



**SUTTER PHYSICIANS ALLIANCE (SPA)**  
2800 L Street, 7<sup>th</sup> Floor  
Sacramento, CA 95816

**SPA Specialty Guideline**  
**Dementia Management**  
Developed May 2005  
Clinical Changes October 2008

Overview.....	Page 2-3
I. Differential Diagnosis of Specific Types of Dementia.....	Page 4-5
II. Treatment for Cognitive Impairment Mild-to-Moderate Dementia .....	Page 6-10
III. Treatment for Cognitive Impairment Moderate-to-Severe Dementia .....	Page 11-13
IV. Agitation Syndromes Seen in Dementia.....	Page 14-20
V. Guideline for Inadequate Response to Initial Treatment .....	Page 21-23
VI. Medication Dosing.....	Page 24-26
VII. Safety, Complicating Conditions of Medication Usage .....	Page 27-29
VIII. The Use of Anti-Psychotic Agents in Persons with Dementia .....	Page 30-32
Signature / Approval Page .....	Page 33

**Overview: Dementia Management Guidelines**

- Recognition and Differential Diagnosis
- Memory Enhancement Treatments
- Managing the Complication Behavioral Syndromes

- 1) The enclosed Practice Guideline represents a compilation of Expert Consensus Publications as of January 2005.
- 2) The evidence clearly recognizes that the first line of Treatment and Management is the appropriate use of the Memory Enhancing Medications. Patients present with Behavioral Syndromes of Agitation and many of these symptoms are ameliorated by the judicious and appropriate use of the full spectrum of available memory enhancing medications, which not only slow the rate of memory decline but also manage coexisting and complication Behavioral Syndromes. These agents are:
  - A) Cholinesterase inhibitors: Aricept, Reminyl, Exelon
  - B) NMDA Receptor Antagonist: Namenda

**Note:** Brand = Generic

Aricept = donepezil

Reminyl = galantamine

Exelon = rivastigmine

Namenda = memantine

- 3) Despite optimum use of Memory Enhancing Agents, many patients with Dementia will continue to exhibit a wide spectrum of neuro psychiatric conditions, which require the addition of psychotropic agents. These guidelines will list the safest psychotropic agents as well as giving guidance for dosing and continuation schedules. These agents are listed as First, Second and Third line recommendations.
- 4) The physician is advised to read the full description of the evidence. Enclosed is an appropriate reference list for the Professional.

### **Components of the Practice Guideline**

- 1) Differential diagnosis of specific types of Dementia.
- 2) Treatments of Cognitive Impairment: Mild-to-Moderate Dementia.
  - A) Choices of Cognitive Enhancers (per Diagnosis)
  - B) Next step in inadequate response to initial treatment
  - C) Next step if unable to tolerate initial treatment
  - D) Common behavioral problems in mild-moderate Dementia:
    - 1) Treating depression in Dementia
    - 2) Medications for depression of Dementia
    - 3) Treatment of anxiety in Dementia
- 3) Treatments for Cognitive Impairment: Moderate-to-Severe Dementia
  - A) Cognitive enhancer and choices
  - B) Medical control issues
  - C) Dosing Cognitive Enhancer Medications
  - D) What to do if this patient deteriorates
  - E) The most common Behavioral Problems in moderate-to-severe Dementia
- 4) Agitation Syndromes seen in Dementia
  - A) Management strategies
  - B) The Algorithmic assessment of agitation syndromes in Dementia and the corresponding guideline to follow:
    - 1) Medical issues – First focus
    - 2) Delirium Guideline
    - 3) Psychosis Guideline
    - 4) Insomnia and Sundowning Guideline
    - 5) Aggression or Anger Guideline
      - (a) Without physical aggression
      - (b) With risk for physical aggression
    - 6) Prominent Pain
- 5) Guideline for Inadequate Response to Initial Treatment
  - A) Switching or Combining medications?
  - B) Defining inadequate response and how long to try a medication
- 6) Medication Dosing:
  - A) When to taper medication if a good response?  
(CMS – LTC Guideline Summary)
  - B) Recommended dosing to treat Agitation Syndromes
- 7) Safety, Complicating Conditions of Medication Usage:
  - A) Long term safety issues
  - B) Combining medication – safety concerns
  - C) Selecting medications for patients with complicating conditions of concern

## **1. Differential diagnosis of specific types of Dementia.**

## I. Diagnosis of Specific Types of Dementia

The clinical features listed below can be helpful in the differential diagnosis of dementing disorders. The high second-line ratings given to apraxia in diagnosing AD and vascular dementia, may reflect the fact that apraxia often appears during the middle of these dementing disorders.

***Bold italics*** = features receiving the highest rating from at least 50% of the experts

Types of dementia	Most important discrimination features	Also consider
Alzheimer's	<b><i>Early prominent problems with memory impairment</i></b> Aphasia Impairment in executive functioning	Apraxia Visuospatial problems Problems with calculation Agnosia Change in personality
Vascular	Impairment in executive functioning*	Apraxia Aphasia Impairment in speed of information processing Early prominent problems with memory impairment Depressive symptoms
Frontotemporal	Change in personality  Impairment in executive functioning	Aphasia
With Lewy bodies	Extrapyramidal symptoms/Parkinsonian symptoms  Visual hallucinations	Alterations in alertness and attention Delusions Impairment in executive functioning Change in personality Gait problems early in the illness Impairment in speed of information processing Visuospatial problems Early prominent problems with memory impairment
Due to HIV	Impairment in executive functioning	Impairment in speed of information processing Change in personality Depressive symptoms Early prominent problems with memory impairment
Substance induced	-----	Impairment in executive functioning Change in personality Depressive symptoms Early prominent problems with memory impairment Cerebellar signs Impairment in speed of information processing Alterations in alertness and attention

\*Very high second line: rated first line by 73% of the experts.

## **2. Treatments for Cognitive Impairment: Mild-to- Moderate Dementia**

## II. Treatments for Cognitive Impairment in Mild-to-Moderate Dementia

### Pharmacological Strategies

The Experts recommend a cholinesterase inhibitor alone as first-line treatment for the cognitive impairment of AD, mixed AD/vascular dementia, and dementia with Lewy bodies.

