Behavioral and Psychological Symptoms of Dementia: Part II—Treatment

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Behavioral and psychological symptoms of dementia (BPSD) are not uncommon in patients with dementia and include noncognitive symptoms and behaviors such as agitation, anxiety, apathy, delusions, depression, and hallucinations. Early diagnosis and treatment of these behaviors will help reduce morbidity, reduce the costs and burden of caring for these patients, and improve patient and caregiver quality of life.[1] In Part I of this two-part article, we discussed the epidemiology, neurobiology, heritability, evaluation, and diagnosis of BPSD.[2] In this article, we review the available data on the evidence-based treatment of BPSD.

Treatment

Current treatment strategies for BPSD include various nonpharmacological (eg, behavior therapy, cognitive stimulation therapy, psychoeducation) and pharmacological (eg, antipsychotics, antidepressants, mood stabilizers, cognitive enhancers) approaches.[3] Pharmacotherapy should be initiated only if the patient's symptoms have not responded adequately to nonpharmacological interventions, if there is no underlying medical condition causing these symptoms, and/or if these symptoms are not related to a medication effect.[3] Although these nonpharmacological and pharmacological treatments are effective in decreasing the burden of BPSD, they usually require sustained input from a multidisciplinary team and ongoing staff training to maintain superior quality of care for patients with BPSD.[3]

Nonpharmacological Treatment

Emerging evidence confirms that a variety of nonpharmacological treatments are useful in the management of BPSD[3] (**Table 1**[4,5]). Available data indicate that these treatments should be considered before pharmacological therapies are prescribed.[3]

TABLE 1

Nonpharmacological Treatments for BPSD[a]

Type of Intervention	Aim of Intervention	Individual/Group Setting	Level of Effectiveness
Psychoeducation	Change caregiver's behavior	Individual	Effective
Instruction for staff	Improve staff's communication skills and enhance staff's knowledge of dementia	Individual or group	Effective
Behavior therapy	Modify patient's behaviors	Individual or group	May be effective
Cognitive stimulation therapy	Stimulate cognition in patient	Individual or group	May be effective
Multisensory therapy	Expose patient to a soothing and stimulating environment	Individual or group	May be effective
Therapeutic activities	Increase patient's goal-directed activities	Individual or group	May be effective
Specialized dementia unit	Locked self-contained units provide a higher level of supervision to treat patients who are agitated and wandering	Group	Not consistently effective

[a] *Contains information from references 4 and 5.*

In a 2005 systematic review, Verkaik et al [4] found some evidence that multisensory stimulation (Snoezelen) in a multisensory room reduces apathy in patients who are in the later stages of dementia. They also found limited evidence that behavior therapy–pleasant events and behavior therapy–problem solving reduce depression in patients with probable Alzheimer's disease (AD) who are living at home with a primary caregiver and that psychomotor therapy groups reduce aggression in nursing home residents with aggression, apathy, and depression who received a diagnosis of probable AD.[4]

Another systematic review in 2005 examined the psychological approaches to treating the neuropsychiatric symptoms of dementia. Livingston and colleagues[5] found that only behavior management therapies, specific types of caregiver and residential care staff education, and possibly cognitive stimulation appear to have a lasting effect in the management of dementia-associated neuropsychiatric symptoms. The authors reported that behavioral management techniques which focus on an individual patient's behavior are generally successful at reducing neuropsychiatric symptoms and, despite qualitative differences, their effects last for months. In addition, psychoeducation for caregivers that is designed to enhance their communication skills and knowledge about dementia can change behaviors and subsequently have a lasting effect on a patient's neuropsychiatric symptoms; psychoeducation appears to be more effective when provided on an individual basis, rather than in a group setting. Therapies such as reminiscence therapy, caregiver training in behavioral management techniques, therapeutic activities, specialized dementia units, and simulated presence interventions or reduced stimulation units were noted to merit further study due to little or no convincing evidence, inconsistent outcomes, mixed evidence, and contradictory or inconclusive findings. Evidence was more positive, however, for cognitive stimulation therapy. Other evidence showed that simple repetitive exercise, reality orientation therapy, validation therapy, "admiral" nurses (specialists in the treatment of dementia who have worked in the community with caregivers of patients with dementia), and Montessori activities (activities that make extensive use of external cues and progress from simple to more complex activities) have no effect on neuropsychiatric symptoms. Finally, other types of therapies—including music therapy and Snoezelen—were found to be effective at ameliorating neuropsychiatric symptoms temporarily, but had no lasting effectiveness.[5]

