



Management of Behavioral and Psychological Symptoms of Dementia

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ABSTRACT

Symptoms of disturbed perception, thought content, mood, or behavior that frequently occur in patients with dementia are defined as the term "Behavioral and Psychological Symptoms of Dementia (BPSD)." The behavioral symptoms of dementia include physical/verbal aggression, agitation, disinhibition, restlessness, wandering, culturally inappropriate behaviors, sexual disinhibition, and hoarding, and the psychological symptoms of dementia are anxiety, depressive mood, hallucinations and delusions, apathy, and misidentification syndrome. With the cognitive decline in Alzheimer's Dementia (AD), the frequency of neuropsychiatric symptoms increases. Apathy, depression, irritability, agitation, and anxiety are the most frequently detected neuropsychiatric symptoms of AD. In the mild stage of AD, affective symptoms are more likely to occur; agitated and psychotic behaviors are frequent in patients with moderately impaired cognitive function. When neuropsychiatric symptoms are first detected, medical conditions, such as delirium, infection, dehydration, diarrhea, and drug interactions, must be ruled out. The treatment of mild BPSD must be started with psychosocial approaches, such as behavioral management, caregiver education, and physical activity. Medications are indicated for BPSD symptoms that are refractory to non-pharmacological interventions or severe or jeopardizing the safety of a patient or others, often in conjunction with non-pharmacological interventions. (*Archives of Neuropsychiatry 2014; 51: 303-312*)

Key words: Alzheimer dementia, behavioral and psychological symptoms of dementia, elderly

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As the global population ages and as life expectancy increases, the prevalence of dementia also increases. There are nearly 35.6 million people with dementia worldwide in 2010, which is estimated to nearly double every 20 years and is expected to reach nearly 115 million by the year 2050 (1).

Alzheimer's disease, the most common form of the dementia, is a devastating disease resulting in a progressive decline in cognition and function. Furthermore, over the course of the illness, nearly 97% of patients develop behavioral or psychiatric symptoms (2), which are referred to as "Behavioral and Psychological Symptoms of Dementia (BPSD)." The International Psychogeriatrics Association consensus group defined the term BPSD as "symptoms of disturbed perception, thought content, mood, or behavior that frequently occur in patients with dementia (3)."

There has been ongoing research for identifying models for characterizing BPSD symptoms neurobiologically; however,

they have been (3) simply grouped as behavioral and psychological symptoms, which are summarized in Table 1 (4).

The overall frequency of BPSD in patients with Alzheimer's disease living in the community is 56%-98% and 91%-96% in care facilities, such as nursing homes (5,6). Behavioral and psychological symptoms of dementia cause significant distress both for the patients and for the caregivers (6,7) and are also a precipitating factor for nursing home care (8). These symptoms are associated not only with burden but also with survival of patients. In a prospective study of 3 years, it was reported that as the number of the BPSD increases (especially the psychotic symptoms), the mortality rate of patients with Alzheimer's disease also increases (9). The most prevalent BPSD symptoms were apathy, depression, and delusions, and the most enduring symptom of BPSD was agitation in a 5-year prevalence study (5).

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Table 1. Behavioral and psychological symptoms of dementia

Behavioral symptoms (Usually identified on the basis of observation of the patient)	Psychological symptoms (Usually and mainly assessed on the basis of interviews with patients and relatives)
Physical aggression	Anxiety
Screaming	Depressive mood
Restlessness	Apathy
Agitation/Catastrophic reactions (Verbal/Physical)	Hallucinations and delusions (Psychosis of Alzheimer's Disease)
Wandering	Misidentification syndromes
Culturally inappropriate behaviors	Sundowning
Sexual disinhibition	Elation
Hoarding	Negativism
Cursing	

The Assessment of the Behavioral and Psychological Symptoms of Dementia

The management of BPSD must begin with a broad clinical assessment and getting information from a reliable caregiver, besides examining the patient. The clinician must ask the caregiver about the most burdensome symptoms, because the symptom that seems to be problematic for the clinician may not be an issue for the caregiver. So, the clinician could be aware of the most distressing symptom, which is to be preferentially treated.