Adding an NMDA antagonist (e.g., memantine {Namenda}) to the cholinesterase inhibitor was a high second-line option for AD and mixed AD/vascular dementia. Control of hypertension and diabetes was a treatment of choice for vascular and mixed AD/vascular dementia, and aspirin was a first-line option, while a lipid-lowering agent was a high second-line option. Controlling hypertension and diabetes was a high second-line recommendation for all other types of dementia.

***Bold italics*** = treatment of choice

Types of dementia	Preferred treatments	Also consider
Alzheimer's	Cholinesterase inhibitor alone Cholinesterase inhibitor	Control of hypertension and diabetes NMDA antagonist plus cholinesterase inhibitor
Vascular	<b><i>Control of hypertension and diabetes</i></b> Aspirin	Lipid-lowering agents (e.g., statins) Cholinesterase inhibitor alone
Mixed (Alzheimer's/vascular)	<b><i>Control of hypertension and diabetes</i></b> Cholinesterase inhibitor alone Aspirin	Cholinesterase inhibitor NMDA antagonist plus cholinesterase inhibitor Lipid-lowering agents (e.g., statins)
Frontotemporal	-----	Control of hypertension and diabetes
With Lewy bodies	Cholinesterase inhibitor alone	Cholinesterase inhibitor Control of hypertension and diabetes

#### A) Choice of Cholinesterase Inhibitors

The experts considered donepezil the treatment of choice, with galantamine another first-line option, and rivastigmine a high second-line option for mild-to-moderate AD, mixed AD/vascular dementia, and dementia with Lewy bodies. If it is decided to use a cholinesterase inhibitor in mild-to-moderate vascular dementia (rated a high second-line strategy), the experts recommended donepezil and galantamine as first-line choices. The experts did not recommend any medication in frontotemporal dementia of mild-to-moderate severity, but would consider donepezil followed by galantamine if it is decided to prescribe a cholinesterase inhibitor in this disorder.

***Bold italics*** = treatment of choice

Types of dementia	Preferred treatments	Also consider
Alzheimer's Mixed (Alzheimer's/vascular) With Lewy bodies	<b><i>Donepezil</i></b> Galantamine	Rivastigmine
Vascular	Donepezil Galantamine	Rivastigmine
Frontotemporal	-----	Donepezil

**B) Nest Step If Inadequate Response to Initial Treatment**

The experts favored combination treatment with an NMDA antagonist plus a cholinesterase inhibitor in patients with an inadequate response to monotherapy. They would also consider switching to monotherapy with a different agent. If the person were already receiving combination treatment, the experts would change the cholinesterase inhibitor in the combination.

<b>Initial treatment</b>	<b>Preferred strategy</b>	<b>Also consider</b>
Donepezil	Add NMDA antagonist (memantine) and continue donepezil	Switch to galantamine
Galantamine	-	Add NMDA antagonist (memantine) and continue galantamine Switch to donepezil
Rivastigmine	-	Add NMDA antagonist (memantine) and continue rivastigmine Switch to donepezil Switch to galantamine
NMDA antagonist	Add donepezil	Switch to donepezil Add galantamine Switch to galantamine
NMDA antagonist plus cholinesterase inhibitor	-	Continue NMDA antagonist (memantine) and switch to a different cholinesterase inhibitor

**C) Next Step If Unable to Tolerate Initial Treatment**

The experts recommend lowering the dose in patients with mild-to-moderate dementia who are unable to tolerate a cholinesterase inhibitor or an NMDA antagonist. They would also consider switching to a different agent, but did not recommend discontinuing drug treatment.

<b>Initial treatment</b>	<b>Preferred strategy</b>	<b>Also consider</b>
Donepezil	Lower the dose	Switch to NMDA antagonist (memantine) Switch to galantamine
Galantamine	Lower the dose	Switch to donepezil Switch to NMDA antagonist (memantine)
Rivastigmine	Lower the dose Switch to donepezil	Switch to galantamine Switch to NMDA antagonist (memantine)
NMDA antagonist (memantine)	-	Lower the dose Switch to donepezil Switch to galantamine

**D) Most Common Behavioral Problems in Mild-to-Moderate Dementia**

The experts considered depression, irritability, sleep disturbance, agitation, and anxiety the most common behavioral problems in patients with mild-to-moderate dementia. Although delusions are not common in mild dementia, they increase in frequency as the severity of dementia increases.

Most frequent	Sometimes
Depression	Apathy
Irritability	Mood lability
Sleep disturbance	Restlessness
Agitation	Delusions
Anxiety	Aggression
	Catastrophic reactions to minor stresses
	Disinhibition
	Hallucinations

**1) Treatment Strategies for Depression in Dementia**

For nonpsychotic depression, an antidepressant was the treatment of choice. The experts considered adding a cholinesterase inhibitor or combining the antidepressant with the psychotherapy high second-line options. For psychotic depression, the experts recommend combination treatment with an antidepressant plus an antipsychotic. Electroconvulsive therapy (ECT) was high second-line option.

*Bold italics* = treatment of choice

Type of depression	Preferred (first line)	Also consider (high second line)	Other second line
Nonpsychotic	<b><i>Antidepressant alone</i></b>	Antidepressant plus cholinesterase inhibitor (if patient not already receiving one)	--
Psychotic	Antidepressant plus antipsychotic	ECT*	--

\*Authors' comment: ECT may cause severe memory loss and other cognitive impairments in a patient with dementia than in a non-demented patient; however, this side effect eventually subsides.

**2) Medications for Depression in Dementia**

Among the antidepressants, the experts gave the highest ratings to the selective serotonin reuptake inhibitors (SSRIs) that are least likely to cause drug interactions. They did not recommend nefazodone or monoamine oxidase inhibitors. If an antipsychotic is needed to treat psychotic depression, the experts recommended risperidone (rated first line by 80% of the experts), followed by quetiapine (first line by 70%), and olanzapine (first line by 50%). They did not recommend olanzapine/fluoxetine combination or conventional low-potency antipsychotics.

Medication class	Preferred (first line)	Also consider (high second line)	Other second line
Antidepressants	Citalopram Sertraline Escitalopram	Venlafaxine XR Mirtazapine	Paroxetine Bupropion
Antipsychotics for use in combination with an antidepressant for psychotic depression	Risperidone	Quetiapine Olanzapine	Aripiprazole

### 3) **Treatment of Prominent Anxiety in Dementia**

In patients with dementia, anxiety may present with verbal or facial expression of worry, nervousness, or fear and/or somatic symptoms such as palpitations, stomach problems, or feelings of tension. Patients may repeatedly request reassurance or complain of somatic symptoms. Worries are often related to memory loss, such as needing repeated assurance that loved ones are safe or are planning to visit, that belongings have not been lost, or that plans and schedules will be kept.