Other studies have indicated that interventions for caregivers such as supportive counseling, increasing "time for self," and providing education and training decrease caregiver burden, improve the caregiver's tolerability of a patient's particular symptom, have a positive impact on patient behavior, and may delay institutionalization of the patient.[6-9]

Pharmacological Treatment

Before starting the patient on pharmacotherapy for BPSD, the healthcare provider must have a discussion on the risks and benefits of pharmacotherapy with the patient and his or her family or caregiver. The potential risks of treatment-related side effects must be weighed against the risks of not treating BPSD, including harm to the patient and others due to aggression, confusion, and falls.[1,3] It is important for the patient and his or her family or caregiver to be informed of the possible risks of either option, and they must provide informed consent before a course can be pursued.

Pharmacotherapy for the treatment of BPSD should be evidence-based and should target specific syndromes that are clinically significant because of their frequency, pervasiveness, or impact on the patient.[1,3] Available evidence indicates efficacy for antipsychotics, mood stabilizers, antidepressants, and cognitive enhancers.[1,3] In this section, we review the efficacy and safety of the various classes of psychotropic medications for the treatment of BPSD (**Table 2**[10-26]).

TABLE 2

Medications Used to Treat BPSD[a]

Class of Medication	Name of Medication	Dosage Range (mg/day)	Common Side Effects of Medication Class
Antipsychotics	Aripiprazole Haloperidol Risperidone Quetiapine Olanzapine	2.5-15 0.5-5 0.25-2 25-200 2.5-15	Sedation, extrapyramidal symptoms, neuroleptic malignant syndrome, metabolic syndrome, QTc prolongation, increased risk of cerebrovascular events and mortality
Antidepressants	Fluoxetine Citalopram Paroxetine Sertraline Trazodone	10-80 10-60 10-50 25-200 25-200	Anxiety, headaches, sedation, gastrointestinal symptoms, sexual dysfunction
Mood stabilizers	Carbamazepine Divalproex sodium Oxcarbazepine	100-400 250-1000 300-600	Sedation, gait and balance issues, falls, liver dysfunction, hyperammonemia, thrombocytopenia
Cognitive enhancers	Donepezil Galantamine Rivastigmine Memantine	5-10 8-24 3-12 5-20	Sedation, gastrointestinal disturbance, confusion, agitation

[a] *Contains information from references 10-26.*

Antipsychotics. A systematic review by Sink et al [10] of double-blind, placebo-controlled, randomized controlled trials or meta-analyses of any drug therapy for patients with dementia that included neuropsychiatric outcomes found that pharmacotherapies are not particularly effective for the management of BPSD. Of the drug therapies studied, including typical antipsychotics, atypical antipsychotics, antidepressants, and mood stabilizers, the atypical antipsychotics risperidone and olanzapine had the best evidence of efficacy, although their effects were modest and were further complicated by their side-effect profiles (ie, increased risk of stroke).[10]

Results of a 2006 meta-analysis of placebo-controlled trials of atypical antipsychotics showed significant improvements in aggression in patients treated with risperidone and olanzapine as compared with placebo and in psychosis in patients treated with risperidone as compared with placebo.[11] Patients treated with risperidone or olanzapine, however, had a significantly higher incidence of serious adverse cerebrovascular events (including stroke), extrapyramidal side effects (including dystonia, akathisia, and parkinsonism), and other important adverse outcomes (sedation, gait impairment, falls, upper respiratory infections, urinary tract infections, and fever). The authors noted a significant increase in dropouts among patients treated with risperidone (2 mg) or olanzapine (5-10 mg). Lastly, the authors found that the data were insufficient to examine the impact of these drugs on cognitive function. The authors concluded that despite the modest efficacy that was observed with risperidone and olanzapine, due to the significant increase in adverse events, neither should be used routinely to treat persons with dementia who have aggression or psychosis unless there are no other treatment options remaining to treat these behaviors.[11]

Another 2006 meta-analysis of randomized, placebo-controlled, double-blind, parallel-group trials of atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) reported efficacy on rating scales for aripiprazole and risperidone, but not for olanzapine.[12] Smaller effects were noted in patients with less severe dementia, outpatients, and patients selected for psychosis. Other results were as follows: approximately one-third of patients dropped out of the trials with no overall differences observed between drug and placebo; common adverse events reported with all drugs were somnolence, urinary tract infection, and incontinence; and extrapyramidal symptoms and abnormal gait were seen with risperidone or olanzapine. Cognitive test scores worsened with all or these drugs, but there was no evidence for increased injury, falls, or syncope. Finally, there was a significant risk of cerebrovascular events, especially with risperidone. The authors concluded that atypical antipsychotics should be considered for the treatment of dementia within the context of medical need and weighed against the safety and efficacy of alternatives. In addition, they noted a need to better assess the clinical significance and effectiveness of these medications.[12]

