Managing Behavioral and Psychological Symptoms of Dementia in the Era of Black Box Warnings

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An in-depth look into the behavioral and psychological symptoms of dementia.

Behavioral and psychological symptoms of dementia (BPSD) are a heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors that are unsafe and disruptive and impair the care of the individual. About one-third of community-dwelling individuals with dementia exhibit BPSD. The prevalence increases to approximately 80% in individuals residing in nursing facilities. Jost and Grossberg found that behavioral symptoms were observed in 72% of individuals more than 2 years before the actual diagnosis of dementia. The prevalence of BPSD increased to 81% 10 months after the formal diagnosis of dementia. Delusions commonly seen in individuals with dementia include false beliefs (e.g., of theft, infidelity, misidentification syndromes). Individuals with dementia who have a family history of depression appear to be at greater risk for a major depressive episode than those without a family history. Disinhibition occurs in approximately one-third of the patients. In patients with hallucination, the most common form is visual hallucination. Irritability and mood lability become more prevalent with the progression of dementia. Findings indicate that BPSD occurs because of the complex interactions between anatomical, functional, and biochemical changes that occur in the brain. Certain genes can predispose individuals to BPSD, and premorbid personality may contribute to the emergence of certain types of behavioral symptoms. Table 1 details the various neurobiological changes that contribute to the development of BPSD. BPSD is associated with greater overall burden of care for individuals with dementia. The emergence of BPSD often results in the referral of patients with dementia to a specialist’s care. Paranoia, aggression, and sleep-wake cycle disturbances are associated with greater caregiver burden, caregiver depression, and the risk of institutionalization. BPSD results in the worsening of activities of daily living, faster cognitive decline, and a poorer quality of life. It also adds to the overall direct and indirect cost of care for individuals with dementia after adjusting for the severity of cognitive impairment and other comorbidities.

Assessment
Assessment includes collateral information from caregivers and/or family members. Collateral information aids in determining the onset, the course, and the differential diagnosis of BPSD. It also helps identify risk and prognostic factors. Environmental factors and psychosocial stressors may be triggers for the onset or the worsening of symptoms. Underlying medical conditions, including pain syndromes, urinary tract infection, and dehydration, can result in exacerbation of symptoms. An evaluation for and management of these disorders will reduce the frequency and severity of BPSD and may mitigate the use of psychotropic medications.

Assessment tools such as the Neuropsychiatric Inventory, the Behavioral Pathology in Alzheimer Disease rating scale, the Consortium to Establish a Registry for Alzheimer Disease Behavior Rating Scale for Dementia, Dementia Behavior Disturbance scale, and the Neurobehavioral Rating Scale can be used to aid diagnosis of BPSD. These instruments help identify behaviors and rate their severity. They can also assist in tracking progression and in monitoring treatment response. An algorithm for the assessment of BPSD is presented in Figure 1.

Management of BPSD
Figure 2 provides an algorithm for the treatment of BPSD. Nonpharmacological strategies should be the primary intervention for patients with BPSD. If the symptoms of BPSD are not well managed with
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Nonpharmacological strategies, judicious pharmacotherapeutic trials can be tried. A decline in cognition can result in the emergence or worsening of BPSD. A trial of cholinesterase inhibitors and/or memantine may be initiated to delay cognitive decline.²

Nonpharmacological management. Findings from a systematic review suggest that caregiver and residential care staff education and possibly cognitive stimulation therapy are effective in the management of BPSD.⁹ However, specialized dementia units were not consistently beneficial; changing the environment visually and unlocking doors reduced wandering.

Nonpharmacological interventions provided by caregivers can reduce the frequency and severity of symptoms and can reduce caregiver burden, with effect sizes similar to those associated with pharmacotherapy.¹⁰ Successful interventions included approximately 9 to 12 individual sessions designed to meet the needs of the patient and his or her caregivers and were delivered in the patient’s home using multiple components over 3 to 6 months with periodic follow-up.

One meta-analysis showed statistically significant results for nonpharmacological interventions on at least one measure of BPSD.¹¹ These interventions included staff training in behavioral management strategies, mental health consultation and treatment planning, exercise, recreational activities, and music therapy or other forms of sensory stimulation. However, there were methodological limitations that suggest a possible risk of bias. Moreover, for many of the interventions, substantial resources from outside services were needed along with considerable time commitments from the nursing staff for the implementation of these strategies.

Pharmacological management. If possible, behaviors should be grouped into different clusters (eg, psychotic, mood). These clusters act as psychobehavioral metaphors of primary psychiatric disorders. If these behaviors are not well managed by individual medication trials, a judicious combination of medications can be tried (eg, an antidepressant with an antipsychotic). Caution must be exercised when prescribing medications, given their adverse-effect profile and the vulnerability of the population being treated. Medication combinations, such as 2 antipsychotics or 3 or 4 different medication classes, should be avoided to minimize serious adverse events. The duration of effective medication trials should be about 3 to 4 months of clinical stability, followed by a trial of medication taper and discontinuation.

A meta-analysis by Ballard and colleagues¹² demonstrated that compared with placebo, risperidone and olanzapine reduced aggression. Individuals treated with risperidone also had significant improvements in psychosis. A meta-analysis by Schneider and colleagues¹³ also found evidence for the efficacy of aripiprazole and risperidone in the management of BPSD.