The experts did not recommend long-term use of benzodiazepines or conventional antipsychotics for the treatment of anxiety in dementia: Both received third-line ratings.

	<b>Preferred (first line)</b>	<b>Also consider (high second line)</b>	<b>Other second line</b>
Short-term / p.r.n.	--	Benzodiazepine Atypical antipsychotic	--
Long-term	SSRI*	--	Atypical antipsychotic

\*Further recommendation: The SSRIs have a gradual onset of action. Benzodiazepines may be used during the early phases of treatment to relieve anxiety until SSRIs exert their action.

### **3. Treatments for Cognitive Impairment: Moderate-to-Severe Dementia**

### III. Treatments for Cognitive Impairment in Moderate-to-Severe Dementia Pharmacological Strategies

- A) Most patients with late stage dementia are not treated with medications that enhance cognitive functioning. Nonetheless, the experts recommend use of such agents in patients with moderate-to-severe dementia. Their strongest recommendation was combination treatment with an NMDA antagonist plus a cholinesterase inhibitor. There was no consensus on the use of cognitive enhancers in frontotemporal dementia.

***Bold italics*** = treatment of choice

<b>IV. Type of dementia</b>	<b>Preferred treatment</b>	<b>Also consider</b>
Alzheimer's	NMDA antagonist plus cholinesterase inhibitor	Cholinesterase inhibitor alone NMDA antagonist (memantine) alone Control of hypertension and diabetes Cholinesterase inhibitor
Vascular	<b><i>Control of hypertension and diabetes</i></b>	NMDA antagonist plus cholinesterase inhibitor Aspirin Cholinesterase inhibitor alone
Mixed (Alzheimer's / vascular)	Control of hypertension and diabetes NMDA antagonist plus cholinesterase inhibitor	Cholinesterase inhibitor alone Aspirin NMDA antagonist (memantine) alone Cholinesterase inhibitor
Frontotemporal	--	--
With Lewy bodies	--	Cholinesterase inhibitor alone NMDA antagonist plus cholinesterase inhibitor

#### B) Choice of Cholinesterase Inhibitors

The experts' preferences among the cholinesterase inhibitors were the same for all phases of dementia.

***Bold italics*** = treatment of choice

<b>Type of dementia</b>	<b>Preferred treatments</b>	<b>Also consider</b>
Alzheimer's	<b><i>Donepezil</i></b> Galantamine	Rivastigmine
Vascular	Donepezil	Galantamine
Mixed (Alzheimer's/vascular)	Donepezil Galantamine	Rivastigmine
Frontotemporal	--	--
With Lewy bodies	Donepezil	Galantamine Rivastigmine

**C) Dosing****Dosing of Cholinesterase Inhibitors and NMDA Antagonists**

Donepezil treatment may be continued at 5 mg/day if the patient has a satisfactory response on this dose since studies have found equal efficacy between 5 and 10 mg/day.

Medication	Average starting docs (mg/day)	Average target docs (mg/day)
Donepezil	5	10
Galantamine	4-8	16-24
Memantine	5	20
Rivastigmine	3	9-12

**D) Strategies for a Patient With Moderate-to-Severe Dementia Who Deteriorates**

If a patient with moderate-to-severe dementia shows signs of cognitive deterioration after 6 to 12 months of treatment with a single agent, the experts recommend combination treatment with a cholinesterase inhibitor plus a NMDA antagonist. If the patient were already receiving combination treatment, the experts would consider changing the cholinesterase inhibitor in the combination regimen.

Initial treatment	Preferred strategy	Also consider
Cholinesterase inhibitor alone	Continue same cholinesterase inhibitor and add NMDA antagonist (memantine)	--
NMDA antagonist alone	Continue NMDA antagonist (memantine) and add a cholinesterase inhibitor	--
NMDA antagonist plus cholinesterase inhibitor	--	Continue NMDA antagonist (memantine) and switch to a different cholinesterase inhibitor

**MODERATE-TO-SEVERE-DEMENTIA****E) Most Common Behavioral Problems in Moderate-to-Severe-Dementia**

In moderate-to-severe dementia, the experts indicated that agitation, aggression, sleep disturbance, sundowning, wandering, restlessness, irritability, disinhibition, and delusions are the most common symptoms. Anxiety and depression are less prominent in moderate-to-severe dementia, although they are quite frequent in mild dementia.

Most frequent	Sometimes
Agitation	Mood lability
Aggression	Anxiety
Sleep disturbance	Catastrophic reactions to minor stresses
Sundowning	Hallucinations
Wandering	Depression
Restlessness	
Irritability	
Disinhibition	
Delusions	

## **4. Agitation Syndromes seen in Dementia**

## MANAGEMENT STRATEGIES FOR AGITATION

### V. Well defined levels of agitation as follows:

#### A) Management Strategies for Agitation

##### Mild Agitation

- Behavior that is somewhat disruptive to others, but is non-aggressive and poses little risk of danger
- Behaviors is constant need of redirection, frequently taxing the caregivers  
*Examples:* patients moans, cries, argues, paces, speaks inappropriately to strangers, asks repetitive questions, makes repetitive movements, uses the telephone inappropriately, wanders but can be redirected.

##### Severe Agitation

- Aggressive, endangering, or disruptive behavior that may pose a threat of physical harm to self or others.
- The agitation is a major source of difficulty to caregivers; commonsense verbal limit-setting and simple redirection by caregivers is ineffective.  
*Example:* patients screams, insists on trying to leave dwelling or often gets lost in public places, makes feeding difficult, throws objects, grabs and scratches caregivers, bangs head or injures self.

After pertinent medical conditions have been identified and managed (see Guideline 21B), significant agitation may still remain and require intervention. An earlier panel of experts recommended that the treatment for agitation in dementia presentation or the length of treatment. This recommendation is especially important because there is often a tendency to neglect environmental interventions in formulation a treatment plan for such patients. For patients with mild agitation, an environmental intervention alone may be sufficient. In severe agitation, medication alone is sometimes appropriate (e.g., if the patient is in danger or the environment cannot be changed).

