surrogate decision-makers, families, and/or caregivers before starting treatment (see [Studies](#) regarding excess mortality associated with antipsychotic medication use in patients with dementia, and [References](#)).

Table 6. Pharmacologic Treatment of Agitation

Symptom	Medication and Usual Dosing
Agitation in context of psychosis	Aripiprazole 2.5–12.5 mg/d ^a , Olanzapine 2.5–10 mg/d ^a , Quetiapine 12.5–100 mg/d ^a , Risperidone 0.25–3 mg/d ^a
Agitation in context of depression	SSRI, eg, citalopram 10–30 mg/d
Anxiety, mild to moderate irritability	Buspirone 15–60 mg/d ^b , Trazodone 50–100 mg/d ^c
Agitation or aggression unresponsive to first-line treatment	Carbamazepine 300–600 mg/d ^d , Divalproex sodium 500–1500 mg/d ^e , Olanzapine (intramuscular) 2.5–5 mg IM ^{a, f}
Sexual aggression, impulse-control symptoms in men	Second-generation antipsychotic or divalproex (see dosages above) If no response, conjugated equine estrogens 0.625–1.25 mg/d or medroxyprogesterone injectable 100mg/wk IM

^a Greater mortality and cerebrovascular events than placebo; use with particular caution in patients with cerebrovascular disease or hypovolemia.
^b Can be given q12h; allow 2–4 wk for adequate trial.
^c Small divided daytime dosage and larger bedtime dosage; watch for sedation and orthostasis.
^d Monitor serum levels; periodic CBCs, platelet counts secondary to agranulocytosis risk. Beware of drug-drug interactions.
^e Can monitor serum levels; usually well tolerated; check complete blood count (CBC), platelets for agranulocytosis, thrombocytopenia risk.
^f For acute use only; initial dose 2.5–5mg, second dose (2.5–5mg) can be given after 2 hr, maximum of 3 injections in 24 hr (maximum daily dose 20mg); should not be administered for more than 3 consecutive days.

SUMMARY OF STUDIES REGARDING EXCESS MORTALITY ASSOCIATED WITH ANTIPSYCHOTIC MEDICATION USE IN PATIENTS WITH DEMENTIA (See also References)

On April 12, 2005, the U.S. Food and Drug Administration (FDA) issued a public health advisory on a newly identified concern associated with the off-label use of second-generation (atypical) antipsychotic medications for the treatment of dementia-related behavioral disorders in older adults. This advisory, based on an FDA analysis of data from 17 randomized, controlled trials that enrolled 5377 older adults with dementia-related behavioral disorders, showed that the risk of death in the drug-treated patients was 1.6–1.7 compared with that of the placebo group. Treatments consisted of aripiprazole, olanzapine, quetiapine, or risperidone. These trials averaged about 10 weeks. The rate of death was about 4.5% in drug-treated patients and about 2.6% in the placebo group. Most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature.

Several studies, summarized in a Cochrane Review and in a systematic review published in the *Journal of the American Medical Association (JAMA)* cite the clinically modest but significant reductions in NPS demonstrated among elderly subjects treated with olanzapine or risperidone. To date, while some efficacy has been noted in published placebo-controlled trials conducted with non-antipsychotic medications such as carbamazepine, citalopram, donepezil, galantamine, or memantine, this data is even more limited than that of the second-generation antipsychotics.

There has also been evidence published from an extensive Centers for Medicare and Medicaid (CMS) database that second-generation antipsychotic medications, compared to

first-generation (typical) antipsychotics, do not appear to be associated with an increased risk of ventricular arrhythmias or cardiac arrest.

Two observational epidemiological studies were published that examined the risk of death in patients who were treated with first-generation antipsychotic medications:

- Gill, et al, performed a retrospective cohort study in Ontario, Canada of 27,259 adults, 66 years of age or older, with a diagnosis of dementia between April 1997 and March 2002. The investigators compared the risk for death with use of a second-generation antipsychotic versus no antipsychotic and the risk for death with use of a first-generation antipsychotic versus a second-generation antipsychotic. They found that second-generation antipsychotics were associated with increased mortality as compared to no antipsychotic use as early as 30 days and persisting until study end at 180 days. The investigators found that first-generation antipsychotic use showed a marginally higher risk of death compared with second-generation antipsychotic use. The causes of death were not reported in this study.
- Schneeweiss, et al, performed a retrospective cohort study in British Columbia, Canada of 37,241 adults, 65 years of age or older, who were prescribed first-generation (12,882) or second-generation (24,359) antipsychotic medications for any reason between January 1996 and December 2004. The investigators compared the 180-day all cause mortality with use of a first-generation antipsychotic versus a second-generation antipsychotic. They found that the risk of death in the group of patients treated with first-generation antipsychotic medications

was comparable to, or possibly greater than, the risk of death in the group of patients treated with second-generation antipsychotic medications. The causes of death with the highest relative risk were cancer and cardiac disease.

The FDA considers that the methodological limitations in these two studies preclude any conclusion that first-generation antipsychotics have a greater risk of death with use than second-generation antipsychotics. The FDA has determined, however, that the overall weight of evidence indicates that first-generation antipsychotics share the increased risk of death in elderly patients with dementia-related psychosis that has been observed for second-generation antipsychotics. Therefore, the prescribing information for all antipsychotic drugs now includes the same information about this risk in a Boxed Warning and the Warnings section.

A recent five-year retrospective study by Rossom, et al, using U.S. Veterans Administration data from more than 89,000 veterans did not find an increased risk of death in veterans with dementia who were prescribed lower doses of olanzapine (<2.5 mg/d), quetiapine (<50 mg/d), or risperidone (<1 mg/d). However, at typically prescribed doses, second-generation

antipsychotics (excluding quetiapine) were associated with an increased risk of death. All doses of haloperidol were associated with increased mortality.

The mechanism(s) for increased mortality associated with antipsychotic use remain uncertain and needs careful examination. One study approaching this problem comes from another recent large epidemiological five-year retrospective nested case-control study of primary care patients in the United Kingdom, by Parker, et al. They found that there was a 32% greater risk for venous thromboembolism (VTE) in those prescribed antipsychotics in the previous 24 months vs non-antipsychotic users. The risk was even greater for new users and for those taking second-generation antipsychotics. The study examined risks by type of antipsychotic, potency and dose, and adjusted for comorbidity and concomitant drug exposure. A total of 25,532 "eligible cases" were selected for this study and a total of 89,491 matched healthy controls were also included. The median age for all participants was 67 years. Understanding mechanisms for adverse events leading to mortality should allow risk profiling of patients and eventually lead to approaches to minimize risk in those patients who otherwise need and benefit from this therapy.

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