Besides that, the caregiver-patient interaction also interferes with BPSD symptoms, such as caregivers who are younger, less educated, more depressed, more burdened, (10). So, the clinician must take into consideration that the caregiver characteristics could influence the BPSD when managing Alzheimer's dementia.

The caregivers are sometimes prone to mention only the burdensome symptoms during the assessment of the patient; thus, an objective assessment with a reliable scale, such as the Neuropsychiatric Inventory, is preferred (11,12). The Neuropsychiatric Inventory is the most extensively used scale for BPSD, for which many different versions are also available, such as Neuropsychiatric Inventory-Nursing Home (NPI-NH; for patients living in nursing homes), NPI- Questionnaire (a shorter form, NPI-Q) and NPI- Clinician (a form in which assessment is made not only by the caregiver but also by the clinician and the patient, as well) (12).

Treatment of the Behavioral and Psychological Symptoms of Dementia:

If any BPSD emerges for the first time, before considering any non-pharmacological or pharmacological therapies, physical health problems must be screened thoroughly, because physical health problems, such as urinary tract-chest-dental infections, diarrhea, dehydration, and pain, may precipitate BPSD symptoms (13). For example, urinary tract infections are atypical or asymptomatic in elderly with dementia or silently come into sight. Also, patients can not declare their symptoms properly; so, it is difficult to detect these infections, which, in

the course of time, cause BPSD symptoms and even delirium (13). Another precipitating factor for BPSD is visual and auditory impairments, which have been correlated with delusions and visual hallucinations (14). The drug-drug interactions must be also overviewed to elicit any side effects inducing BPSD symptoms, such as hyponatremia caused by serotonergic antidepressants, which may cause agitation or confusion.

After screening any physical health problem or drug-induced side effects that may precipitate BPSD, the symptoms of BPSD that are not so severe must be evaluated with non-pharmacological interventions (15,16,17). Optimizing the anti-dementia drugs is also recommended as the next step, because psychotropics are not yet perfectly suitable for the treatment of BPSD due to not having enough efficacy, such as antipsychotics and antidepressants. Besides, having many serious side effects, such as stroke, myocard infarctus and pneumonia in dementia patients limits the usage of the antipsychotics.

If BPSD can not be controlled/reduced by the non-pharmacological interventions or if BPSD are so severe that it may cause harm to the patient or the caregiver, pharmacological treatment must be considered with on-going non-pharmacological interventions (17). The algorithm for the treatment for the BPSD of Alzheimer's dementia is shown in Figure 1 (17,18,19,20).

Non-Pharmacological Treatments of BPSD

As mentioned before, non-pharmacological treatment strategies are recommended as the firstline management strategy for BPSD by many guidelines (17), such as the American Association for Geriatric Psychiatry (21) and American Geriatric Society (18). There have been many different types of non-pharmacological interventions for the BPSD, which are listed in Table 2 (22,23,24). According to the meta-analysis conducted by Brodaty et al. (22), nonpharmacological interventions were effective in reducing behavioral and psychological symptoms, with an overall effect size of .34 (95% CI=.20-.48; z=4.87; p<.01), as well as in ameliorating caregiver reactions to these behaviors, with an overall effect size of .15 (95% CI=.04-0.26; z=2.76; p=.006). Another systematic review examining the non-pharmacological interventions identified a modest effect of behavior management therapies, education of the caregiver and the staff of nursing home, and also the cognitive stimulation techniques (25). However, the effect of cognitive rehabilitation was not longstanding in the studies (26) and also needs equipment and education, which are not yet practical. Emerging evidence about alternative and easy-to-use non-pharmacological interventions, such as aromatherapy with lavender oil and Melissa oil (lemon balm), to reduce agitation is accumulating (27,28,29,30). But, in one randomized controlled trial (RCT) with strong methodology, Melissa oil had a 37% improvement in the NPI scores, the same as donepezil and placebo, which could be interpreted as touching and interacting with the patient having the main effect (31).