***Bold italics*** = strategy of choice

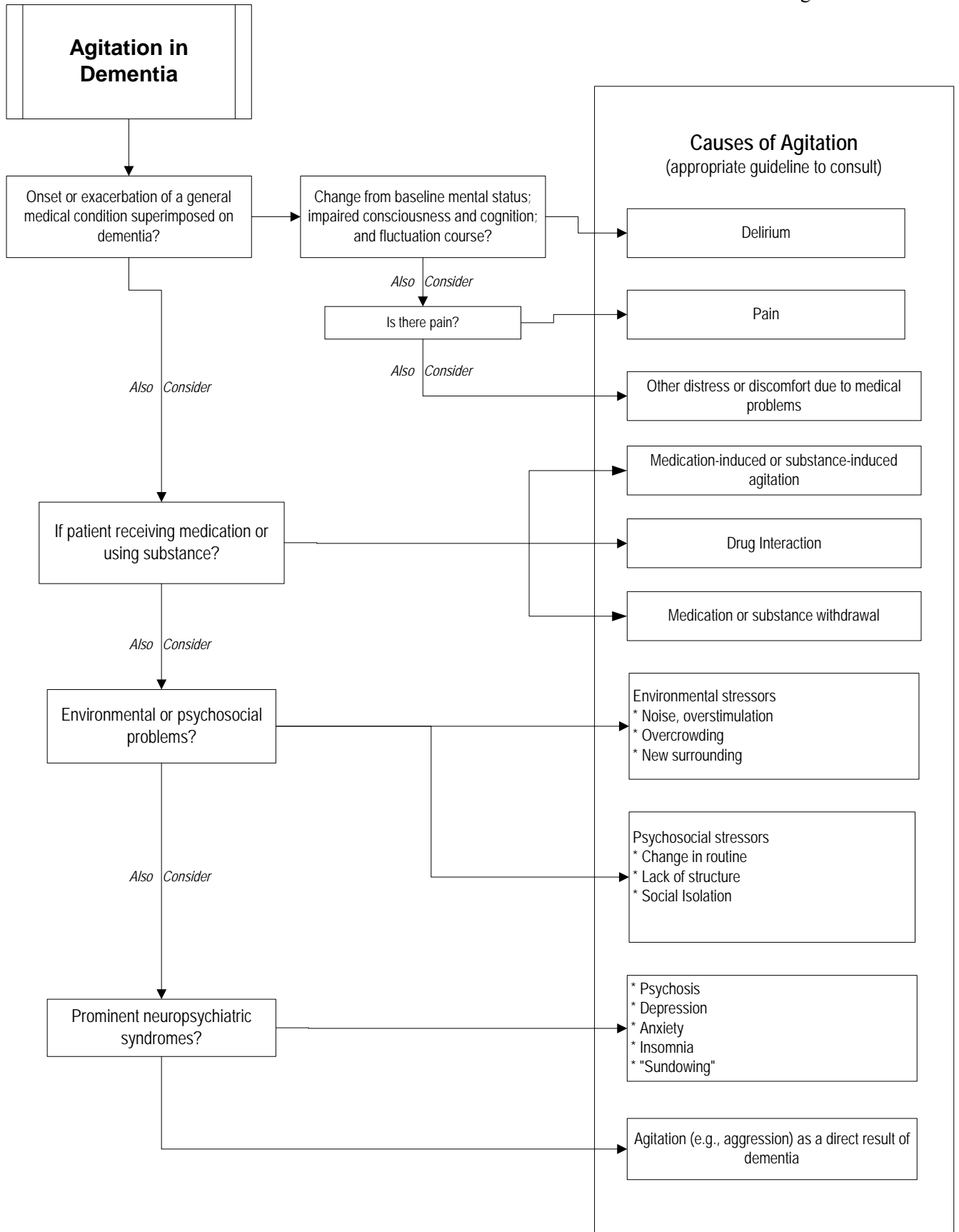
	<b>Acute and long-term management strategies</b>	
	<b>First Line</b>	<b>Also Consider</b>
Mild Agitation	Environmental intervention plus medication	Environmental intervention alone
Severe Agitation	<b><i>Medication plus environmental intervention</i></b>	Medication use

## MANAGEMENT OF AGITATION AND BEHAVIORAL DISTURBANCES IN DEMENTIA

### B) Assessment of Agitation in Dementia

#### Differential Diagnosis

- 1) Patients with dementia often have general medical illnesses and/or neuropsychiatric syndromes that may be responsible for their agitation. Therefore, before a treatment plan can be developed, it is crucial to conduct a systematic differential diagnosis focusing on the common causes of agitation in this context.



**1) Medical Causes of Agitation in Dementia**

The experts considered it critical to evaluate for medical contributions to agitation.

***Bold italics*** = receiving the highest rating from at least 50% of the experts

<b>Most Important causes to evaluate</b>	<b>Also consider</b>
<b><i>Delirium (e.g. due to multiple medications with anticholinergic properties, dehydration or electrolyte imbalance, infection (URI, TUI), COPT or pneumonia)</i></b>	Dyspnea
Pain / physical discomfort (e.g. due to osteoarthritis, dental problems)	
Urinary retention or constipation	
Environmental factors (e.g. noisy roommate, overheated room)	

**Clinical Assessment and Diagnostic Tests**

In assessing agitation, an earlier panel of experts gave priority to careful bedside evaluation of the patient's psychiatric, cognitive, medical, and neurological status. The panel also recommended routine laboratory studies and serum drug levels of commonly used medications that can cause agitation if present in toxic levels. Additional more specialized testing was recommended as needed based on an evaluation of the results of these initial screening efforts. (Note that this guideline is directed towards comorbid medical problems that may cause agitation, but does not cover the diagnostic work-up for dementia itself, which is covered in Guidelines 6-8.)