In the CATIE-AD (Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease) study, [13] a 42-site, double-blind, placebo-controlled trial assessing the effectiveness of atypical antipsychotics in persons with AD, 421 outpatients with AD and psychosis, aggression, or agitation were randomly assigned to treatment with olanzapine (mean dose, 5.5 mg/day), quetiapine (mean dose, 56.5 mg/day), risperidone (mean dose, 1.0 mg/day), or placebo. Researchers found no significant differences among the different treatments with regard to the median time to treatment discontinuation for any reason (olanzapine, 8.1 weeks; quetiapine, 5.3 weeks; risperidone, 7.4 weeks; and placebo, 8.0 weeks; $P = .52$). Median time to discontinuation of treatment because of a lack of efficacy was longest for olanzapine (22.1 weeks) and risperidone (26.7 weeks) as compared with quetiapine (9.1 weeks) and placebo (9.0 weeks) ($P = .002$). The time to the discontinuation of treatment due to adverse events or intolerability favored placebo ($P = .009$). Overall, 24% of patients on olanzapine, 16% of patients on quetiapine, 18% of patients on risperidone, and 5% of patients on placebo discontinued treatment because of intolerability. Researchers noted no significant differences among the groups with regard to improvement on the Clinical Global Impression of Change (CGIC) scale: improvement was observed in 32% of patients on olanzapine, 26% of patients on quetiapine, 29% of patients on risperidone, and 21% of patients on placebo ($P = .22$). They concluded that the adverse effects found with the use of atypical antipsychotics for the treatment of psychosis, aggression, or agitation in persons with AD offset advantages in their efficacy.[13]

Although antipsychotic medications have some—albeit limited—efficacy in the treatment of BPSD, concerns have been raised regarding their safety in treating elderly persons. In the next few paragraphs, we discuss the recent safety concerns with the use of antipsychotics in the treatment of elderly patients with BPSD.

In 2002, the health regulatory agency in Canada first raised concerns about the association of risperidone with cerebrovascular adverse events in clinical trials of elderly patients with dementia.[27] In 2003, the US Food and Drug Administration (FDA) published warnings about cerebrovascular adverse events and required changes in the prescribing information for risperidone.[28] In 2004, the European Agency for the Evaluation of Medicinal Products (now known as the European Medicines Agency) issued public advice about the increased risk of cerebrovascular adverse events and mortality in elderly patients with dementia receiving olanzapine.[29] That same year, the United Kingdom's Committee on Safety of Medicines (now known as the Commission on Human Medicines) advised prescribers that risperidone and olanzapine should not be used to treat BPSD because of clear evidence of an increased risk of stroke.[30] In 2005, the FDA determined that the treatment of behavioral disorders in elderly persons with dementia with atypical (second-generation) antipsychotics is associated with increased mortality.[31] Of 17 placebo-controlled trials investigating olanzapine, aripiprazole, risperidone, or quetiapine in elderly persons with dementia and concomitant behavioral disorders, 15 showed numerical increases in mortality in the group receiving drug treatment as compared with the group receiving placebo. A total of 5106 patients were enrolled in these studies, and several analyses have demonstrated an approximate 1.6- to 1.7-fold increase in mortality in these studies. Most of these deaths were found to be due to either heart-related events (eg, heart failure, sudden death) or infections (mostly pneumonia).

Because of these findings, the FDA asked the manufacturers of these drugs to include a Boxed Warning in their labeling to describe this risk and note that these drugs are not approved for the treatment of this indication. In addition to olanzapine, aripiprazole, risperidone, and quetiapine, the atypical antipsychotic medications clozapine and ziprasidone and a combination product containing olanzapine and fluoxetine that is approved for the treatment of depressive episodes associated with bipolar disorder were included in the request.[31] In 2008, the FDA required the manufacturers of conventional antipsychotic drugs to add a Boxed Warning to the drugs' prescribing information about the risk of mortality in elderly persons treated for dementia-related psychosis,[32] which was similar to the Boxed Warning added in 2005 to the prescribing information for the atypical antipsychotic drugs. These advisories also mention that antipsychotic medications are not approved for use in the treatment of dementia-related psychosis.[31,32]

