Management of the behavioral and psychological symptoms of dementia

Review of current data and best practices for health care providers

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Management of the behavioral and psychological symptoms of dementia

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These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient’s clinical condition.
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INTRODUCTION

Dementia is characterized by cognitive impairment and memory loss but some of the behavioral and psychological symptoms of dementia (BPSD), specifically agitation, aggression, and psychosis, can be even more troubling or disabling for patients, and can significantly burden family members and caregivers. Managing BPSD is often frustrating for clinicians and family members because available treatment options remain sub-optimal. Although antipsychotic medications are frequently used as part of the larger pharmacologic armamentarium for treating patients with BPSD, this use is controversial because of the documented risks of morbidity and mortality with these drugs coupled with relatively weak evidence for their efficacy in older adults with dementia. In contrast, appropriately-used non-pharmacologic management strategies and interventions pose far fewer risks, can improve the health and well-being of patients with BPSD, and may ease the burden on family members and caregivers. The judicious use of selected pharmacologic agents for the management of specific and well-defined behavioral or psychological symptoms may provide modest benefits. Psychoactive medications, however, should be used with great caution to minimize the harmful adverse events these agents can cause in fragile older patients with dementia.

This monograph summarizes the current medical literature relevant to BPSD and offers pragmatic strategies for managing both non-emergent and emergent BPSD to help clinicians safely and effectively address symptoms and improve patients’ quality of life.
DEMENTIA

DEFINITION

Dementia describes a range of disease states characterized by a progressive, irreversible impairment in cerebral functioning.* Dementia may involve memory loss, loss of social and occupational functioning, impaired executive function, speech deficits, personality changes, and behavioral and psychological disturbances. Although dementia is more common in advanced age, it is not a normal part of aging. Dementia poses major physical and emotional challenges for patients, families, and other caregivers. With the aging of the population, the problem also places a heavy burden on health care systems and society at large.¹,²

CLINICAL FEATURES OF THE TYPES OF DEMENTIA

Dementia varies in both severity and form. People with mild dementia have problems with memory, language, or other mental functions that are severe enough to be noticeable to other people and be documented on tests. People with severe dementia must depend completely on others for basic activities of daily living.¹ Dementia follows a deteriorating course, with a median life expectancy after diagnosis of 5 to 6 years. The cardinal features of the major types of dementia are summarized in Table 1.

* The term neurocognitive disorder (NCD) has replaced the term “dementia” in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, although the term “dementia” is retained as a descriptor for certain sub-types of major NCD. The key feature of NCDs is that the primary clinical deficit is in cognitive function that is acquired rather than developmental.
<table>
<thead>
<tr>
<th>Type of dementia</th>
<th>Prevalence*</th>
<th>Clinical features</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease (AD)</td>
<td>60–90% of dementia cases</td>
<td>Insidious symptom onset; initial forgetfulness progressing to profound memory loss with one or more of: aphasia, apraxia, agnosia, or impaired executive function.</td>
<td>Symptoms generally begin after age 60. May coexist with vascular dementia (mixed-picture dementia).</td>
</tr>
<tr>
<td>Vascular dementia (VD)</td>
<td>Population prevalence: 0.2% (age 65-70) to 16% (age 80 and older)</td>
<td>Stepwise rather than gradual deterioration; focal neurological deficits, emotional lability, impaired judgment, early neuropsychiatric symptoms and/or gait disorders</td>
<td>Sudden decline usually indicates a stroke. Progressive subcortical small vessel ischemia may cause slow progression.</td>
</tr>
<tr>
<td>Lewy body disease (LBD)</td>
<td>2% - 30% of dementia cases</td>
<td>Involves any 2 of the following: visual hallucinations, parkinsonism or repeated unexplained falls, and fluctuation in mental state in the absence of delirium.</td>
<td>Earlier age of onset than either AD or VD. Cognitive impairment affects both memory and ability to carry out complex tasks and can fluctuate within 1 day, so may be confused with delirium.</td>
</tr>
<tr>
<td>Parkinson’s disease dementia (PDD)</td>
<td>In people with PD, as many as 75% will develop PDD sometime in the course of their disease.</td>
<td>Diagnosis of PDD may be difficult as there is often overlap with AD, VD, and DLB. In PDD, parkinsonism is usually diagnosed years before dementia.</td>
<td>Older age and the severity of parkinsonism are risk factors for the development of PDD.</td>
</tr>
<tr>
<td>Frontotemporal dementia (FTD)</td>
<td>2-10 cases per 100,000 in general population</td>
<td>Personality changes, mood lability, and alterations in behavior (such as disinhibition and lack of insight). May be difficult to differentiate from bipolar disorder.</td>
<td>Cognitive deficits may be poorly detected by the Mini-Mental Status Examination (MMSE). Anger, apathy and withdrawal may make it difficult to differentiate from depression.</td>
</tr>
<tr>
<td>Traumatic Brain Injury (TBI)</td>
<td>1.7 million instances of TBI annually. ~2% of US population lives with TBI-associated disability.</td>
<td>Course of recovery from TBI is variable depending on specifics of injury and cofactors such as age, previous injury, and substance abuse.</td>
<td>Severity of the TBI itself may not correspond to severity of the resulting neurocognitive disability.</td>
</tr>
<tr>
<td>Substance/medication-induced</td>
<td>Unknown</td>
<td>Substance use disorders begin during adolescence and peak in 20s &amp; 30s.</td>
<td>Substantial or complete recovery of neurocognitive functions is common among those who achieve stable abstinence prior to age 50.</td>
</tr>
<tr>
<td>HIV related</td>
<td>33% - 50% of HIV-</td>
<td>Neurocognitive disorders</td>
<td>Rapid progression to</td>
</tr>
</tbody>
</table>
### Table of Neurocognitive Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Population Prevalence</th>
<th>Mean Age at Diagnosis</th>
<th>Psychiatric and Cognitive Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington’s disease</td>
<td>5.7 per 100,000 in North America, Europe, and Australia</td>
<td>40 years</td>
<td>Gradually progressive with median survival ~15 yrs after motor symptom diagnosis</td>
</tr>
<tr>
<td>Prion disease</td>
<td>Prevalence unknown, but very low</td>
<td>Prion disease may develop at any age in adults. Prodromal symptoms: fatigue, anxiety, problems with appetite or sleep; difficulties concentrating</td>
<td>Disease typically progresses very rapidly to major impairment over several months</td>
</tr>
</tbody>
</table>


* Prevalence figures do not sum to 100% because of the wide variability in prevalence estimates and the possibility that patients may experience more than one type of dementia simultaneously.

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**Epidemiology**

General prevalence estimates for dementia (major neurocognitive disorder) vary with age and range from approximately 1% - 2% of the population at age 65 to as high as 30% by age 85. Estimates of the prevalence of mild neurocognitive disorder among older adults vary widely due to the sensitivity of the estimates to the definition of the term “dementia,” but they range from 2% to 10% at age 65 and 5% to 25% by age 85.

Estimates for the prevalence of Alzheimer’s disease (AD), the most common form of dementia, suggest that between 2.4 million and 5.1 million Americans have AD, with the number of people with the condition doubling every 5 years. In addition to its enormous human toll, the growing number of people with AD and the costs associated with the disease also impose a heavy economic burden. The national direct and indirect costs of caring for people with AD are estimated to be more than $100 billion a year. If current trends continue, total federal Medicare spending to treat persons with AD will increase from $62 billion in 2000 to $189 billion in 2015.

**Etiology and Risk Factors**

Many conditions and diseases cause cognitive impairment and dementia. Genetic, environmental, and
lifestyle factors can also play an important role. Non-modifiable risk factors for dementia include:\textsuperscript{4,5}

- Advanced age
- Family history
- Female gender
- Low IQ
- Genetic predisposition

Potentially modifiable risk factors for cognitive impairment include:\textsuperscript{5}

- Medication adverse effects
- Depression
- Risk factors for vascular disease (hypertension, diabetes, dyslipidemia, smoking, obesity)
- Excessive alcohol consumption
- Diabetes
- Poor nutrition
- Dehydration
- Thyroid, kidney, or liver disorders

Many of these conditions can be treated and may be reversible, which underscores the need for a thorough diagnostic workup and initial assessment. Testing beyond the items listed above should be pursued if there are signs or symptoms suggesting a specific disorder. A full description of diagnostic criteria for the different types of dementia and methods for their assessment is beyond the scope of this monograph. See the \textit{DSM-5} for more information.

\textbf{MANAGEMENT OF COGNITIVE IMPAIRMENT}

Although no satisfactory treatment for dementia yet exists, appropriate use of available interventions can have a substantial positive effect on the well-being of patients. In some cases, this could mean the difference between the ability to continue living independently in the community and the need for institutional care. Although cognitive impairments are not strictly part of BPSD, they are inextricably related to these symptoms and some treatments for cognitive impairments may help improve behavioral or psychological symptoms of dementia, hence a brief review of management strategies for cognitive impairment is included here.
Non-pharmacologic interventions to improve, or slow deterioration of, cognitive function are at an early stage of development. There are few well-designed trials of cognitive interventions for dementia, and few systematic assessments of outcomes. Nonetheless, despite limited evidence for efficacy, cognitive interventions are increasingly used to help preserve autonomy and quality of life. For older adults with normal cognition, these interventions focus on training in cognitive skills to enhance current function, with the goal of delaying or preventing future cognitive decline. For people with dementia, the goals are to optimize and extend cognitive and functional skills for the longest possible period.