***Bold Italics*** = assessments of choice

<b>Priorities to perform</b>	<b>Consider as needed</b>
<b><i>At the bedside:</i></b>	Thyroid-stimulating hormone (TSH)
<b><i>Focused psychiatric history and examination</i></b>	Electrocardiogram (ECG)
<b><i>General physical history and examination</i></b>	Serum vitamin B <sub>12</sub> (Cobalamin)
<b><i>Routine cognitive examination and/or rating scale</i></b> (e.g. <i>Mini-Mental State examination</i> )	Urine culture
<b><i>Focused neurological examination</i></b>	Chest X-ray
<b><i>Routine laboratory:</i></b>	Brain computed tomography (CT) scan
<b><i>Urinalysis</i></b>	Thyroid panel without TSH (T <sub>4</sub> T <sub>3</sub> uptake)
Complete blood count	Serum folate
Sequential multichannel autoanalyzer (SMA) or similar chemistry screen	Brain magnetic resonance imaging (MRI)
<b><i>Serum drug levels if patient is taking:</i></b>	Toxicology screen (alcohol, drugs of abuse)
Digoxin	Sedimentation rate
Anticonvulsant	
Theophylline	
Tricyclic antidepressant	

**2) Delirium**

Delirium presents as a change in the patient’s mental status characterized by impairment in attention and other intellectual functions. The disturbances in attention often fluctuate over minutes or hours. Delirium is caused by drug toxicity, dehydration, metabolic derangement, infections, or organ failure and constitutes a medical emergency. Patients with dementia are at an increased risk for delirium. Treatment of delirium should target the underlying causative medical condition. For symptomatic treatment of agitation associated with delirium, the experts recommended use of antipsychotics as shown in the table below, but would avoid mood stabilizers, conventional low-potency antipsychotics, and benzodiazepines. They would avoid using olanzapine in delirium that occurs in the context of diabetes.

<b>If patient has delirium due to:</b>	<b>Preferred medications (first line)</b>	<b>Also consider (high second line)</b>	<b>Other second line</b>
Congestive heart failure COPD or pneumonia Dehydration or electrolyte imbalance Infection (URI, UTI)	Risperidone	Quetiapine	Conventional high-potency antipsychotic Olanzapine
Diabetes	--	Risperidone	Quetiapine Conventional high-potency antipsychotic
Medication (or substance) toxicity or interaction*	Reduce or stop offering medication; address substance use	--	--
Benzodiazepine withdrawal*	Prescribe a benzodiazepine that has a short half-life and is metabolized well in older adults (e.g. lorazepam)	Prescribe a lower dose of whatever benzodiazepine the patient was previously using and taper slowly	--

**3) Psychosis**

Psychotic symptoms in demented patients often consist of delusions related to forgotten recent events. For example, patients may forget where they put things and believe that someone has stolen them, may believe their spouse is having an affair because they do not recall seeing him or her for periods of time, or believe that family members or caregivers have been replaced by imposters. Hallucinations should be distinguished from confabulated delusional memories, such as reports of nonexistent visitors or burglars at night “Insomnia and Sundowning”.

For severe agitation accompanied by psychotic symptoms, the experts recommended Risperidone and quetiapine for both short and long-term use. They would also consider olanzapine or a conventional high-potency antipsychotic for short-term use; the high second-line ratings given to a conventional antipsychotic may reflect the need for an IM preparation. For long-term use, aripiprazole or olanzapine were high second-line options. The experts would avoid long-term use of mood stabilizers, low-potency conventional antipsychotics, and benzodiazepines. Quetiapine was first line for psychotic symptoms related to dopaminergic medication in patients with Parkinson’s disease, perhaps because of its low affinity for the dopamine D<sub>2</sub> receptor.

Clinical situation	Preferred (first line)	Also consider (high second line)	Other second line
Short-term / p.r.n. use	Risperidone Quetiapine	Olanzapine Conventional high-potency antipsychotic	Aripiprazole
Long-term use	Risperidone Quetiapine	Aripiprazole Olanzapine	--
Ongoing use in a patient with Parkinson's disease whose psychotic symptoms are due to dopaminergic medication (e.g. L-dopa)	Quetiapine	--	Aripiprazole

#### 4) **Insomnia and Sundowning**

Insomnia is a common source of distress in the elderly who often sleep less and have reduced sleep efficiency as part of the aging process. Insomnia may also be due to an identifiable cause that should be treated appropriately, such as pain or distress associated with a medical condition, psychosis, depression, or anxiety. Sundowning consists of agitation, confusion, and disorientation that often starts in the late afternoon and becomes especially severe at night. It may be the result of a number of causes, including loss of visual cues in the dark and instability in circadian rhythm. Sundowning may result in dangerous behavior such as falls from wandering or climbing over bed rails. It may be helpful to use orienting environmental interventions such as night-lights or reassuring check-ins from caregivers. Medication can help promote sleep and diminish confusion.

The experts preferred trazodone for both long-term and acute treatment of insomnia. Benzodiazepines received a second-line rating only for short-term use, while the experts would avoid long-term use of benzodiazepine for insomnia.

Clinical situation	Preferred (first line)	Also consider (high second line)	Other second line
Short-term / p.r.n. use	Trazodone	Quetiapine Zolpidem	Zaleplon
Long-term use	Trazodone	Quetiapine	--

#### 5) **Aggression or Anger Not Due to Other Causes** (e.g. *Psychosis, Depression, Anxiety, Insomnia*)

This guideline deals with aggression or anger that is not primarily explained by another syndrome such as psychosis or anxiety. Mild anger (i.e. without physical aggression) may be limited to specific situations (e.g., bathing, getting out of bed) or may be continuous. Severe anger with physical aggression is characterized by acts directed at caregivers and other people (e.g., forcefully pushing away a hand offering food; pushing, slapping, or scratching; extremely loud and disruptive yelling for extended periods.)

##### (a) **Medications for Anger Without Physical Aggression**

The experts had no first-line medication recommendations for anger without physical aggression, indicating lack of strong support for pharmacotherapy. SSRIs received high second-line ratings, probably because anger and irritability may be clinical expressions of underlying depression.

Clinical situation	Preferred (first line)	Also consider (high second line)	Other second line
Short-term / p.r.n. use	--	--	Quetiapine Risperidone
Long-term use	--	SSRI	Quetiapine Risperidone

(b) **Medications for Anger With Risk of Physical Aggression**

Clinical situation	Preferred (first line)	Also consider (high second line)	Other second line
Short-term / p.r.n. use	Risperidone	Quetiapine Olanzapine	Conventional high-potency antipsychotic
Long-term use	Risperidone* Quetiapine*	Olanzapine	Aripiprazole Divalproex

\*Very high second line: rated first line by more than 2/3 of the experts.