In a 2005 meta-analysis, Herrmann and Lanctôt[33] evaluated risperidone and olanzapine trials and suggested that some of the increased incidence of cerebrovascular adverse events may be accounted for by nonspecific events that were not strokes. A larger number of subjects with vascular and mixed dementias were included in the risperidone studies than in the olanzapine studies, which likely accounts for the increased incidence of cerebrovascular adverse events in the risperidone trials as compared with the olanzapine trials. The authors concluded that the association between atypical antipsychotics and cerebrovascular adverse events requires further clarification and, at the present time, this association is another factor that clinicians should consider when weighing the risks and benefits of treating BPSD with pharmacotherapy.[33] Large, observational, administrative health database studies appear to confirm the findings of Herrmann and Lanctôt[33] that risperidone and olanzapine are not associated with an increased risk of stroke in elderly patients as compared with elderly patients with dementia who are taking typical antipsychotics or who are not treated with antipsychotics.[34,35]

A 2005 meta-analysis assessing the evidence for increased mortality from atypical antipsychotic drug treatment in persons with dementia included 15 trials (6 published, 9 unpublished), with a general duration of 10 to 12 weeks, that contrasted atypical antipsychotics (aripiprazole [n = 3], olanzapine [n = 5], quetiapine [n = 3], and risperidone [n = 5]) with placebo.[36] In these studies, a total of 3353 patients were randomized to the study drug and 1757 were randomized to placebo. The authors found that death occurred more often among patients taking drugs than among patients taking placebo (118 [3.5%] vs 40 [2.3%], respectively). The overall odds ratio (OR) by meta-analysis for death in patients taking drugs as compared with placebo was 1.54 (95% confidence interval [CI], 1.06-2.23; *P* = .02); the risk difference was .01 (95% CI, 0.004-.02; *P* = .01). Evidence for differential risks for individual drugs, severity, sample selection, or diagnosis was not shown in sensitivity analyses. The authors concluded that, compared with placebo, atypical antipsychotics may be associated with a small increased risk for death. This risk, however, should be considered within the context of the medical need for the drugs, medical comorbidity, efficacy evidence, and the efficacy and safety of alternative treatments.[36] In a population-based, retrospective cohort study conducted in Ontario, Canada, of older adults with dementia in which a total of 27,259 matched pairs were identified, new use of atypical antipsychotics was associated with a statistically significant increased risk of death at 30 days as compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio [HR], 1.31; 95% CI, 1.02-1.70; absolute risk difference, 0.2 percentage point) and the long-term care cohort (adjusted HR, 1.55; 95% CI, 1.15-2.07; absolute risk difference, 1.2 percentage points).[37] Conventional antipsychotic use was associated with an even greater risk of death than that observed with atypical antipsychotic use, and this risk was evident at 30 days (community-dwelling cohort: adjusted HR, 1.55; 95% CI, 1.19-2.02; adjusted risk difference, 1.1 percentage points; long-term care cohort: adjusted HR, 1.26; 95% CI, 1.04-1.53; adjusted risk difference, 1.1 percentage points, respectively). The increased mortality risk associated with conventional antipsychotic use versus atypical antipsychotic use and new atypical antipsychotic use versus nonuse persisted to 180 days in both patient populations (community-dwelling cohort: adjusted HR, 1.23; 95% CI, 1.00-1.50; absolute risk difference, 2.6 percentage points; long-term care cohort: adjusted HR, 1.27; 95% CI, 1.09-1.48; absolute risk difference, 2.2 percentage points, respectively). The investigators concluded that, compared with nonuse, atypical antipsychotics are associated with an increased risk of death among older persons with dementia, and this risk may be greater with conventional antipsychotics than with atypical antipsychotics.[37]

In another population-based cohort of elderly persons living in British Columbia, Canada, who were prescribed conventional and atypical antipsychotic medications, 1822 patients (14.1%) in the conventional drug group and 2337 patients (9.6%) in the atypical drug group died within the first 180 days of use (mortality ratio, 1.47; 95% CI, 1.39-1.56).38 Multivariable adjustment resulted in a 180-day mortality ratio of 1.32 (CI, 1.23-1.42). Further, haloperidol was associated with the greatest increase in mortality (mortality ratio, 2.14; 95% CI, 1.86-2.45) and loxapine was associated with the lowest increase in mortality (mortality ratio, 1.29; 95% CI, 1.19-1.40) as compared with risperidone. Investigators found that persons taking higher doses (above median) of conventional antipsychotics (mortality ratio, 1.67; 95% CI, 1.50-1.86) and those in their first 40 days of drug therapy (mortality ratio, 1.60; 95% CI, 1.42-1.80) had the greatest increase in mortality. It was concluded that the risk of death associated with conventional antipsychotics is comparable to—and possibly greater than —the risk of death associated with atypical antipsychotics among elderly persons.[38]