A discrepancy between the patient's capacity and the demands of the caregivers may trigger BPSD (32). So, the psycho-education or support groups focusing on providing caregivers

Table 2. The non-pharmacological interventions for the treatment of BPSD

- Cognitive Interventions
 - Cognitive Rehabilitation
 - Cognitive Stimulation Therapy
 - Computerized Cognitive Therapy
 - Reality Orientation Therapy
- Stimulant Based Interventions
 - Reminiscence Therapy
 - Validation Therapy
 - Music Therapy
 - Snoezolen (Multisensory stimulation)
 - Simulated Family Presence Therapy
 - Massage and Touch
 - Aromatherapy/Pet Therapy
- Social Activity/Social Interaction
- Physical Activity/Exercise/Dance
- Environmental Interventions
- Interventions For Caregivers and Staff of Nursing Homes
 - Psychoeducation
 - Caregiver Support Group Therapy
 - Case Management/ Counselling
- Multicomponent Interventions

with knowledge of dementia, skills, and/or support to help them cope with the stress of caregiving may reduce the BPSD and even delay nursing home placement of the patient (33,34).

Another non-pharmacological intervention is encouraging social and physical activity in the demented elderly, which is still one of the main strategies for the prevention of dementia (35,36). In the real-life residential facilities and dementia clinics, non-pharmacological interventions, such as psychoeducation and support of the caregiver, providing social/physical activities for the elderly seems to be more easily put into practice.

Pharmacological Treatment of BPSD

Acetylcholinesterase inhibitors: Although most guidelines address adding or maximizing the dose of acetylcholinesterase inhibitors (ChEIs) for the treatment of BPSD (17), the efficacy of ChEIs is generally significant but small according to the RCTs and meta- and pooled analyses (37,38,39,40,41).

Acetylcholinesterase inhibitors are more beneficial for depression/dysphoria, anxiety, and apathy/indifference (42,43). However, some studies using ChEIs suggest that ChEIs did not confer any significant effect on clinically prominent agitation for short-term (3 months) treatment, which was speculated to be a subgroup of AD patients with more treatment-resistant BPSD symptoms or the heterogeneous precipitants of agitation, such as environmental factors, sleep disorders, etc. (44,45,46).

Albeit it not so effective in neuropsychiatric symptoms of Alzheimer's dementia, ChEIs have shown more treatment benefits for the apathy, anxiety, and psychotic symptoms, such as visual hallucinations, in dementia with Lewy bodies (47).

In the absence of alternative safe and effective psychotropic options, currently, the use of ChEIs is an appropriate pharmacological strategy for the management of BPSD in Alzheimer's disease.

Memantine: With regard to meta-analyses and pooled analyses, memantine has some advantages over placebo for the BPSD, such as agitation/aggression, irritability/lability, and psychosis (48,49,50,51). In the most recent Cochrane meta-analysis, 2.76 points of decrease was reported on the 144-point NPI (95% CI 0.88 to 4.63, $P=.004$) in patients with moderate to severe AD with memantine, but no efficacy on NPI and activities of daily living was assessed for the mild to moderate AD at 6 months (52). But, memantine was shown to be slightly less likely to develop agitation against placebo (7.7% versus 9.3%, OR .78, 95% CI .61 to .99, $P=.04$) (52). However, all this evidence has been drafted from the secondary outcomes. The only RCT evaluating the effect of memantine directly on clinically significant agitation (Cohen-Mansfield Agitation Inventory- CMAI score ≥ 45) as primary outcome did not find any significant advantage of memantine versus placebo at Week 6 or 12. But, memantine showed a difference on the total NPI at Weeks 6 (-6.9; -12.2 to -1.6; $p=.012$) and 12 (-9.6; -15.0 to -4.3 $p=.0005$) (53). Another recently published trial, although having some sort of methodological limitations, did not find any efficacy of memantine on severe agitation as a primary outcome in community-dwelling elderly patients with moderate to severe Alzheimer's dementia (54). The effect of memantine for milder agitation in dementia has not been searched yet.

The evidence for the efficacy of combination therapy (ACEI and memantine combination) has been scarce for the BPSD as a primary outcome (55). One study did not find any benefit of donepezil and memantine combination therapy on cognition and behavior, either (56). The latest meta-analysis revealed a small but significant advantage of adding memantine to ACEI therapy on behavior and mood (SMD=-.17, 95% CI -.32 to -.03) and cognition (SMD=-.25, 95% CI -.36 to -.14) but not on function/ADL at 6 months (57).