6) **Prominent Pain**

Musculoskeletal pain from chronic osteoarthritis is a common cause of agitation and is often resistant to drug therapy. Comfortable positioning, physical therapy, local heat, and other pain management techniques can be helpful. Treatment with acetaminophen or nonsteroidal anti-inflammatory drugs should also be tried. Despite these measures, patients may become agitated due to continued pain and may benefit from treatment with certain psychotropic medications.

An earlier panel of experts had no first-line recommendations, but favored Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and trazodone over codeine compounds when dealing specifically with agitation.

Preferred medications (first line)	Also consider (high second line)	Other second line
--	--	Tricyclic antidepressant SSRI Trazodone

## **5. Guideline for Inadequate Response to Initial Treatment**

**V. Inadequate Response to Initial Treatment for Agitation or Behavioral Problems**

Before changing or adding medication in a patient who is having no response or only a partial response, it is important to ask the following questions and take appropriate action:

1. Has the medication been given for an adequate duration and at an adequate dose?
2. Are medication side effects or drug interactions causing problems?
3. Is the medication being taken as prescribed?
4. Have environmental stressors been evaluated and altered?
5. Have underlying medical disorders and delirium been ruled out or treated?
6. Have neuropsychiatric syndromes related to dementia (e.g., psychosis, depression, anxiety) been properly identified and treated appropriately?
7. If the response is difficult to determine or fluctuates over time, have you considered using a rating scale to quantify change?

**A) Should You Switch Medication or Combine?**

An earlier panel of experts suggested avoiding polypharmacy in these vulnerable patients and recommended using drugs one at a time in most situations. In mild or severe agitation with no response to the first drug, the experts favored switching to a new medication. In severe agitation, however, they would add a second medication if the patient has had a partial response to the first, since the recurrence of full-blown agitation might be more dangerous than the potential risk of drug interactions. In mild agitation with partial response to the first drug, the experts had no first-line recommendation and supported either switching or combining. When combinations are chosen, care should be taken to select new medications that do not interact negatively with those already being taken.

Level of agitation	No response		Partial response	
	Preferred strategy	Also consider	Preferred strategy	Also consider
Mild	Switch to a second medication	(Combinations generally not preferred)	--	Switch to a second medication  Combine with a second medication <sup>†</sup>
Severe	Switch to a second medication	Combine with a second medication <sup>†</sup>	Combine with a second medication <sup>†</sup>	Switch to a second medication

**B) Defining Inadequate Response: How Long to Try a Medication**

Agitation in dementia is often a chronic problem requiring long-term management and it may take many weeks of treatment at gradually adjusted doses to determine if a certain medication and dosage schedule are useful. Sometimes, brief use of a medication may help stabilize a patient during an acute crisis.

**1. For longer-term management**

Among medications used to treat agitation, some work rapidly while others have a delayed onset of action. An earlier panel of experts generally recommended trials of two (2) weeks or longer for divalproex and antidepressants. Antipsychotics, trazodone, benzodiazepines may produce a response in one (1) week or less.

Medication	How long to try a first medication before switching to or adding another medication if response inadequate.	
	Shortest	Longest (weeks)
Antipsychotic	4-7 days	2-4
Benzodiazepine	3-4 days	1-3
Divalproex	1-2 weeks	3-6
SSRI	10-14 days	4-6
Tricyclic antidepressant	10-14 days	4-6
Trazodone	7-10 days	3-4

**2. In acute management**

To determine if a medication will be helpful in an acute situation, the earlier panel of experts recommended trying an antipsychotic for at least 2 or 3 days and a benzodiazepine for at least 1 or 2 days. If the response to the initial treatment is not adequate, the clinician should wait no longer than one (1) week before deciding on the next step.

Medication	How long to try a first medication before switching to or adding another medication if response inadequate.	
	Shortest (days)	Longest (days)
Antipsychotic	2-3	6-8
Benzodiazepine	1-2	4-6

## **6. Medication Dosing**

## VI. Dose and Duration of Treatment

### A) When to Taper Medication in a Patient With a Good Response

Although some patients require long-term treatment, it is important to taper and try to discontinue medication periodically after a period of satisfactory improvement. An earlier panel of experts generally suggested attempting to taper medication in 2 to 3 months in patients with milder agitation and in 6 to 9 months in patients with severe agitation. The recommended period of treatment tends to be somewhat shorter for antipsychotics and benzodiazepines. Repeated relapses suggest the need for continuing medication indefinitely.

Authors' comment: In deciding whether to continue or taper a medication for agitation, the authors recommend considering the following:

- For patients in nursing homes, clinicians should consult [CMS Long Term Care Guidelines](#),<sup>†</sup> which are briefly summarized here:
- Benzodiazepines and other sedative-hypnotics for sleep: If used for more than ten (10) continuous nights, gradual dose reduction should be attempted at least three (3) times within six (6) months before concluding that dose reduction is contraindicated.
- Benzodiazepines and other anxiolytics (excluding buspirone) for uses other than promote sleep: Gradual dose reduction should be attempted at least twice within one (1) year before concluding that the gradual dose reduction is contraindicated.
- Antipsychotics: Gradual dose reductions should be attempted at least twice within one (1) year unless the patient has had psychotic symptoms (hallucinations or delusions) due to dementia or another psychiatric disorder that has stabilized on medication.
- Antidepressants: There are no time points for discontinuation, only a requirement for documentation of the rationale for continued use.
- Behavioral monitoring charts are recommended to document continued need for medication.
- If response is uncertain, clinicians should consider using a behavioral monitoring chart to quantify the levels of agitation and the effects of medication.

Medication	Length of Time to Treat Before Trying to Taper and Discontinue			
	Mild agitation		Severe agitation	
	Fewest months	Most months	Fewest months	Most months
Antidepressant (not for depression)	2-3	6-8	3-4	7-9
Antipsychotic	1.5-2	4-6	2-3	6-8
Benzodiazepine	1-2	3-6	1.5-2	4-6
Divalproex	2-3	6-8	3-4	7-9
Trazodone	2-3	6-8	2.5-4	7-9

Further recommendations: Tapering should be done gradually (e.g. 25% every week or two.) Most of the experts did not recommend continuing medication indefinitely, especially in milder agitation.