In a recent systematic review of the literature examining the risk of cerebrovascular adverse events and death with antipsychotic treatment in elderly persons with dementia, the authors found 22 studies that evaluated the risk of cerebrovascular adverse events and 14 studies that evaluated the risk of death.[39] Of the studies addressing the risk of cerebrovascular adverse events, only two were placebo-controlled studies; the majority were population-based studies or retrospective analyses. The available data indicate that the risk of cerebrovascular adverse events was about 1.3 to 2 times higher in the drug-treated groups than in the placebo-treated groups. Although preliminary, the existing data comparing atypical antipsychotics with typical antipsychotics suggest that the risk of cerebrovascular adverse events is similar in both groups. No one drug has been found to be safer than the other in terms of the rate of cerebrovascular adverse events. A higher-than-median dose of a drug, older age, a diagnosis of dementia (especially vascular dementia), and comorbid atrial fibrillation have been noted as risk factors for cerebrovascular adverse events. Finally, it appears that the time frame for which the risk of cerebrovascular adverse events remains elevated is approximately 20 months. In the same systematic review, only three of the 14 studies that addressed the risk of death were placebo-controlled. Preliminary data indicate that risk of death with atypical and typical antipsychotics was about 1.2 to 1.6 times higher than in the placebo groups or the groups that did not use antipsychotic medications. Like the data for cerebrovascular adverse events, existing data for atypical versus typical antipsychotics indicate that the risk of death is similar in both groups, and no one drug has been found to be safer than the other in terms of the risk of death. Older age, male gender, severe dementia, and functional impairment are associated with a higher risk of death and this risk remains elevated within the first 30 days of starting medication and possibly for up to 2 years.[39]

Antidepressants. In the aforementioned review by Sink et al,10 the authors found five randomized controlled trials of antidepressants (sertraline, fluoxetine, citalopram, and trazodone) in the treatment of BPSD. Of these five studies, only the citalopram trial showed any benefit in the treatment of BPSD.[14] In this double-blind, placebo-controlled study, 85 hospitalized patients with at least one moderate-to-severe target symptom of BPSD (aggression, agitation, hostility, suspiciousness, hallucinations, or delusions) were randomly assigned to receive either citalopram, perphenazine, or placebo for up to 17 days. Both the citalopram and perphenazine groups showed significant improvement from baseline with respect to the agitation/aggression, psychosis, and lability/tension Neurobehavioral Rating Scale (NRS) factors, and the citalopram group also showed significant improvement in the cognition and retardation NRS factors. Persons receiving placebo did not demonstrate significant change in any NRS factor. This trial had a high dropout rate, with more than half of patients in each group failing to complete the study, most commonly because of a lack of efficacy.[14]

In a recent systematic review of the literature, Henry et al15 found a total of 19 randomized controlled trials that used an antidepressant medication for the

treatment of BPSD. Of the 19 trials, 15 involved a selective serotonin reuptake inhibitor (SSRI) compound and four involved trazodone. Eight trials using an SSRI compound and three trials using trazodone showed benefit in the treatment of BPSD. The antidepressant drug was well tolerated in at least 14 of the 19 trials, with information about tolerability in one trial not provided in the study (paroxetine or placebo for frontotemporal dementia). These findings indicate that antidepressants can be effective in the treatment of BPSD and are generally well tolerated in elderly persons with dementia.[15]

Mood Stabilizers. The three randomized controlled trials identified by Sink et al10 that investigated valproate did not show any efficacy over placebo in the treatment of BPSD. In addition, a Cochrane database review of valproate for the treatment of agitation in persons with dementia indicates that low-dose sodium valproate is ineffective in the treatment of agitation in persons with dementia and that high-dose divalproex sodium is associated with an unacceptable rate of adverse effects (sedation: OR, 2.64; gastrointestinal disturbance: OR, 4.12; urinary tract infection: OR, 3.02; falls without injury: OR, 2.08).[16] The authors concluded that, based on the current evidence, valproate preparations cannot be recommended for the treatment of agitation in persons with dementia.[16]