Three major types of psychological interventions focus on cognition:

- **Cognitive stimulation**: engagement with activities and materials involving some degree of cognitive processing, usually in a social context, with an emphasis on enjoyable activities.
- **Cognitive training**: individual or group training exercises geared to specific cognitive functions, which may include practice and repetition, and computer-assisted learning.
- **Cognitive rehabilitation**: working on personal goals, often using external cognitive aids and/or learning strategies.

Other approaches include: reminiscence work, characterized by prompting and discussion of remote memories, which may be individual or group based; validation therapy, a group-based approach which encourages communication at an emotional level in a safe, facilitative environment; and “snoezelen” – stimulation of a number of senses using aromas, hand massage and other tactile stimulation, visual light displays, and atmospheric music and sounds.

Some evidence supports the use of cognitive stimulation for people with mild to moderate dementia. Improvements in quality of life have been demonstrated, in addition to modest improvements in cognitive function, and such interventions are likely to be cost effective. One study evaluated the effect of 6 months of cognitive stimulation in addition to donepezil (Aricept) compared to donepezil alone in patients with mild to moderate AD. All participants had been treated with donepezil for at least 3 months. There was a small, statistically significant benefit of combined therapy compared to donepezil alone, with a net difference between the two groups of 2.9 points on the Alzheimer’s Disease Assessment Scale-cognitive (ADAS –Cog) ($P = 0.01$). Whether this difference is actually detectable or has any meaningful clinical impact is debatable. No randomized studies have directly compared cognitive stimulation with medications...
such as cholinesterase inhibitors, so it is difficult to compare the magnitude of effects with these treatments.\textsuperscript{5} Another trial examined the effect of a cognitive stimulation program in patients with mild to moderate dementia.\textsuperscript{10} The program involved 14 sessions over 7 weeks using money, word games, and famous faces. None of the participants had been prescribed a cholinesterase inhibitor. There was a small, statistically significant benefit of the intervention compared to the control group (no intervention), with a net difference between the 2 groups of 1.14 points on the Mini Mental State Exam (MMSE) (\(P = 0.044\)) and 2.37 points on ADAS-Cog (\(P = 0.014\)).

Cognitive training has not been associated with benefits beyond the particular tasks trained. There is insufficient evidence to fully evaluate the effects of cognitive rehabilitation, reminiscence therapy, or validation therapy in relation to cognitive function in dementia.\textsuperscript{5} A Cochrane review found no evidence that snoezelen therapy had any significant effects on behavior, social interactions, or mood in people with dementia.\textsuperscript{11}

A review of non-pharmacological interventions for cognition found that techniques effective in improving memory in Alzheimer’s disease include “spaced-retrieval technique,” procedural motor memory training, and dual cognitive support.\textsuperscript{7} The goals of these interventions are to optimize and extend cognitive and functional skills for the longest possible period.

Spaced-retrieval technique involves incorporating progressive increases of intervals between the presentation of information to be remembered and the recall of that information. These intervals are filled with distracting conversation to prevent rehearsal. If an error occurs when retrieving the information, feedback is provided to the patient, and the interval between stimulus presentation and recall is decreased to the previous interval in which recall was correct. The approach has been used to teach a range of skills to patients with AD, including object naming, recalling of personal information, and learning face-name and object-location associations.\textsuperscript{12-15}

Another technique that has been effectively used in patients with AD is the activation of procedural motor memory, which is often preserved in mild and moderate AD. For example, patients with severely impaired recent memory are often able to achieve normal motor learning and skill retention in tasks such as learning to dance.\textsuperscript{7}

Dual cognitive support involves activating prior knowledge by linking the recall of new material to personal and salient life events. This type of support may be particularly effective when the information to be
recalled has an emotional significance to the patient.16

Bottom line
Non-pharmacologic strategies for managing cognitive impairment have not been shown to change long-term outcomes, but they are increasingly used to help preserve autonomy, improve quality of life and reduce caregiver burden. Independent of any other therapeutic approaches, referral to a social worker or psychologist can provide emotional support and psychosocial input. Additionally, this may facilitate work on important decisions regarding legal issues, financial planning, health care proxies, and advanced directives.

Limited evidence supports the use of non-pharmacologic approaches such as cognitive stimulation for people with mild to moderate dementia, with modest improvements possible in quality of life and cognitive function. Cognitive stimulation may add somewhat to the effects of treatment with a cholinesterase inhibitor in mild to moderate AD.

PHARMACOLOGIC MANAGEMENT
Two medication classes are available to manage the cognitive symptoms of dementia: cholinesterase inhibitors and memantine. These drugs do not alter the underlying pathology of dementia. Some, but not all, clinical trials suggest that these agents may delay the time to nursing home placement, but this remains controversial.17,18

Many of these drugs have been evaluated and approved based on changes in scores on cognition assessment tools, but these outcomes may not be meaningful, or even noticeable, in daily life. For example, a \( \geq 4 \) point reduction in the ADAS-Cog or a \( \geq 3 \) point increase on the MMSE are often accepted as significant improvements in cognition in clinical trials. As with similar changes of these magnitudes seen in studies of non-pharmacological treatments, it remains unclear if these make a detectable impact on a patient's functional status or quality of life. With pharmacologic interventions, of course, this question is of relatively greater importance since these interventions entail considerably more risks of side effects or adverse events than non-pharmacologic interventions. Give these considerations, assessment of global functioning with tools such as the Clinician’s Interview-Based Impression of Change (CIBIC) or Clinical Global Impression of Change (CGIC) is important. These are subjective tools used by a clinician who makes an assessment of whether a patient has changed in any important way. They assess concentration, orientation, memory,
language, behavior, initiative, and activities of daily living. The CIBIC-Plus allows for caregiver input, and the 7-point rating scale ranges from very much improved (1), to no change (4), to very much worse (7). By definition, a change in CIBIC or CGIC is likely to be clinically significant.

Because of patient and caregiver expectations and the placebo effect, it is difficult to objectively assess the effectiveness of drugs like the cholinesterase inhibitors and memantine in routine practice, and some patients/caregivers may perceive a benefit from these agents even in the face of progressive deterioration in cognitive function. For this reason, in the absence of randomized controls, it is challenging to make judgments regarding the efficacy of these agents in an individual patient. If it occurs, improvement should be seen within 3 months of beginning treatment. Long-term improvements, however, are rare. Many patients will be back to or below baseline 6-12 months later, and all will likely be below baseline 18-24 months after treatment initiation.

Before starting pharmacologic therapy for cognitive impairment in dementia:

- Consider and treat potentially reversible causes of impaired cognition, such as depression, delirium, hypothyroidism, B-group vitamin deficiencies, dehydration, hyponatremia, sleep apnea, and normal pressure hydrocephalus.
- Review the patient’s medication profile and minimize exposure to drugs that can impair cognition, e.g., alcohol, benzodiazepines, antihistamines, tricyclic antidepressants, some antipsychotics, indomethacin, opiates, corticosteroids, antihistamines, and anticholinergics (including amitriptyline, doxepin, imipramine and oxybutynin) which can impair cognition and functional performance from effects such as sedation, agitation, confusion, and delirium.19,20

Mechanisms of action

The cholinesterase inhibitors donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon) increase activity of the neurotransmitter acetylcholine in the central nervous system. Most randomized controlled trials (RCTs) of these drugs in patients with dementia have typically lasted 12–24 weeks, with only a few trials of longer duration. Many have involved community-dwelling patients with mild to moderate AD.21,22 A small number of trials have involved patients with more severe forms of dementia.22,23

Memantine (Namenda) is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. Most trials with memantine have been for 6 months or less, and there are no head-to-head trials comparing memantine with cholinesterase inhibitors.
Duration of therapy
No evidence exists that any of the possible benefits of cholinesterase inhibitors or memantine therapy increase with duration of therapy. A number of open-label extension studies and observational studies of the effects of cholinesterase inhibitors beyond the 12-24 weeks typical of RCTs suggest that initial response may be maintained for 6-12 months, possibly up to 18 months. After this time, the beneficial effect on cognition declines, with cognition scores falling below baseline.22

In light of the weak evidence base, clinical judgment combined with caregiver and family preferences must be used to determine how long patients should be treated with these agents.22 With both cholinesterase inhibitors and memantine, it would be reasonable to discontinue the drug after 6 months if there is no improvement.

Safety
Medications with anticholinergic activity may produce interactions with cholinesterase inhibitors that can impair cognition and functional performance from effects such as sedation, agitation, confusion, and delirium. Such drugs include antihistamines, tricyclic antidepressants, antipsychotics, and drugs such as oxybutynin that are used to treat urinary incontinence. These medications may reduce or negate any beneficial effect on cognition by cholinesterase inhibitors.