### B) Recommended Doses to Treat Agitation

	Average starting dose (mg/day)	Average target dose (mg/day)	Usual highest final dose (mg/day)
Aripiprazole	2.5 - 5	7.5-12.5	10-20
Carbamazepine	100-200	400-600	800-1000
<i>Blood level (mg/mL)</i>	2-5	7-8	10-11
Divalproex DR and ER	250-375	625-825	1250-1750
<i>Blood level (mg/mL)</i>	20-50	50-85	80-120
Haloperidol <sup>†</sup>	0.5-1.0	1.5-2.0	5-7
Lorazepam	0.5-1.5	1.5-2.5	3-5
Olanzapine	2.5-5.0	5.0-10	7.5-15
Quetiapine	12.5-25	50-200	100-400
Risperidone <sup>†</sup>	0.25-0.5	0.5-1.5	1.0-3.5
Trazodone	25-50	50-100	250-300
Ziprasidone	20-40	20-80	40-160

\*Alexopoulos GS, Silver JM, Kahn DA, et. al. The expert's consensus guideline series: treatment of agitation in older persons with dementia. Post grad Med Special Report 1998; April: 34

<sup>†</sup>If it is decided to use a single p.r.n. dose of an intramuscular medication to treat severe agitation in a medically stable patient with dementia, the experts preferred haloperidol (high second-line option) at an average dose of 1.5 mg. <sup>Question 55</sup> The experts did not recommend the use of long-acting depot conventional antipsychotics in this population. There was no consensus about the use of long-acting risperidone (rated first line by 32%, second line by 32%, and third line by 36%), but if used, the experts recommended a dose of 25 mg every two (2) weeks. <sup>Question 56</sup>

## **7. Safety, Complicating Conditions of Medication Usage**

## VII. Safety, Complicating Conditions, and Medication Combinations

### A) Medications for Long-Term Safety

The medications listed in the first two (2) columns of the table below were rated as safest for long-term use. The experts gave third-line ratings to benzodiazepines and conventional antipsychotics.

Least likely to cause serious problems (first line)	Also consider (high second line)	Other second line	Not recommended (third line)
Donepezil Galantamine NMDA antagonist (memantine) SSRI Trazodone	Rivastigmine Buspirone Quetiapine Bupropion Venlafaxine	Risperidone Aripiprazole Divalproex Ziprasidone Olanzapine Carbamazepine Tricyclic antidepressant	Benzodiazepine Conventional antipsychotic

### B) Combining Medications

We asked the experts to rate the safety of cholinesterase inhibitors and memantine when combined with other medications using 3 ratings: 1 = no expected drug interaction, 2 = need for extra monitoring for possible side effects; and 3 = combined use contraindicated. The combinations listed in the table are those to which the majority (50% or more) of the experts gave a score of 2 or 3.

Extra monitoring for side effects needed when combining a dementia drug with:			
	An antidepressant	Another psychotropic*	Other drug
Donepezil	Fluoxetine Fluvoxamine MAOI Nefazodone Paroxetine TCA	Carbamazepine	Ketoconazole Tramadol
Galantamine	Fluoxetine Fluvoxamine MAOI Nefazodone Paroxetine TCA	Carbamazepine	Codeine Ketoconazole Tramadol
Memantine	MAOI TCA	--	--
Rivastigmine	Nefazodone TCA	Carbamazepine	--

### C) Selecting Medications for Patients With Complicating Conditions

This table presents ratings for medications that combine safety and efficacy for patients with comorbid conditions.

+++ = preferred (first line)  
 ++ = high second line  
 + = second line  
 -- = not recommended (third line)  
 ( ) = no consensus

Complicating Condition	Cognitive enhancers				Atypical antipsychotics				
	Donepezil	Galantamine	Rivastigmine	Memantine	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Angina	++	++	++	+++	++	++	++	++	+
Cardiac conduction disease	++	++	++	+++	++	+	++	++	-
CHF	++	++	++	+++	++	+	++	++	(+)
Orthostatic hypotension	++	++	++	+++	+	+	+	+	(+)
COPD	++	++	++	+++	++	++	++	++	++
Liver disease	++	++	++	++	++	+	++	++	+
Prostatic hypertrophy	+++	+++	++	+++	++	+	++	++	++
Falling due to gait problems <sup>†</sup>	+++	+++	++	+++	+	+	++	+	+
Obesity	+++	+++	++	+++	++	--	++	++	++
Stroke or TIA	+++	+++	++	+++	+	(+)	++	(+)	+

<sup>†</sup> Other than Parkinsonism

Complicating condition	High-potency conventional antipsychotic	Low-potency conventional antipsychotic	Benzodiazepine	Divalproex	Carbamazepine	SSRIs	Tricyclic antidepressants	Trazodone
Angina	++	+	++	++	+	++	- <sup>†</sup>	+
Cardiac conduction disease	++	--	++	++	+	+++	--	+
Concern over weight gain	+	--	+	+	+	++	--	+
CHF	++	--	+	++	+	++	- <sup>†</sup>	+
Constipation	+	--	+	++	+	+++	--	+
COPD	++	+	--	++	+	++	+	+
Falling due to gait problems other than Parkinsonism	+	--	--	++	+	+++	--	+
Insomnia	++	+++	+++	+++	+++	--	+++	+++
Lethargy	+	--	--	+	+	++	+	--
Liver disease – elevated LFTs	+	+	+	-	-	+	+	+
Nausea or poor appetite	++	+	+	+	+	+	+	+
Orthostatic hypotension	++	--	(+)	+	+	++	--	-
Potential drug abuse or dependence	++	++	--	++	++	++	+	++
Prostatic hypertrophy	+	--	+	++	+	+++	--	+
Renal insufficiency	++	+	+	+	+	++	+	+
Seizure disorder	+	--	++	+++	+++	+	+	+
Very poor memory	++	--	--	++	+	+++	--	+

### **VIII. The Use of Anti-Psychotic Agents in Persons with Dementia**

- A) The goals of pharmacologic treatment for dementia are to stabilize or slow cognitive and functional decline, ameliorate behavioral and psychological symptoms, reduce caregiver burden, and if possible, delay institutionalization. Currently, there are two (2) pharmacologic class options approved for the US Food and Drug Administration (FDA) for the treatment of dementia: cholinesterase inhibitors (ChEIs) tacrine (mild-to-moderate Alzheimer's disease [AD]), rivastigmine (mild-to-moderate AD and Parkinson's disease), galantamine (mild-to-moderate AD), and donepezil (mild-to-severe AD); and an N-methyl-D-aspartate glutamate receptor antagonist, memantine (moderate-to-severe AD).