Sink et al[10] reported on two small, randomized controlled trials of carbamazepine for the treatment of BPSD. [17,18] In the first study, which was a 6-week, randomized, multisite, parallel-group study of nursing home patients with agitation and dementia, participants were randomized to individualized doses of carbamazepine or to placebo.[17] At 6 weeks, the modal carbamazepine dose was 300 mg per day, the mean daily dose of carbamazepine was 304 mg per day, and the mean serum level was 5.3 µg/mL. Over the study period, CGIC ratings showed global improvement in 77% of patients taking carbamazepine and in 21% of patients taking placebo, and the mean total Brief Psychiatric Rating Scale (BPRS) score decreased by 7.7 points for the carbamazepine group and 0.9 point for the placebo group. The secondary analyses confirmed that the positive changes were due to decreased agitation and aggression. Carbamazepine was generally well tolerated, and no changes in cognition or functional status were observed among participants. The authors also found that the perception of staff time needed to manage agitation showed a decrease for the drug but not for placebo.[17] The second carbamazepine study identified by Sink et al[10] was a 6-week, randomized, double-blind, placebo-controlled, parallel-group trial involving 21 persons with agitation (16 completers) who had been treated unsuccessfully with antipsychotics.[18] Patients were randomized to carbamazepine (400 mg/day) or to placebo. The authors found greater improvement on the CGIC (*P* = .055) and the BPRS Hostility item (*P* = .009) in the group taking carbamazepine; however, there was a trend toward worsening on the BPRS Hallucination item (*P* = .067) in persons taking carbamazepine. Overall, the drug demonstrated modest clinical benefit in these patients, with particular benefit in reducing hostility. Adverse events from the drug were mild in severity, occurring in four of nine carbamazepine-treated persons and eight of 12 placebo-treated persons. Of the 13 adverse events reported in the carbamazepine-treated group, diarrhea was the most common, occurring in three subjects intermittently for less than 2 weeks. Of the 18 adverse events reported among persons receiving placebo, vomiting was the most common, occurring in two subjects.[18] Based on the findings of these two trials, [17,18] along with the fact that there is a Black Box warning on hematologic toxicity for carbamazepine [40] and on potential drug-drug interactions between carbamazepine and other drugs commonly prescribed to elderly individuals, there is insufficient evidence of benefit to recommend the routine use of carbamazepine in the treatment of BPSD.[10]

In a 2008 review by Konovalov et al19of anticonvulsant mood stabilizer trials, two randomized controlled trials of carbamazepine and five of valproate were identified. The authors reported the following: one study showed statistically significant improvement of BPSD in the medication group as compared with the placebo group; five studies showed no significant differences in the primary outcomes between the two groups; one study showed statistically significant worsening of the symptoms experienced in the medication group as compared with the placebo group; and the majority of the studies reported that adverse effects were significantly more frequent in the medication group than in the placebo group. The authors concluded that, although anticonvulsant mood stabilizers are clearly beneficial in some patients, these agents cannot be recommended for routine use in the treatment of BPSD at the present time.[19]

Cognitive Enhancers. Sink et al[10] reported on two meta-analyses[20,21] and six randomized controlled trials of various cholinesterase inhibitors with neuropsychiatric symptom outcomes. Five of the eight studies reported statistically significant benefit with these medications. In the first meta-analysis, the investigators included two trials of galantamine that provided data for BPSD using the Neuropsychiatric Inventory (NPI) total scores.[20] The 3-month trial failed to reach statistical significance, while the 6-month trial demonstrated statistically significant results in favor of treatment with galantamine at daily doses of 16 mg (weighed mean difference [WMD], -2.4; 95% CI, -4.5 to -1.3) and 24 mg (WMD, -2.4; 95% CI, -4.6 to -0.1). In general, galantamine appeared to be well tolerated but, as expected, tended to produce a higher frequency of gastrointestinal adverse events. In the second meta-analysis, the investigators found that patients randomized to cholinesterase inhibitors (donepezil, galantamine, metrifonate, physostigmine, tacrine, and velnacrine [of these drugs, only donepezil and galantamine are FDA-approved for the treatment of AD]) improved 1.72 points on the NPI (95% CI, 0.87-2.57 points) and .03 point on the Alzheimer's Disease Assessment Scale-Noncognitive (ADAS-noncog; 95% CI, 0.00-0.05 point), as compared with placebo.[21] No difference was found in efficacy among the various cholinesterase inhibitors. The authors concluded that, based on these results, cholinesterase inhibitors have a modest beneficial impact on neuropsychiatric and functional outcomes for persons with AD.[21]