The most common adverse effects of cholinesterase inhibitors are anorexia, nausea, vomiting, and diarrhea. These drugs have also been associated with dizziness, hypertension, syncope, bradycardia, QT interval prolongation, arrhythmia, angina pectoris and heart block. Meta-analyses suggest that the mean frequency of dizziness with cholinesterase inhibitors is 10% (8% with donepezil, 10% with galantamine and 22% with oral rivastigmine). Dizziness may be a clinical manifestation of changes in blood pressure and heart rhythm, and may result in syncope and falls. In studies, 29% of patients stopped therapy due to adverse effects. Donepezil may cause fewer adverse effects than oral rivastigmine.

Doses of cholinesterase inhibitors should be slowly titrated upwards on an individual basis to minimize adverse effects. Transdermal administration of rivastigmine appears to improve GI tolerability compared to oral rivastigmine.

Memantine has been well-tolerated in clinical trials, with most finding the overall incidence of adverse
effects, and dropout rates due to adverse effects, to be similar to that of placebo. Common adverse effects are hypertension, confusion, dizziness, drowsiness, headache, hallucinations, constipation, dyspnea, vomiting, cough, and fatigue. Serious adverse effects include Stevens-Johnson syndrome and seizures.

Dosing

No additional benefit has been shown with donepezil 10 mg/day compared to 5 mg/day. Similarly, no significant difference in efficacy has been demonstrated with 16 mg/day of galantamine compared to higher doses. However, significant improvements in cognition and global function have been found with oral rivastigmine across the entire dose range from 6 to 12 mg daily (in two divided doses). Dosages of memantine above 20 mg/day have not been studied. Table 2 shows the recommended dosing of the cholinesterase inhibitors and memantine.

Table 2. Dosing of cholinesterase inhibitors and memantine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (Aricept)</td>
<td>5 mg once daily</td>
<td>Increase to 10 mg once daily after 4-6 weeks according to response</td>
</tr>
<tr>
<td>Galantamine (Razadyne)</td>
<td>4 mg orally twice daily</td>
<td>Increase by 8 mg/day (given in 2 divided doses) every 4 weeks according to response, maximum 24 mg/day</td>
</tr>
<tr>
<td></td>
<td>8 mg orally once daily</td>
<td>Increase by 8 mg/day every 4 weeks, maximum 24 mg/day</td>
</tr>
<tr>
<td>Rivastigmine (Exelon) - oral</td>
<td>1.5 mg orally twice daily</td>
<td>Increase by 3 mg/day (given in 2 divided doses) every 2 weeks according to response, maximum 12 mg/day</td>
</tr>
<tr>
<td>Rivastigmine (Exelon) - transdermal</td>
<td>4.6 mg/24 hour patch once daily</td>
<td>Increase to 9.5 mg/24 hour patch once daily after 4 weeks according to response; starting dose varies if switching from oral to transdermal therapy</td>
</tr>
<tr>
<td>Memantine (Namenda)</td>
<td>5 mg once daily</td>
<td>Increase by 5 mg/day every week to a target dose of 10 mg twice daily; give bid if dose &gt; 5 mg per day</td>
</tr>
</tbody>
</table>
Bottom line

Some patients with dementia show modest improvement or stabilization in cognition and global assessment of change with cholinesterase inhibitors or memantine. Although these improvements have been statistically significant compared to placebo, their clinical significance is questionable. Most evidence of efficacy is in patients with AD or vascular dementia, with limited data for other forms of dementia. It is not possible to predict responders to these agents, and all agents are generally equivalent in efficacy. Given the significant potential for adverse effects, even with lower doses of cholinesterase inhibitors and memantine, these agents should be used cautiously and continued only when assessment shows a meaningful improvement in cognitive symptoms.
BPSD BASICS†

DEFINITION AND DISTINCTIONS

BPSD represents a diverse constellation of symptoms\textsuperscript{34,35} including calling out, screaming, verbal and physical aggression, agitation, apathy, hostility, sexual disinhibition, defiance, wandering, intrusiveness, repetitive behavior and/or vocalizations, hoarding, nocturnal restlessness, psychosis (hallucinations or delusions), emotional lability, and paranoid behaviors.\textsuperscript{36,37}

This entire constellation of diverse symptoms is often used as a single primary outcome measure in clinical trials. As a result, the efficacy of therapies for specific symptoms can be difficult to determine.\textsuperscript{38} BPSD can range from the merely annoying to those that endanger the patient and/or others. Clinically, the key symptoms are aggression, agitation, psychosis, and mood disorders.\textsuperscript{34,38}

Management of BPSD should be based on the characteristics and severity of the symptoms, and should be individualized to meet the needs of the patient. To this end, it is critically important to differentiate between two broad classes of BPSD: emergent and non-emergent. People with emergent BPSD are in severe distress, pose an imminent danger to themselves or caregivers, or have severely disruptive or dangerous behavioral disturbances. People with non-emergent BPSD do not have symptoms that rise to this level of severity at the time of evaluation but may have had symptoms at that level in the past. Their baseline behavior may or may not be bothersome to themselves or others, but their symptoms may be inconvenient, may disrupt their functioning in daily life, or otherwise may erode quality of life. Non-emergent BPSD calls for a different clinical and behavioral approach using a different range of therapeutic options (or options tried in a different order).

Admittedly, the line between emergent and non-emergent BPSD is not always clear. If the patient is calm when seen by the prescribing clinician but was assaultive ten minutes ago and had been exhibiting these behaviors very often over the previous day, the treatment might follow the guidelines for an emergent case. However, if the patient had an outburst days ago and has been in control since then, the protocol for non-emergent BPSD may be appropriate. This distinction is important, though it has seldom been recognized in published guidelines on the care of people with dementia. This monograph does so with the aim of clarifying and improving clinical strategies and overall quality of care. (The authors thank Rajesh Tampe, M.D. for suggesting this approach.)

\textsuperscript{†} The terms “neuropsychiatric symptoms of dementia,” or “behavioral disturbance in dementia” are sometimes used interchangeably with BPSD.
PREVALENCE

BPSD symptoms are 4 times more common in patients with dementia than older adults without dementia.38 The prevalence of behavioral symptoms is greater in nursing homes than in community settings.35 Up to 90% of patients with dementia have such symptoms at some stage during their illness.34,35,37,39 The prevalence of BPSD in community-dwelling patients with dementia is estimated at 60–88%.40,41 Apathy, depression, and agitation/aggression are the most common features, followed (in descending order) by sleep disturbance, anxiety, delusions, and hallucinations.34,42,43

NATURAL HISTORY

BPSD symptoms usually fluctuate over the course of dementia.34,37,44,45 A study of patients with mild AD found that wandering and purposeless/inappropriate activities persisted or increased in severity over 2 years in about 85% of patients who had these symptoms at baseline, while paranoid ideation persisted in approximately 66% of patients.43 Hallucinations and depressive symptoms were the least persistent symptoms: less than half of the patients with depressive symptoms still had the symptoms one year later. Depressive symptoms often occur in the early stages of dementia. As dementia progresses, other behavioral and psychological symptoms may predominate.

BURDEN

Behavioral symptoms, especially paranoia and aggression, often contribute more to caregiver burden than cognitive impairment, and are frequently responsible for placement in nursing homes.34,35,38,46 Other complications associated with BPSD, such as incontinence, can further diminish quality of life and increase the likelihood of nursing home placement.47 Patients with BPSD also have a poorer overall prognosis, accelerated rate of cognitive decline, greater impairment in activities of daily living, and diminished quality of life, compared with patients with cognitive impairment alone.34

BPSD CLUSTERS

Adverse symptoms tend to occur in clusters, as outlined in Table 3.
Table 3. BPSD clusters

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Sadness, tearfulness, hopelessness, low self esteem, anxiety, guilt</td>
</tr>
<tr>
<td>Apathy</td>
<td>Withdrawal, anhedonia</td>
</tr>
<tr>
<td>Aggression</td>
<td>Aggressive resistance, physical or verbal aggression (often accompanies delusions)</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>Aimless walking, pacing, shadowing, restlessness, repetitive actions, dressing/undressing, sleep disturbance</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Delusions: that others are stealing, misidentification (patient no longer recognizes home or spouse/family), delusions of abandonment and sexual infidelity. Hallucinations: less common than delusions in patients with AD. Visual hallucinations are more common than other forms of hallucinations and are particularly prevalent in Lewy body dementia. Hallucinations are not necessarily disturbing and may not need treatment if the patient has some degree of insight.</td>
</tr>
</tbody>
</table>

**BOTTOM LINE**

BPSD represent a diverse constellation of symptoms, with aggression, agitation, psychosis, and mood disorders being most important clinically. BPSD frequently accelerate cognitive decline, impair activities of daily living, diminish quality of life, and increase the likelihood of patient placement in nursing homes. It can be helpful to differentiate between emergent and non-emergent BPSD. People with emergent BPSD are in severe distress, pose an imminent danger to themselves or caregivers, or have severely disruptive or dangerous behavioral disturbances. People with non-emergent BPSD do not have symptoms that rise to this level of severity at the time of evaluation but may have had symptoms at that level in the past.
MANAGEMENT OF NON-EMERGENT BPSD

Figure 1. Management algorithm

Consider the “ABC”

Antecedents: What are the triggers for the behavior?
- Treat any conditions that may contribute to BPSD (e.g., pain, depression, delirium)
- Adjust medications that may contribute to BPSD (e.g., anticholinergics, psychotropics)

Behavior: What is the behavior being targeted?