Several studies have highlighted the benefits of early pharmacologic intervention with ChEIs to reduce the progression of cognitive decline.

Additionally, gaps in treatments of six (6) weeks or more reduce the effectiveness of ChEI therapy; therefore, persistent therapy is essential to maintain dementia patients' cognitive and functional status. Patients with moderate-to-severe AD may also benefit from ChEI treatment as demonstrated by the results of a number of placebo-controlled ChEI trials.

An additional benefit of the ChEI and memantine therapies may be positive effects on some behavioral symptoms, including the possibility of secondary prevention (i.e., prevention of the emergency of behavioral symptoms not present at baseline).

- B) The role of antipsychotics for agitation and behavioral symptoms in patients with dementia continues to be scrutinized.

Antipsychotic therapy is often used for intractable behavioral symptoms or psychosis not responding to nonpharmacologic interventions and antidementia medications; however, the risk/benefit ratio for each patient should be critically evaluated because treatment with atypical antipsychotics has been associated with serious adverse events, including increased risk for death in older adults with dementia.

Although there currently is no cure for AD and related dementias, a variety of treatment options exist. Antidementia medications may slow the rate of decline in cognition and function, as well as ameliorate some behavioral symptoms. Antipsychotic medications may be appropriate for treatment of severe behavioral and psychological disturbances in dementia patients when other interventions fail to adequately manage these symptoms. In most cases, utilizing an individualized combination of pharmacologic and nonpharmacologic therapies leads to improved quality of life for both the patient and the caregiver.

For many patients and families, the most problematic aspects of dementia are neuropsychiatric symptoms: depression, sleep disturbance, psychosis, and aggression. Psychosis affects approximately 40% of persons with AD, whereas  $\geq$  80% of persons with dementia experience agitation at some point in the illness.

These symptoms can lead to:

- Caregiver morbidity
- Poor patient quality of life, and
- Early patient institutionalization.

Although no drug has been FDA-approved for treating dementia’s neuropsychiatric symptoms, psychiatrists often use off-label psychotropics – especially antipsychotics – to ameliorate them. Nonetheless, because dementia patients with psychosis and severe agitation / aggression can pose risks to themselves and those around them, efforts to treat these symptoms are warranted.

## **5 Step Evaluation of Dementia Patients With Psychosis and/or Agitation/Aggression:**

### **1. How Dangerous is the situation?**

- a. If the patient or others are at significant risk and the patient does not respond quickly to behavioral strategies (such as verbal redirection/reassurance, stimulus reduction, or change of environment), consider acute pharmacotherapy. For instance, offer the patient an oral antipsychotic (possibly dissolvable tablets) and then if necessary consider intramuscular olanzapine, aripiprazole, haloperidol, or lorazepam.
- b. For less acute situations, more thoroughly investigate symptom etiology and obtain informed consent before treatment.

### **2. Establish a clear diagnosis / etiology for the symptoms**

- a. Rule out causes of delirium (such as urinary tract infection, subdural hematoma, pneumonia) through appropriate physical examination and diagnostic studies.
- b. Rule out iatrogenic causes such as recent medication changes.
- c. Rule out physical discomfort from arthritis pain, unrecognized fracture, constipation, and other causes.
- d. Assess for potentially modifiable antecedents to symptom flares, such as seeing a certain person, increased noise, or social isolation.
- e. Explore other common causes of behavioral disturbances, including depression, anxiety and insomnia.

### **3. Establish symptom severity and frequency, including:**

- a. Impact on patient quality of life,
- b. Impact on caregiver quality of life,
- c. Instances in which the safety of the patient or others has been jeopardized,
- d. Clear descriptions of prototypical examples of symptoms.

### **4. Explore past treatments/caregiver strategies used to address the symptoms and their success and/or problematic outcomes.**

### **5. Discuss with the patient/decision-maker what is and is not known about possible risks and benefits of pharmacologic and nonpharmacologic treatments for psychosis and agitation/aggression in dementia.**

No evidence-based treatment exists for psychosis or agitation/aggression in dementia. Atypical antipsychotics carry a “black box” warning for increased risk of death and cerebrovascular events in dementia; typical antipsychotics appear no safer. If you choose atypical antipsychotics, use them judiciously as part of a shared decision with the

patient's proxy decision-maker. Consider gradual withdrawal after three to six months and monitor for symptom recurrence.

Previously, in April 2005, the FDA informed healthcare professionals and the public about the increased risk of mortality in elderly patients receiving atypical antipsychotic drugs to treat dementia-related behavioral psychosis. At that time, the analysis of elderly patients with dementia-related behavioral disorders revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g. pneumonia) in nature. Based on this analysis, FDA requested that the manufacturers of atypical antipsychotic drugs include information about this risk in a *Boxed Warning* and the *Warnings* section of the drugs prescribing information.

**Note:** The FDA has determined that the overall weight of evidence indicates that the conventional antipsychotics share the increased risk of death in elderly patients with dementia-related psychosis that has been observed for the atypical antipsychotics. The prescribing information for all antipsychotics will now include the same information about this risk in a Boxed Warning and the Warnings section.

**FDA Alert [6/16/2008]:** The FDA is notifying healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.

Antipsychotics are not FDA approved for the treatment of dementia-related psychosis.

#### Consideration for Healthcare Professionals

- Elderly patients with dementia-related psychosis treated with conventional or atypical antipsychotic are at an increased risk of death.
- Antipsychotic drugs are not approved for the treatment of dementia-related psychosis. Furthermore, there is no approved drug for the treatment of dementia-related psychosis. Healthcare professionals should consider other management options.
- Physicians who prescribe antipsychotics to elderly patients with dementia-related psychosis should discuss this risk of increased mortality with their patients, patients' families, and caregivers.

**APPROVAL:**

  
\_\_\_\_\_  
SPA Medical Director

  
\_\_\_\_\_  
Behavioral Health Medical Director

12-18-08  
\_\_\_\_\_  
Date

12-16-08  
\_\_\_\_\_  
Date

---

**Approval / Revision Summary:**

SIP AMD's

SMG Division Chiefs

SMF QM Committee

SPA Steering Committee

Date: November 24, 2008

Date: November 24, 2008

Date: November 24, 2008

FYI: Only