In a randomized, double-blind, placebo-controlled trial, outpatients with Alzheimer disease and psychosis, aggression, or agitation were randomly assigned to olanzapine, quetiapine, risperidone, or placebo. There were no significant differences among the active agents regarding the time to discontinuation of treatment for any reason.¹⁴ The median time to discontinuation of treatment because of a lack of efficacy favored olanzapine and risperidone over quetiapine and placebo. The time to the discontinuation of treatment because of adverse events or intolerability favored placebo compared with the active agents.

Sertraline and citalopram were associated with a reduction in symptoms of agitation.¹⁵ No differences in behavioral symptoms were seen when trazodone was compared with haloperidol. Both SSRIs and trazodone appear to be well tolerated compared with placebo, typical antipsychotics, and atypical antipsychotics. SSRIs and trazodone showed some benefit in the management of BPSD and were well tolerated.¹⁶

Low-dose sodium valproate is ineffective in treating agitation in individuals with dementia, and high-dose divalproex sodium is associated with an unacceptable rate of adverse effects.¹⁷ In a literature review, Konovalov and colleagues¹⁸ found one study that showed statistically significant benefit of carbamazepine compared with placebo in the treatment of BPSD. However, most studies demonstrated no significant differences. In a majority of the studies, adverse effects were more frequent with the active medication.

Cholinesterase inhibitors provided modest improvements in neuropsychiatric and functional outcomes, with no differences in efficacy among the different drugs in this class.¹⁹ A meta-analysis showed modest improvements in symptoms with memantine.²⁰ Moreover, it is well tolerated—the only adverse effects are confusion and sedation.

There is insufficient evidence to justify the use of benzodiazepines for managing BPSD.²¹ There have been only 5 controlled trials, which were of short duration and with a limited number of subjects. The efficacy data were limited and the adverse-effect profile was not benign. The data for using pharmacotherapeutic agents in the management of BPSD are limited. There are no robust data on the efficacy of these drugs, but there are data on the adverse-effect profiles.
Although limited, the best evidence for efficacy was found for antipsychotics, especially risperidone, olanzapine, and aripiprazole, and for SSRI antidepressants, namely sertraline and citalopram (Table 2).

**Antipsychotic use in elderly persons with dementia**

Individuals at high risk for adverse effects of antipsychotics are those who are 85 years or older and who have vascular or mixed dementias or active cerebrovascular or cardiovascular diseases and significant impairments in activities of daily living. However, if the symptoms of BPSD are not sufficiently managed by other strategies, the use of antipsychotics may be justified.

When prescribing antipsychotic medications, it is sensible to use the lowest effective dose and for the shortest time to manage the symptoms. Close monitoring for adverse effects and their swift management in case they do arise will minimize serious adverse events.

Herrmann and Lanctôt completed a post hoc analysis of pooled results from randomized controlled trials of persons with dementia who were treated with risperidone and olanzapine. Their results indicate an increased incidence of cerebrovascular adverse events. Some of the increased incidence could be accounted for by nonspecific events other than stroke. There were a greater number of persons with vascular and mixed dementias in the risperidone trials than in the olanzapine trials. In contrast to this post hoc analysis, other results show no increased risk of stroke in older individuals treated with risperidone and olanzapine compared with individuals treated with typical antipsychotics or untreated individuals with dementia.

FDA findings indicate that the use of atypical antipsychotics in individuals with BPSD is associated with increased mortality. The majority of placebo-controlled trials of olanzapine, aripiprazole, risperidone, and quetiapine showed 1.6- to 1.7-fold increases in mortality. Deaths were due to heart-related events (heart failure or sudden death) or infections (mainly pneumonia). The FDA asked the manufacturers of these drugs to include a black box warning in their labeling describing this risk and noting that these drugs are not approved for BPSD. Similar changes to the labeling for typical antipsychotics have also been added.

A meta-analysis by Schneider and colleagues found that the risk of death was greater among individuals who were treated with atypical antipsychotics. The sensitivity analyses did not show any evidence for differential risks for individual drugs, severity of dementia, sample selection, or the diagnosis. Wang and colleagues found that conventional antipsychotic medications were associated with a significantly higher adjusted risk of death than were atypical antipsychotic medications.

The risk of cerebrovascular adverse events was 1.3 to 2 times higher with active treatment compared with placebo; the risk of death was about 1.2 to 1.6 times higher. The risk is similar for typical and atypical antipsychotic agents. A higher than median dose of a drug, older age, a diagnosis of vascular dementia, and comorbid atrial fibrillation have been noted as risk factors for cerebrovascular adverse events. Older age, male sex, severe dementia, and functional impairment are associated with higher risk of death.

**Conclusion**

Common in individuals with dementia, BPSD is associated with poorer outcomes and greater burden of care. Data show that BPSD is caused by underlying neuroanatomical and neurochemical changes in the brain and a premorbid personality structure. Pharmacotherapy should be combined with nonpharmacological approaches for optimum results. The risk of prescribing medications for patients with BPSD (who are often elderly) should be carefully weighed with possible benefits. These medications should only be prescribed within the recommended dosage to reduce the risk of serious adverse events. Close monitoring of risk factors will also help mitigate serious adverse events.
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Figure 2. Algorithm for the management of behavioral and psychological...

TABLE 2: Pharmacotherapeutic agents for behavioral and psychological s...

Disclosures:
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