Consequences: What are the consequences of the behavior for the patient and others?
- If the behavior is not harmful, additional management beyond monitoring typically is not necessary

Nonpharmacologic BPSD management

- Match interventions to the patient’s specific needs and capabilities
- Can pursue multiple management strategies simultaneously

For symptoms of agitation* and aggression,* consider:
- Music therapy
- Massage/touch therapy
- Exercise therapy
- Aromatherapy
- Snoezelen multisensory stimulation therapy
- Caregiver education in managing behavioral problems
- Light therapy

*Limited evidence

Pharmacologic BPSD management

- **DO NOT** use benzodiazepines or related medications (e.g., zolpidem)
- **AVOID** polypharmacy
  - Complete therapeutic trials with a single medication
  - If ineffective then discontinue and initiate an alternative medication
- Inform caretakers that risks of pharmacotherapy (e.g., death with antipsychotics) often outweigh benefits

For symptoms of agitation, aggression, and psychosis, consider:
- Cholinesterase inhibitors and memantine (may provide a small benefit for BPSD – see text)
- SSRI
  - Sertraline
  - Escitalopram > citalopram
  - Fluvoxamine
- Trazodone
- Atypical antipsychotic
  - Risperidone
  - Aripiprazole
- Gabapentin (limited evidence)
- Carbamazepine (limited evidence)
- Prazosin (very limited evidence)

- Monitor for drug-drug interactions (particularly with paroxetine, atypical antipsychotics, and carbamazepine)
- Monitor for adverse events (e.g., cardiac effects with atypical antipsychotics, and hyponatremia and liver toxicity with carbamazepine)
- Reassess the patient 3 to 6 months after treatment success
  - Consider tapering and discontinuing the medication

[538x45]19
CONSIDER THE "ABCs"

When a patient presents with non-emergent BPSD, the first course of action should be to perform a comprehensive assessment of the symptom(s), considering the "ABCs":

- **Antecedents:** What are the triggers for the behavior(s)?
- **Behavior:** Which behavior, or behaviors, are targets for intervention?
- **Consequences:** What are the consequences of the behavior(s) for the patient and others?

Family, caregivers, and nurses are often in the best position to answer these questions. Understanding these factors may reveal simple and effective interventions. Complex, expensive management strategies and interventions may not be required.

A patient’s medical condition or a medication the patient is taking may be the primary trigger for BPSD or may contribute to BPSD. Thus, the assessment of a new-onset behavioral symptom in an older patient with cognitive impairment must start with an assessment of reversible causes by performing a patient history, a physical examination, and basic laboratory tests (including CBC, glucose, electrolytes, and BUN/creatinine, as well as more specific tests suggested by the initial evaluation). Although identifying a trigger through patient history and/or physical examination can be challenging if the patient's cognitive impairment is severe, clinicians should persist and include family and caregivers in the process, if possible. Treatment of a reversible medical problem can be much more effective and safe than deploying either non-pharmacologic or pharmacologic interventions. Reversible causes of new-onset behavioral disorders in the elderly include:

- Acute infection (e.g., urinary tract infection, sepsis)
- Delirium (an acute state of confusion which itself can be the result of a new-onset medical condition)
- Depression
- Dehydration
- Hypoxia (e.g., congestive heart failure, pneumonia, anemia due to gastrointestinal hemorrhage)
- Pain (e.g., vertebral or hip fracture, or acute abdominal pain)
- Medication side effect
- Emotional stress
- Reactions to changes in care, caregivers, or caregiver behaviors
- Boredom

Optimizing the management of the cognitive symptoms of dementia may minimize or eliminate BPSD. For
example, using adequate anticoagulation may prevent transient ischemic attacks/microstrokes in cases of vascular dementia, as evidence suggests an association between transient ischemic attacks and cognitive impairment. 48

As noted earlier, many medications routinely used by older adults can cause or worsen behavioral and psychological problems. For example, anticholinergic agents increase the risk of visual hallucinations, agitation, irritability, delirium, and aggressiveness. Psychotropics, such as benzodiazepines, can impair cognition, be disinhibiting, and may contribute to falls. Adverse drug effects are one of the most common reversible conditions in geriatric medicine. They present an opportunity to effect a cure by stopping the offending drug or lowering the dose. This has led to the recommendation that “any new symptom in an older patient should be considered a possible drug side effect until proven otherwise.” 49

NON-PHARMACOLOGIC MANAGEMENT OF NON-EMERGENT BPSD

Evidence suggests that non-pharmacologic approaches to non-emergent BPSD can produce equivalent outcomes, in a much shorter time and at less overall risk and cost, than pharmacologic therapies. 3,50 A meta-analysis of community-based non-pharmacologic interventions for BPSD found significant reductions in symptoms as well as improvements in caregiver’s reactions to these symptoms. 50 Behaviors more likely to respond to such interventions are: agitation, aggression, disruption, shadowing, depression, and repetitive behaviors. Non-pharmacologic interventions should always be matched to the specific needs and capabilities of the patient, and they can be used concurrently with any pharmacologic therapies that might be employed. 51,52,53

ENVIRONMENTAL MANAGEMENT STRATEGIES

Behavioral and psychological symptoms often arise in response to a wide range of factors that can make life uncomfortable, frightening, worrisome, irritating, or boring for people with dementia. Paying close attention to such environmental factors, and eliminating or correcting them, should be the first priority for caregivers. 36 This may require patience, diligence, and a willingness to see the world through the eyes and other senses of the person whose behaviors are challenging. Because sensory deficits are common in older adults, and because vision and hearing deficits, in particular, can increase fearfulness, anxiety, and agitation, any patient displaying non-emergent BPSD should be assessed for these deficits, and, if any are found, they should be corrected promptly with glasses, improved lighting, magnifying devices, hearing aids, or other techniques.
Other environmental factors that can increase agitation include: temperature (too hot or too cold), noise (in or outside the room or dwelling unit), lighting (too much, too little, or quality), unfamiliarity (new people, new furniture, new surroundings), disrupted routines, needing assistance but not knowing how to ask, being uncomfortable from sitting or lying on one position for too long, or inability to communicate easily because of language difficulties.

The evidence supporting non-pharmacological interventions for non-emergent BPSD varies. Table 4 summarizes selected interventions and the evidence that supports them (as of 2012).

<table>
<thead>
<tr>
<th>Improving functional performance</th>
<th>Supporting evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior modification, scheduled toileting, prompted voiding to reduce urinary incontinence</td>
<td>Strong</td>
</tr>
<tr>
<td>Graded assistance, practice, and positive reinforcement to increase functional independence</td>
<td>Good</td>
</tr>
<tr>
<td>Low lighting levels, music and simulated nature sounds to improve eating</td>
<td>Weak</td>
</tr>
<tr>
<td>Intensive multi-modality group training to improve activities of daily living</td>
<td>Weak</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improving behavior</th>
<th>Supporting evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Music, particularly during meals and bathing</td>
<td>Good</td>
</tr>
<tr>
<td>Walking or other forms of light exercise</td>
<td>Good</td>
</tr>
<tr>
<td>Simulated presence therapy, such as use of videotapes of family</td>
<td>Weak</td>
</tr>
<tr>
<td>Massage</td>
<td>Weak</td>
</tr>
<tr>
<td>Comprehensive psychosocial care programs</td>
<td>Weak</td>
</tr>
<tr>
<td>Pet therapy</td>
<td>Weak</td>
</tr>
<tr>
<td>Commands tailored to the patient’s comprehension level</td>
<td>Weak</td>
</tr>
<tr>
<td>Bright light, white noise</td>
<td>Weak</td>
</tr>
<tr>
<td>Cognitive remediation</td>
<td>Weak</td>
</tr>
</tbody>
</table>

The potential effectiveness of non-pharmacologic interventions was demonstrated in a 2012 randomized,
placebo-controlled clinical trial. Agitated nursing home residents with advanced dementia from 9 nursing homes in 5 locations in Maryland were randomized into an intervention group (n = 89) or a placebo group (n = 36). A set of individualized non-pharmacologic interventions, Treatment Routes for Exploring Agitation (TREA), was used with the intervention group for 2 weeks, and observations of agitation and affect were recorded. Relative to the control group, patients receiving the TREA interventions (e.g., social contact, reading, music, physical activity) showed significant declines in physical (P < .001), and verbal agitation (P = .004) and significant increases in pleasure (P < .001) and interest (P < .05). The authors conclude that putting these kinds of non-pharmacologic interventions into practice is “sorely needed” although they note that this would require structural changes such as dedicating staff time to observing each agitated resident, determining unmet needs, obtaining appropriate intervention materials, conducting the individualized non-pharmacologic interventions, and evaluating results to determine the efficacy of the specific non-pharmacologic interventions used.

MANAGEMENT OF PSYCHOLOGICAL FACTORS

Patients with BPSD may benefit from psychological interventions such as individual, family, or group psychotherapy, depending on their level of cognitive functioning. Such interventions may help patients understand or express their feelings, correct or address cognitive errors or maladaptive thinking patterns, and develop practical steps for changing behaviors or responses to different situations.