In their meta-analysis, Sink et al[10] found that although memantine may be of benefit in cognitive and functional domains, it does not appear to provide a clinically significant benefit in the treatment of BPSD in patients with moderate-to-severe AD. A database analysis of two randomized studies regarding the effects of memantine treatment on behavioral symptoms measured using the 12-item version of the NPI found that, in both studies, the change in NPI total scores at end point was consistently in favor of treatment with memantine as compared with placebo and donepezil, reaching statistical significance in the study of combination therapy with memantine and donepezil (*P* = .002).[22] The authors concluded that memantine has a beneficial effect on the behavioral symptoms of patients with moderate-to-severe AD, with the most pronounced effect found in the agitation/aggression domain of the NPI.[22] A 2008 meta-analysis included six randomized, parallel-group, double-blind studies that rated BPSD with the NPI; the overall efficacy of memantine on the NPI was measured using a t-test to determine the average difference between means across the studies and applying a random effects model.[23] Data on NPI outcomes were available for five of the six studies. In those five studies, patients taking memantine (n = 868) improved by 1.99 points on the NPI scale (95% CI, -.08 to -3.91 points) as compared with patients taking placebo (n = 882) (*P* = .041). The authors pointed out that there are a number of limitations with the current data, including the relatively small effect size for memantine, and concluded that it is unclear at the present time whether memantine produces significant clinical benefit.[23]

Benzodiazepines. In the only double-blind study of a benzodiazepine compound to treat BPSD, Meehan et al [24] compared the efficacy and safety of intramuscular olanzapine, lorazepam, and placebo in treating agitation associated with AD and/or vascular dementia. The investigators found that, at 2 hours, olanzapine (5 mg and 2.5 mg) and lorazepam (1 mg) showed significant improvements over placebo on the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) and the Agitation-Calmness Evaluation Scale (ACES). Olanzapine (5 mg) and lorazepam (1 mg) also showed superiority over placebo on the Cohen-Mansfield Agitation Inventory. At 24 hours, olanzapine (5 mg and 2.5 mg) maintained superiority over placebo on the PANSS-EC, but lorazepam (1 mg) did not. Olanzapine (5 mg) and lorazepam (1 mg) improved ACES scores more than placebo. Sedation (ACES ≥8), adverse events, and laboratory data

were not significantly different between placebo and any of the treatment groups. The Simpson-Angus and Mini-Mental State Examination scores did not change significantly from baseline in any of the medication groups. Finally, no significant differences among treatment groups were seen in extrapyramidal symptoms or in corrected QT interval at either 2 hours or 24 hours, or in vital signs, including orthostasis.[24]

Others. In reviewing the literature, we could not find any published, randomized, controlled trials of lithium, gabapentin, or buspirone for the treatment of BPSD.[10,25,26]

Summary of Pharmacological Treatments

Current evidence indicates the efficacy of short-term pharmacological treatment for BPSD. Although limited, available evidence remains in favor of using atypical antipsychotic drugs, especially risperidone, aripiprazole, and, to a lesser extent, olanzapine in the first-line treatment of BPSD that is resistant to nonpharmacological interventions.[11,12] Evidence indicates that these antipsychotic medications generally should not be continued for longer than 12 weeks [11-13,36]; however, longer-term therapy may be needed in patients who have persistent symptoms, although the data for longer-term treatment with antipsychotics are limited.[11-13] The possible benefits of prescribing these medications should always be weighed carefully against the risks. Careful monitoring and treatment of risk factors for cerebrovascular adverse events such as hypertension, atrial fibrillation, hyperlipidemia, and diabetes mellitus should help reduce not only the risk of cerebrovascular adverse events, but also the risk of death.[39] Antipsychotics should also be prescribed within the recommended dosage ranges to reduce the risk of serious adverse events such as cerebrovascular adverse events and death.[39]

TABLE 3

Common Scales for Assessing Severity of Dementia[a]

Name of Scale	Score Range	Higher Score Signifies
Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)	0-70	Worse cognition
Clinical Dementia Rating (CDR)	0-3	More severe dementia
Functional Assessment Staging (FAST)	1-7	Worse functioning
Global Deterioration Scale (GDS)	1-7	Worse functioning
Mini-Mental State Examination (MMSE)	0-30	Better cognition
Severe Impairment Battery (SIB)	1-100	Better cognition