MANAGEMENT OF PHYSIOLOGICAL FACTORS

As noted earlier, a number of common, though often-overlooked, physiological factors may play a primary or contributing role to BPSD. These include:

- Urinary tract infections (sub-clinical infections are common and can cause or exacerbate behavior problems)
- Pain
- Constipation
- Nocturia
- Hunger or thirst
- Dehydration
- Hyponatremia
- Hypothyroidism
- Hypercalcemia
• B12 or folic acid deficiency

Dietary and eating-related issues should be carefully assessed. An inability to chew properly or swallow easily can increase agitation, hence a patient’s dental integrity, use of false teeth or other orthodontia, and swallowing ability should be considered. If a patient’s appetite or cycle of hunger/satiety is not synchronized with the timing of meals provided by an institution, consider options to individualize the availability of food and/or food choice. Difficulty preparing or eating meals, confusion about mealtimes, apathy, agitation, and paranoid ideation about food and fluids may all contribute to weight loss, which is common in patients with dementia. Avoidance of alcohol and caffeine can promote good sleep hygiene and may help stabilize mood.56

PHARMACOLOGIC MANAGEMENT OF BPSD: GENERAL PRINCIPLES

The evidence base for drug treatment of BPSD (both emergent and non-emergent) is generally weak but with some recent encouraging lines of development.56,57,58 No medications are FDA-approved for these indications. Pharmacological management strategies for BPSD have evolved haphazardly over the years and in anecdotal ways involving off-label uses of many classes of medications including antipsychotics, anticonvulsants, antidepressants, anxiolytics, cholinesterase inhibitors, and NMDA modulators. Although pharmacologic interventions may be necessary in some circumstances, they should only be considered if the patient is not responding to appropriate, sustained, patient-tailored non-pharmacologic interventions.

For patients with non-emergent BPSD, two classes of medications should be avoided whenever possible: benzodiazepines and antipsychotics. Long-term use of benzodiazepines and similar-acting medications, (e.g., zolpidem), should be avoided in the treatment of both emergent and non-emergent BPSD because these agents have risks that outweigh their benefits in patients over the age of 60.59 They may cause or exacerbate a range of problems including:53,59,60

• Cognitive impairment
• Rebound insomnia (i.e., if taken as needed, patients sleep worse on the nights that they omit it than if they had taken placebo)61
• Risk of falls
• Risk for accidents if driving
• Paradoxical agitation
• Physical dependence with regular use62
• Aspiration and its consequences
Benzodiazepine use may also be an independent risk factor for new-onset dementia. A 2012 prospective population based study found that during a 15-year follow-up period, new use of benzodiazepines was associated with an increased risk of dementia (multivariable adjusted hazard ratio 1.60, 95% CI = 1.08 to 2.38). Results of a complementary nested case-control study showed that ever use of benzodiazepines was associated with an approximately 50% increase in the risk of dementia. These results suggest that, in addition to being contraindicated in patients with dementia, the indiscriminate and widespread use of benzodiazepines in the general population should be avoided.

Antipsychotic medications (APMs), while of potential utility in patients with emergent BPSD, should be avoided in patients with non-emergent BPSD until other reasonable medications have been tried because of the minimal efficacy of these agents for the symptoms typical of non-emergent BPSD and their relatively high risk of side effects and adverse events, including possible death. In June 2008, the US Food and Drug Administration (FDA) determined that both conventional and atypical antipsychotics increase the risk of death in elderly patients, and reiterated that antipsychotics are not indicated for the treatment of dementia-related psychosis. All antipsychotic drugs carry the same information about this risk in a Black Box Warning and in the Warnings section of the full prescribing information.

APMs may be more appropriate for patients with a history of emergent BPSD for whom APMs were effective in the past and who are presenting with non-emergent BPSD. (The use of antipsychotic medications for emergent BPSD is covered later in this monograph.)

Given that many older adults are on multiple medications and the inherent difficulty of determining efficacy if multiple medications are used to address a given condition, any therapeutic trial of a medication for non-emergent BPSD should be completed with a single medication. If the single medication is deemed ineffective after an adequate trial, the medication should be discontinued and an alternative medication should be initiated. Partial but suboptimal responses should be carefully assessed to determine whether the partial effect was due to non-specific causes or other changes in clinical status, before assuming that the medication should be continued and another medication added for additional effect. Before any medication is administered, patients, family members, and/or caregivers should be informed of the possible risks of pharmacotherapy.

Psychotropic medications traditionally used for BPSD have been implicated in a variety of serious adverse
effects including falls, fractures, delirium, and over-sedation. Elderly patients are particularly vulnerable to injury from psychotropic medications because of increased frequency of use, slower metabolic clearance, increased CNS receptor sensitivity, and reduced physiologic reserve. Lower starting and target doses are often needed in older people to avoid adverse events. A reduced initial dose for elderly patients is endorsed by the FDA, which mandates that drug manufacturers state a recommended geriatric dose for all medications that have been evaluated in a significant number of patients older than 65 years. Unfortunately, drug trials often under-represent older patients--especially those who are over 80 or frail, so the database for such recommendations is frequently inadequate.

Initiation of any medication for non-emergent BPSD should be at the lowest possible dose, with slow titration upwards if needed to the lowest effective dose. Patients must be monitored closely for both adverse effects and drug-drug interactions. If a medication is demonstrated to be effective, the patient should be reassessed after 3-6 months, since BPSD symptoms are inherently unstable and subject to remission. No psychoactive medication should be continued indefinitely and attempts at drug withdrawal should be made regularly.56

PHARMACOLOGIC MANAGEMENT OF NON-EMERGENT BPSD

With the general caveats just reviewed, the following pharmacologic agents may be considered for patients with non-emergent BPSD, with use guided by the algorithm presented in Figure 1 on page X.

CHOLINESTERASE INHIBITORS AND MEMANTINE

Although some studies of cholinesterase inhibitors and memantine have found small, statistically significant beneficial effects on BPSD, as measured by the Neuropsychiatric Inventory (NPI) and other scales, the clinical significance of these changes is unclear. For example, a 2008 meta-analysis examined the efficacy of cholinesterase inhibitors in treating BPSD in patients with AD and found a statistically significant improvement on BPSD, but with a small effect size (-1.38 points on the NPI overall; -1.92 points in mild AD; -0.06 points in patients with severe AD).69 A 2007 meta-analysis of cholinesterase inhibitors in patients with mild to moderate vascular dementia found no behavioral or functional benefits except with 10 mg daily donepezil.70 A 2006 Cochrane systematic review found that treatment of mild, moderate, or severe Alzheimer’s disease with a cholinesterase inhibitor for 6 months produced a small, statistically significant improvement in the NPI (-2.44 points), but, again, the clinical relevance of these results is questionable.71 Rivastigmine may modestly improve behavioral and psychological symptoms (in particular visual
hallucinations) in patients with Dementia with Lewy Bodies.  

The situation for memantine is similar. A 2008 pooled analysis of 6 randomized controlled trials of patients with moderate to severe AD found small but statistically significant beneficial effects of memantine on the NPI in treatment and prevention of symptoms such as delusions, hallucinations, disinhibition, irritability, agitation, and aggression. A 2008 systematic review of memantine for BPSD found a statistically significant improvement in NPI scores with treatment, but the effect size was small (-1.99 points). A retrospective pooled analysis of randomized controlled trials found memantine use was associated with a higher percentage of patients having some improvement in agitation or aggression, compared to placebo (56% versus 44% improved at 12 weeks in treatment versus placebo group, respectively).

If the prescribing clinician plans to treat the patient’s cognitive symptoms with a cholinesterase inhibitor or memantine and the patient also has significant BPSD, it seems reasonable to allow some time to assess whether the agent selected can benefit both problems. If another medication is started at the same time to target the non-emergent BPSD symptoms, it will be difficult to know which medication was responsible for any subsequent benefits or side effects. Cognitive enhancers would not be the first-line choice for BPSD management except as above.

**Antidepressants**

Up to 40% of patients with dementia will have significant depressive symptoms at some stage, and some of the symptoms related to depression (e.g., irritability, sleep disturbances) overlap with those of BPSD. Alleviating depression in patients with dementia has been reported to lessen behavior disturbances, improve activities of daily living, and reduce caregiver distress. Even in dementia patients without depression, a growing evidence base finds antidepressants helpful for BPSD. Antidepressants, therefore, may be a reasonable choice for treating symptoms of non-emergent BPSD. Among the classes of antidepressants, the SSRIs have been the most widely studied. Compared to other medication treatments, they have relatively favorable risk and side effect profiles.

A 2011 Cochrane review of antidepressants for BPSD found modest evidence for efficacy and tolerability with certain agents. The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies, and sertraline, citalopram, and the serotonin antagonist and reuptake inhibitor (SARI) trazodone appeared to be tolerated reasonably well when compared to placebo or antipsychotics. However, in the same year, another review assessed 19 trials of antidepressants
(including eleven trials with SSRIs and three trials with trazodone) for the treatment of BPSD. Effectiveness was demonstrated in 11 of the 19 trials and these agents were well-tolerated in 14 of the trials.\textsuperscript{58} A 12-week randomized controlled trial in non-depressed patients with dementia showed that citalopram was as effective as the antipsychotic risperidone in decreasing psychosis and agitation, with a more desirable side effect profile.\textsuperscript{79} A Cochrane review of 2 of the small trials of trazodone found that this agent was as effective as the antipsychotic haloperidol in reducing agitation, with (surprisingly) no difference in adverse event rates.\textsuperscript{80} The most recent randomized, controlled trial involved a comparison of fluvoxamine (Luvox) and risperidone (N=60).\textsuperscript{81} The medications were equally effective but the side effects were less severe on the SSRI and there was one sudden death on risperidone at day 22, due probably to a myocardial infarction.

Prescribers may want to consider one or two antidepressant trials (e.g. an SSRI or trazodone) for non-emergent BPSD before proceeding to other medication options. Note, however, that citalopram has a recent (2011) package insert warning about QTc prolongation; the maximum dose was reduced to 40 mg (20 mg in the elderly). Escitalopram would be preferred given its lower effects on QTc.\textsuperscript{82}

**ANTIPSYCHOTICS**

Although the evidence shows that antipsychotics (APMs) have only limited efficacy in BPSD, they are prescribed in up to 15\% of nursing home patients and outpatients with dementia aged 65 and older, creating substantial safety concerns.\textsuperscript{83,84,56}

As noted earlier, none of the antipsychotics are approved in the U.S. for BPSD, despite at least 17 large randomized trials, most of them unpublished.\textsuperscript{58} Meta-analysis of these studies has indicated very limited efficacy and large potential for harm. Serious possible adverse effects associated with antipsychotics include: strokes, TIAs, seizures, extrapyramidal side effects, drowsiness, cognitive decline, confusion, increased risk of falls, parkinsonism, tardive dyskinesia, social withdrawal, QT prolongation, diabetes, postural hypotension, neuroleptic malignant syndrome, angioedema, and increased mortality.\textsuperscript{85} The evidence of these risks has primarily emerged from studies conducted in patients with non-emergent BPSD.

The risk for adverse cardiovascular events with APMs is elevated in the first 30 days and continues for up to 3 years thereafter.\textsuperscript{85} The use of both atypical and conventional antipsychotic drugs in patients with dementia is associated with a 60\% to 70\% increased relative risk of mortality, which is highest in the first
40 days of use and increases with higher doses.86 This heightened risk is reflected in the black box warning that is required for all antipsychotics.87 Expressed in terms of “Number Needed to Harm” calculations, the likelihood of benefit vs. fatal outcome from the use of atypical antipsychotic drugs for BPSD is small: for every 9-25 patients helped with these medications (who would not have improved on placebo), there would be one death.86 However, a recent report slightly mitigates the negative perspective from the previous studies regarding the safety of these agents. In a cohort of 957 patients with probable AD living in the community, treatment with an APM (n=241) was not associated with a greater risk of death.88 However, most studies finding an increased risk of mortality have been conducted in nursing home patients.89 In the 2009 DART-AD study, survival (compared to placebo) was found to gradually decline in patients on antipsychotics: 46% vs. 71% at 24 months and 30% vs. 59% at 36 months.90 There were insufficient numbers to determine if the risk differed among patients using different antipsychotics.

Thus, although antipsychotics may help control the acute symptoms of BPSD in certain patients, they must always be used carefully and with informed consent (from the patient, if possible, or from family members and other caregivers) regarding the possible benefits and risks.

Table 5: Starting and maximum doses of antipsychotics in elderly with dementia syndromes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>aripiprazole</td>
<td>5 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>olanzapine</td>
<td>1.25 mg-5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>quetiapine</td>
<td>12.5 mg-50 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>risperidone</td>
<td>0.25 mg-1 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>paliperidone</td>
<td>1.5 mg</td>
<td>3-6 mg</td>
</tr>
</tbody>
</table>

Conventional antipsychotics

Reviews and meta-analyses of clinical trials involving conventional antipsychotics (e.g., haloperidol [Haldol], thioridazine [Mellaril] and chlorpromazine [Thorazine]) in the management of BPSD found modest improvement in aggression over 3-8 weeks of treatment compared to placebo.53,67,91,92 There is no consistent evidence that any one conventional antipsychotic is more effective than another,91 and there are insufficient data to draw conclusions about the efficacy of conventional vs. atypical antipsychotics for BPSD.93

Discontinuation rates due to adverse effects were significantly higher with conventional antipsychotics than
with placebo, and the troublesome adverse effects associated with conventional antipsychotics (e.g., extrapyramidal side effects) limit the usefulness of these agents. Stroke risk also may be higher with conventional antipsychotics compared to the atypicals. Importantly, recent studies show that haloperidol use is associated with a 50-100% higher risk of death compared to other antipsychotics. As for chlorpromazine, this antipsychotic is no longer recommended for intramuscular treatment in emergencies with agitated, aggressive psychotic patients due to evidence of risks of severe hypotension.

Atypical antipsychotics

The evidence base for the effectiveness of atypical antipsychotics for BPSD is generally weak, but at least some degree of confidence in efficacy exists for aripiprazole (Abilify) and risperidone (Risperdal), whereas olanzapine (Zyprexa) and quetiapine (Seroquel) were not found effective in meta-analyses of their various published and unpublished trials. In England, risperidone is approved for the management of BPSD. None of the others are approved there and, as noted, none are approved in the U.S. In the CATIE-AD study, the results with all antipsychotics were minimal, but caregivers of treated patients rated their “burden” (rated by the “Burden Interview” and “NPI Caregiver Distress” scales) as lower than caregivers of patients on placebo (effect sizes were small).

Risperidone

The evidence for the efficacy of risperidone in patients with BPSD rests on studies showing small but statistically significant effect sizes on symptom rating scales. The clinical value of such results, however, is debatable. In patients who responded to treatment, improvement tended to occur within the first 2 to 4 weeks. Increased attention to the patient, non-pharmacologic interventions, and symptom fluctuation may have contributed to the improvements seen.

A 2006 Cochrane review found significant improvement in aggression and symptoms of psychosis in Alzheimer’s disease patients treated with risperidone (2 mg) compared with placebo. Risperidone treated patients, however, had a significantly higher incidence of serious adverse cerebrovascular events (including stroke), extra-pyramidal side effects, and other important adverse outcomes, which was reflected in the significant drop-out rate among risperidone-treated patients. One review found that risperidone caused more strokes than olanzapine, but a more recent study found no difference, and another review found lower association with all-cause risk of death with risperidone. Another advantage for risperidone over olanzapine is in the impact on cognition: olanzapine worsens it slightly, probably due to its anticholinergic effects, while risperidone improves it slightly.
In the CATIE-AD Effectiveness Trial, patients on risperidone showed greater improvement relative to patients on placebo on scores of hostile suspiciousness and psychosis. There were no significant differences between risperidone and placebo on cognition, functioning, care needs, or quality of life.

A double-blind comparison of olanzapine versus risperidone in the acute treatment of dementia-related behavioral disturbances in extended care facilities showed that both drugs produced significant reductions in CGI and NPI scores (p < .0001), and there was no significant difference between drugs. The mean daily doses were: olanzapine 6.65 mg/day; risperidone 1.47 mg/day. The positive drug effect was not accompanied by decreased mobility, and there was improvement on a quality-of-life measure. The chief adverse events were drowsiness and falls. At baseline, 42% (16/38) of subjects in both groups had extrapyramidal symptoms that increased slightly, but not significantly, by the end of the study.

Aripiprazole
In a meta-analysis, aripiprazole showed small, but statistically significant positive effects on symptom rating scales. In one study in a population of patients with AD, aripiprazole (10 mg/day) significantly reduced psychosis symptoms compared to placebo.

Olanzapine (Zyprexa)
As noted earlier, in a meta-analysis, no efficacy was observed for olanzapine using standard rating scales of BPSD. A 2006 Cochrane review, however, found a statistically significant improvement in aggression with olanzapine treatment compared to placebo. Olanzapine-treated patients, however, had a significantly higher incidence of serious adverse cerebrovascular events (including stroke), extra-pyramidal side effects and other important adverse outcomes.

In the CATIE-AD Effectiveness Trial, patients on olanzapine demonstrated no difference from placebo on the primary outcome measure of time to discontinuation of treatment for any reason. However, olanzapine showed greater improvement relative to placebo on the Neuropsychiatric Inventory total score, and the Brief Psychiatric Rating Scale (BPRS) hostile suspiciousness factor. There was worsening on the BPRS withdrawn depression factor and on functioning in activities of daily living. There were no significant differences between olanzapine and placebo on cognition, care needs, or quality of life.
Sub-population considerations

Patients with severe liver disease may be considered for the use of paliperidone (Invega), which is the active metabolite of risperidone and is primarily renally excreted. The starting dose would be 1.5 mg and typical dose 3-6 mg/day with a maximum dose of 3 mg/day for patients with severe renal impairment.