[a] *Contains information from references 41-46.*

The best pharmacological alternatives to antipsychotics in the treatment of BPSD are anticonvulsants, antidepressants, cholinesterase inhibitors, and memantine, although these drugs may have better efficacy in treating nonaggressive behaviors such as apathy than in treating agitation, aggression, and psychotic symptoms such as delusions and hallucinations.[14-26] Despite the growing evidence for pharmacotherapy for BPSD, none of the medication classes discussed in this article have been FDA-approved for these behaviors and symptoms.[3,10]

Information on common scales used to assess the severity of dementia is listed in **Table 3**.[41-46] An algorithm for the treatment of BPSD is provided in the **Figure**.[1,3-23,39,41-46]

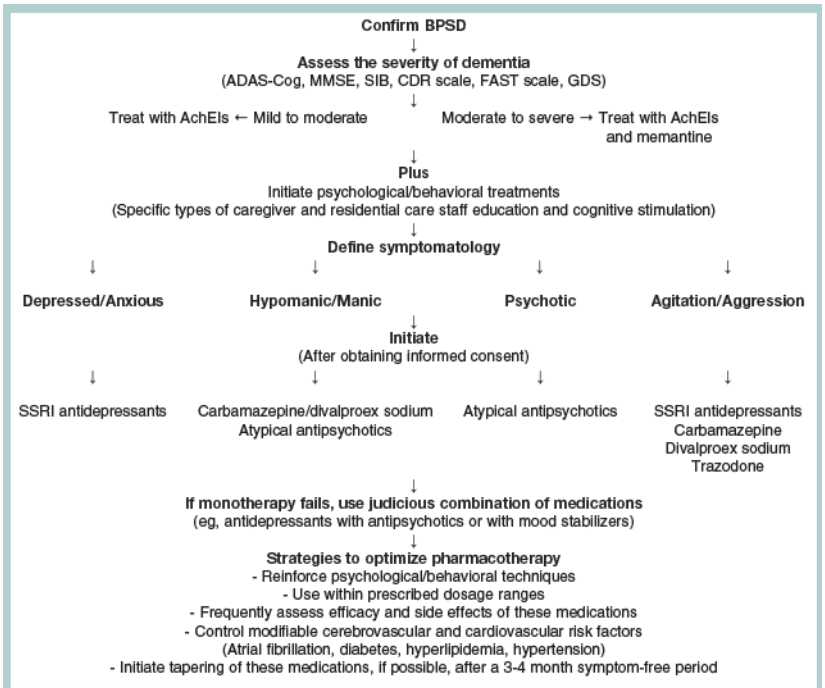

Figure. Algorithm for the treatment of BPSD.

Abbreviations: AchEIs, acetylcholinesterase inhibitors; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive; BPSD, behavioral and psychological symptoms of dementia; CDR, Clinical Dementia Rating; FAST, Functional Assessment Staging; GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination; SIB, Severe Impairment Battery; SSRI, selective serotonin reuptake inhibitor.

Contains information from references 1, 3-23, 39, and 41-46.

Conclusion

BPSD are not uncommon in patients with dementia. Early detection of BPSD will enable clinicians to treat these problem behaviors and thereby reduce morbidity, reduce the costs and burden of caring for these patients, and improve patient and caregiver quality of life. Effective treatment strategies for BPSD include various nonpharmacological and pharmacological approaches. The treatment of these behaviors should ideally start with nonpharmacological approaches, with pharmacotherapy reserved for behaviors that are severe, persistent, and/or resistant to nonpharmacological treatments. Nonpharmacological treatments that have been found to be effective include psychoeducation of caregivers, behavioral therapy, and multisensory therapy.

Evidence indicates short-term efficacy for atypical antipsychotic drugs, especially risperidone, aripiprazole, and, to a lesser extent, olanzapine, in the first-line treatment of BPSD. Pharmacological alternatives to antipsychotics include anticonvulsants, antidepressants, cholinesterase inhibitors, and memantine, although these drugs may have better efficacy in treating patients with nonaggressive behaviors such as apathy. Careful risk-benefit assessment and judicious prescription of these drugs with careful monitoring and treatment of risk factors will reduce the risk of serious adverse events such as cerebrovascular adverse events and death.

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Dr. Tampi is from Yale University School of Medicine, New Haven, CT; Dr. Tampi, Ms. McEnerney, Ms. Thomas, and Ms. Cash are from Masonicare, Wallingford, CT; Ms. Williamson is from St. Francis Medical Center, Hartford, CT; and Dr. Mittal is from BJC HealthCare System, Farmington, MO.

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