Patients with Parkinson’s disease dementia and dementia with Lewy bodies have an increased risk of extrapyramidal side effects and neuroleptic sensitivity reactions, hence antipsychotics, and particularly risperidone, should be avoided in these patients.91 Lewy body dementia patients may be sensitive to adverse effects from non-APM medications as well: uncontrolled reports suggest gabapentin is poorly tolerated.107 A case report indicates efficacy of low-dose clozapine for psychosis in DLB, and open trials indicate safety for treatment of psychosis in DLB and PDD with quetiapine.108 Randomized controlled trials indicate that quetiapine is less effective than clozapine against psychotic symptoms in both conditions, although comparatively safe.108 Cholinesterase inhibitors, especially rivastigmine, are a therapeutic alternative for treating both psychotic and cognitive symptoms in both conditions.108

GABAPENTIN

There have been 11 case reports and 5 uncontrolled case series employing the anticonvulsant gabapentin in BPSD.107,109 These uncontrolled data suggest relative safety with some significant potential effectiveness. Doses ranged from 200 mg to 3600 mg daily. In the most recent report of 7 consecutive cases treated with a maximum dose of 600 mg in two divided doses, there was impressive response and tolerability.109

CARBAMAZEPINE

The anticonvulsant carbamazepine (Carbatrol, Equetro, Tegretol, others) may be considered at a low dose and in a time-limited trial for dementia-related agitation/aggression if other interventions have been exhausted, with close monitoring for response, adverse effects, and drug interactions.53,110 One of two recent studies showed positive results.111

PRAZOSIN

Prazosin (Minipress, Vasoflex, others) is an alpha-1 receptor antagonist used primarily in the treatment of benign prostatic hypertrophy and (now, rarely) hypertension. The drug also antagonizes norepinephrine release in the central nervous system, which may be why it can reduce agitation and aggression in some patients with dementia. A small (N=22) placebo-controlled 8-week study of prazosin found that those in the
treatment group had significantly more improvement on two agitation rating scales, with no differences between the groups in blood pressure or adverse events (at a mean dose of 6 mg). Improvement in the Neuropsychiatric Inventory was large: -19 points versus -2 on placebo. This study needs replication with larger samples of patients, but prazosin may eventually represent a promising option for non-emergent BPSD. In another neuropsychiatric condition, posttraumatic stress disorder, prazosin has recently emerged as an unexpected but potentially valuable treatment with larger effect sizes than any other medication treatment yet studied.

MEDICATIONS WITH INSUFFICIENT EVIDENCE TO SUPPORT USE IN PATIENTS WITH BPSD (BOTH NON-EMERGENT AND EMERGENT)

Quetiapine (Seroquel, Xeroquel, Ketipinor)
In the CATIE-AD Effectiveness Trial, patients on quetiapine did not show significant improvements compared to placebo on most symptom outcome measures (Neuropsychiatric Inventory total score, the Clinical Global Impression of Changes, the Brief Psychiatric Rating Scale [BPRS] hostile suspiciousness factor, and the BPRS psychosis factor). The limited quetiapine impact on symptoms may have been due to the low dose of quetiapine prescribed (final dose mean 57 mg). Sedation, however, occurred in this group at rates comparable to the other drugs. In another study, quetiapine significantly improved agitation at a dose of 200 mg/day compared to placebo, but not at lower doses. This is, however, a fairly high dose for this drug in this indication. Of note, in 2011 the FDA required a new package insert warning for quetiapine regarding QTc prolongation, stipulating that it should not be combined with 12 listed drugs with known QTc problems (amiodarone, ciprofloxacin etc.).

The lack of adequate efficacy and the potential adverse effects of quetiapine make it undesirable for the treatment of most patients with emergent or non-emergent BPSD. It is possible, however, that it could have a role when it is desirable to use medication with low affinity for the dopamine receptor, such as in patients with Parkinson’s disease. Research is needed to test that hypothesis.

Valproic acid (Valproate)
A 2004 Cochrane review concluded that valproic acid cannot be recommended for management of agitation in dementia. A more recent trial of sodium valproate for BPSD also found it to be no more effective than placebo. Valproic acid also failed to attenuate agitation and clinical progression of Alzheimer’s disease in
a 2011 study and was associated with significant toxic effects. Finally, some evidence suggests that valproic acid can increase brain atrophy in Alzheimer’s disease patients.

**BOTTOM LINE**

First-line approaches for the management of non-emergent BPSD should focus on identifying any relevant environmental, psychological, or physiological factors that might be causing or contributing to symptoms. Non-pharmacologic management strategies should be exhausted before pharmacologic treatments are considered. Of the pharmacological agents commonly used, antidepressants such as escitalopram, sertraline, or trazodone appear to provide the most favorable risk-benefit profile for addressing non-emergent BPSD, with or without depression. One or two trials of these agents should be the first-line approach, though if the patient is going to receive a trial of an anticholinesterase inhibitor or memantine for cognitive impairment, wait to see if this will be helpful for the BPSD before starting another medication. After the antidepressants, it is reasonable to consider an antipsychotic: risperidone or aripiprazole are preferred. The evidence base supporting the use of gabapentin, carbamazepine, and prazosin is weak and the clinical significance of the effects reported in the literature are often questionable, though some recent reports suggest that some agents have significant potential in selected patients. Valproate, however, seems ineffective. Benzodiazepines should not be used for patients with new-onset non-emergent BPSD because the risks associated with these agents such as falls and cognitive impairment outweigh any demonstrated benefits. Whenever possible, prescribing clinicians should try one psychotropic agent at a time for the symptoms of BPSD.
MANAGEMENT OF EMERGENT BPSD

Medical staff are frequently called upon to sedate agitated patients in hospitals, nursing homes, or other care settings, often after hours, with limited access to relevant medical information and history. Safe and effective management requires adequate assessment of the possible causes of the agitation, exhausting all non-pharmacological strategies, and resorting to pharmacological treatment and/or physical restraint only when necessary and for the shortest time possible, with frequent review and the obtaining of consent as soon as possible.122

For patients with emergent BPSD (agitation, aggression, psychosis), non-pharmacologic and pharmacologic interventions should be considered simultaneously. The immediate goal is to create a safe environment for the patient and others, and to facilitate assessment and treatment of the acute situation, followed by implementation of a longer-term management plan once the patient has transitioned to non-emergent status. Older people are particularly vulnerable to psychological and physical harm, hence all interventions must be used cautiously, particularly pharmacological treatments or physical restraints. Patients in the midst of emergent BPSD may benefit from a range of environmental modifications and non-pharmacological strategies to maximize their safety and well-being. Limited evidence supports a range of pharmacological options, which include both traditional and atypical antipsychotics. Physical restraints should only be considered after appropriate assessment and trial of alternative treatments or if the risk of restraint is less than the risk of the behavior.

IS IT DELIRIUM?

A common differential diagnostic issue when evaluating emergent BPSD is distinguishing symptoms of delirium from those of BPSD. The essential feature of delirium is a disturbance of attention or awareness accompanied by a change in baseline cognition that cannot be better explained by a pre-existing neurocognitive disorder.3 Delirious patients are easily distracted, and the disturbance in awareness is manifested by a reduced orientation to the environment or, at times, even to oneself. Importantly, delirium develops over a short period of time, usually hours or a few days, and tends to fluctuate during the course of the day.3 The deficits in dementia tend to be stable or progressive, and level of consciousness is unaffected. Because memory impairment occurs in both delirium and dementia, a new diagnosis of dementia cannot be made when delirium is present. Urgent diagnosis and treatment of the cause(s) of the delirium is the highest priority. Pharmacological management of BPSD in patients with delirium has not been extensively studied.
Risperidone and other atypicals seem effective but they are not clearly better or safer than haloperidol,[123] which can be given IM or IV. Benzodiazepines must be avoided.

**Figure 2. Management algorithm for emergent BPSD**

**Acute evaluation**
- Is the patient in severe distress?
- Is the patient an imminent danger to him/herself or caregivers?
- Does the patient have severely disruptive or dangerous behavioral disturbances?

**Manage according to algorithm for non-emergent BPSD (page XX)**

**Pursue simultaneous management and evaluation strategies for emergent BPSD**
- Focus on stabilizing the acute situation followed by transition to a longer-term, non-emergent management plan.

**Pharmacologic acute stabilization**
- **DO NOT** use benzodiazepines or related medications
- **AVOID** new administration of multiple pharmaceutical agents
  - Complete therapeutic trials with a single medication. If ineffective then discontinue and initiate an alternative medication
- **INFORM** caretakers that risks of pharmacotherapy, especially with antipsychotics, often outweigh benefits

**Non-pharmacologic acute stabilization**
- Create a safe and comfortable environment for the patient and caretakers
  - Move the patient to a safe treatment area (e.g., inpatient facility)
  - Prevent access to means of harm (e.g., stairwells, sharp objects)
  - Involve family members (familiar faces) in care
- Manage any acute factor that may be causing emergent symptoms (e.g., metabolic disorder, sepsis, cerebrovascular event, environmental factor, emotional or physical discomfort, medication or substance toxicity or withdrawal)
- Use restraints only as a last resort and with great caution

**Recommended antipsychotic medications**
- Aripiprazole
  - PO: 2 mg to 5 mg
  - IM: 1.875 mg to 7.5 mg
- Risperidone
  - PO: 0.25 mg to 1 mg
  - Olanzapine
    - PO: 2.5 mg to 5 mg
    - IM: 2.5 mg to 5 mg

- Consider PO administration first; certain situations may require IM administration (e.g., patient refusal of medication)
- If symptoms are not controlled after the first dose, doses (PO or IM) may be repeated every 30 minutes to 1 hour for a total of 3 doses/day
- Monitor for drug-drug interactions
- Monitor for adverse events (e.g., cardiac effects)
- Reassess the patient after stabilization
  - Consider tapering medication 4 to 6 weeks after stabilization (taper over a 2 week period)
NON-PHARMACOLOGIC MANAGEMENT

All of the non-pharmacologic strategies reviewed previously for the management of non-emergent BPSD should be brought to bear in any situation involving emergent BPSD. These strategies include:

- Assessing the situation to identify any potentially reversible causes of emergent behaviors (e.g., emotional or physical discomfort, medication or substance toxicity or withdrawal, urinary tract infection)
- Moving the patient to a safe area or facility (e.g., inpatient facility)
- Preventing access to means of harm (e.g., stairwells, sharp objects)
- Involving family members (familiar faces) in care and consultation
- Use of restraints only as a last resort and with great caution

PHARMACOLOGIC MANAGEMENT

Most patients with dementia will exhibit disruptive behavioral symptoms at some point during the course of their disease, some of which will be psychotic symptoms. Of the psychotic symptoms, delusions are more common than hallucinations in dementia patients, and hallucinations are usually visual, but can be auditory. If these psychotic symptoms are not disruptive, dangerous, or distressing to the patient or caregiver (i.e. the patient has non-emergent BPSD) then the pharmacotherapies reviewed in this section are usually not warranted.

Pharmacologic intervention may be appropriate (used simultaneously with behavioral treatments and if all other potentially reversible or remediable causes have been ruled out) to treat:

- Physically aggressive or violent behavior that poses a danger to the patient or others
- Hallucinations or delusions that are distressing to the patient, lead to dangerous behavior, or significantly impair normal functioning

Pharmacologic interventions appropriate for emergent BPSD are generally not warranted to address behaviors such as:

- Wandering
- Unsociability
- Poor self-care
- Restlessness
- Nervousness
• Fidgeting
• Hoarding
• Sexual disinhibition
• Sundowning
• Shadowing
• Impaired memory
• Uncooperativeness without aggressive behavior
• Inattention or indifference to surroundings
• Verbal expressions or swearing that does not pose a danger to the patient or others

GENERAL GUIDANCE

As summarized in Figure 2, begin with a single dose of a medication within the recommended dosage ranges for the age of the patient in question. Consider oral administration first, although some situations may require IM administration (e.g., patient refusal of medication or inability to swallow). If symptoms are not controlled after the first dose, the dose may be repeated or increased. If an agent is ineffective, it should be discontinued and an alternative medication should be started.

Monitor for drug-drug interactions and adverse events (e.g., cardiac effects). Reassess the patient after he or she has stabilized. Continue treatment for up to 4 months if it is deemed effective and is well-tolerated, though the potential risks of treatment should be reiterated to both the patient and caregivers. In general, psychoactive medications should not be continued indefinitely and attempts at drug withdrawal should be made regularly.56 Note, however, that patients must be closely monitored for symptom relapse following medication discontinuation.57 A 2012 randomized controlled trial in patients with AD who had responded to the antipsychotic risperidone showed an increased risk of relapse when the medication was discontinued.57

Once a patient has been stabilized and no longer exhibits emergent BPSD, he or she should be treated and managed according to the guidelines presented earlier for non-emergent BPSD.
ANTIPSYCHOTICS

Please refer to the full discussion of antipsychotic use in non-emergent BPSD for analysis of their benefits and risks when used both short- and long-term. A few additional comments on their specific uses in the emergent situation will be made here.

Aripiprazole

Ten or 15 mg of IM aripiprazole administered in divided doses was safe and well-tolerated for treatment of agitation associated with Alzheimer’s, vascular, or mixed dementia in long-term care.\(^{124}\) A higher incidence of adverse events occurred with IM aripiprazole (50% to 60%) than IM placebo (32.0%), but over 90% of events were mild or moderate in severity. Aripiprazole also has an advantage of having the least QTc prolongation of any of the atypicals.\(^ {125,126}\)

Olanzapine

A meta-analysis of studies of dementia patients with acute agitation in an emergency department setting showed that IM olanzapine (2.5 mg) (1–3 injections/24 h) significantly reduced agitation compared with placebo with no more sedation than lorazepam (1.0 mg).\(^ {127}\) As previously noted, in a double-blind randomized trial comparing the efficacy and safety of IM olanzapine (dosages of 2.5 and 5.0 mg) with lorazepam (1.0 mg) or placebo in patients with agitation associated with Alzheimer's disease and vascular dementia, both olanzapine and lorazepam showed superiority after 2 hours over placebo in terms of reduced agitation.\(^ {62}\) Olanzapine is therefore a reasonable second line IM medication (after aripiprazole) for emergent severe BPSD.

Initiating an antipsychotic

Non-pharmacological interventions should be continued simultaneously with any pharmacological therapy for emergent BPSD.\(^ {53}\) The target symptoms or behavior should be identified prospectively, and methodically documented both before and following medication initiation for at least two weeks, with regular review for response, adverse effects and drug interactions.\(^ {128}\)

Initiate antipsychotics at the lowest possible dose, and gradually titrate upwards according to tolerability and response.\(^ {110}\) The dose of the antipsychotic, or other agent trialed for emergent BPSD, should take into account the physical size, age, and general condition of the patient. A maximal daily dose including PRN doses should be clearly specified (e.g., “total dose within any 24 hour period is not to exceed [specify dose] mg”).
Consider a PRN regimen for the management of episodic or rapidly changing agitation, aggression, or psychosis. Specifically define the clinical circumstances warranting use, including the symptoms to trigger administration, dose, frequency, duration and maximum dose for any 24 hour period. Carefully defined PRN regimens and drug-free days can help minimize overall psychotropic load. If appropriate, consent should also be sought from the patient’s family or guardian. The administration of PRN medication may be difficult in the community with a sole caregiver. If symptoms begin to flare, the patient may be suffering from delirium and need a full medical workup.

There is no evidence to support the use of more than one antipsychotic at a time for BPSD (for example, a regularly dosed antipsychotic with another antipsychotic dosed on a PRN basis). Using more than one antipsychotic at a time could increase the risk of serious adverse effects.

Withdrawal of antipsychotics in emergent BPSD
Antipsychotics should be tapered slowly to minimize the risk of a withdrawal syndrome (unless significant adverse effects or a drug interaction necessitates abrupt cessation). A reduction in antipsychotic dose by 25–50% every 2 weeks and ceasing after 2 weeks on the minimum dose is generally recommended. Close attention should be paid to behavior in response to reducing doses, since, as previously noted, a 2012 study of patients with AD showed an increases risk of relapse when risperidone was discontinued.

BENZODIAZEPINES
For an episode of acute anxiety or agitation, a short-acting benzodiazepine (rather than an antipsychotic) has been found useful in a few studies: as discussed earlier, lorazepam (Ativan) 1 mg IM was comparable to olanzapine 2.5 or 5 mg at two hours and better than IM placebo. At 24 hours, the lorazepam effect was no longer present while olanzapine’s effect persisted. Given the many adverse effects of benzodiazepines, such as confusion, ataxia, and falls documented in other studies, further systematic trials need to be performed before they can be recommended for emergent cases of BPSD.

BOTTOM LINE
Antipsychotic drugs may be considered for the behavioral management of emergent BPSD, while simultaneous offering non-pharmacologic modalities to the extent possible. Occasionally, restraint may be required if other methods do not work and the behavior poses a serious risk to the patient or others. First,
try oral medication if the patient will accept it. Though no medication is FDA-approved for this indication, aripiprazole and risperidone may provide modest benefit, but other antipsychotics have questionable benefits and/or even greater risks. If IM medication is required, the first choice is aripiprazole and the second choice is olanzapine. Treatment may be repeated once or twice in 30 to 60 minutes if necessary. Most evidence of efficacy from clinical trials is for aggression, agitation, and psychosis. The use of antipsychotics in elderly patients increases the risk of death.

Patients with dementia requiring antipsychotics may benefit from referral to a psychiatrist when available. In extreme cases, patients have been admitted to neuropsychiatry units and successfully treated with electroconvulsive therapy.\textsuperscript{130}

\textbf{CONCLUSIONS}

Managing patients with both emergent and non-emergent BPSD can often be frustrating for clinicians and family members because no optimal treatments exist. Nonetheless, the appropriate use of non-pharmacologic management strategies and interventions can improve the well-being of many patients with BPSD, and may reduce the burden on family members and caregivers. The initial approach to the management of BPSD should always include non-pharmacologic therapies. Medications may also have a role, and the algorithms in this document can help guide clinicians identify situations when medications may be indicated and select the dose and duration for treatment. The symptoms of BPSD change over times, and frequent reassessment of a patient’s clinical status and active treatments are key for guiding both pharmacologic and non-pharmacologic approaches.
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These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient’s clinical condition.