Antidepressants: Serotonergic dysfunction has been shown to contribute to the pathogenesis of some BPSD symptoms, such as aggressive, impulsive behavior and psychosis (58). With the emerging data about the serious side effects of antipsychotics, antidepressants have been increasingly prescribed for the treatment of BPSD (59). For the treatment of BPSD, a recent Cochrane review analyzing 9 RCTs concluded that the SSRIs sertraline and citalopram were associated with a modest improvement in symptoms of agitation when compared to placebo, and SSRIs are well tolerated against placebo, typical antipsychotics, and atypical antipsychotics (60).

Table 3. Psychotropics mainly used for the treatment of BPSD in elderly (Adapted from references 18,19,20)

Psychotropic	Starting dose (mg/day)	Incremental dose (mg)	Average target daily dose	Common side effects in elderly
Antipsychotics				
Risperidone	.25-.5	.25-.5	1-1.5	Sedation, extrapyramidal symptoms, metabolic syndrome, falls, akatisia
Olanzapine	2.5	2.5	5	
Quetiapine	12.5-25	12.5-25	150	
Aripiprazole	2.5-5	2.5-5	10-20	
Antidepressants				
Citalopram	10	10	10-40	Gastrointestinal symptoms, anxiety, insomnia
Escitalopram	5	5	10-20	sexual dysfunction, QT prolongation, SIADH, sedation
Sertraline	25	25	50-200	
Mirtazapine	7.5-15	15	15-45	
Venlafaxine	37.5	37.5	37.5-150	
Trazodone	25	25	50-200	
Benzodiazepine/ Non-benzodiazepine Hypnotic				
Lorezapam	.25	.25	1	Sedation, falls, memory impairments,
Zopiclone	3.75	3.75	7.5	dependence, rebound insomnia

There have not been any statistically significant differences in the effectiveness between SSRIs and atypical or typical antipsychotics for the treatment of BPSD (61,62).

The evidence for how long the antidepressants would be used for BPSD is lacking, although in recent small studies, discontinuation of antidepressants was associated with significantly worse depressive symptoms (63) and a significant worsening of neuropsychiatric symptoms (64).

There is still insufficient evidence on the long-term safety of antidepressant use for the elderly and for neuropsychiatric symptoms in patients with dementia, as well (65).

Although having some benefit for the treatment of BPSD, the meta-analysis and RCTs did not show any efficacy of SSRIs and mirtazapine for the depression in the dementia (66,67,68). The lack of evidence for the efficacy of antidepressants in depression of dementia can be attributed to the diagnostic criteria of depression in dementia, because depression could be a symptom of dementia or a syndrome different from dementia, only having an overlapping symptom profile from the neurobiological perspective (68).

For milder depression, non-pharmacological interventions, such as physical activity and planned positive activities, may be recommended (69,70). However, if moderate to severe depressive symptoms are apparent in dementia, antidepressants, such as SSRIs, venlafaxine, and mirtazapine, should be chosen (Table 3).

Trazodone has long been used as an augmenting agent in depression or as a relatively safe sleeping pill for insomnia (71). For the treatment of BPSD, 2 RCTs (72,73) and a Cochrane review (74) examining the efficacy of trazodone demonstrated that trazodone with doses 50-300 mg per day was not different

than placebo in efficacy or in adverse events. Trazodone could be preferred as a sedative drug for the insomnia and also agitation associated with insomnia in dementia patients at doses between 25-200 mg per day.

With the evidence of antidepressants having modest efficacy for BPSD and having additional benefit for depression and being more well tolerated than antipsychotics, starting an antidepressant with mild-moderate neuropsychiatric symptoms in Alzheimer's dementia is recommended (70,75) (Figure 1). Which antidepressant is to be chosen generally for the BPSD and depression in dementia depends on drug interactions, side effects, and protein-binding capacity of the drugs (Table 3). Although they do not have any risk for the death in dementia patients, serotonergic antidepressants have some serious adverse effects, such as falls, fractures (76), bleeding (77), and hyponatremia (78) in the elderly.

Antipsychotics: Antipsychotics had been widely used for BPSD treatment, especially because of their sedative properties. But, due to emerging data about the serious side effects and increased risk of mortality in patients with dementia (79), the percentage of antipsychotic usage for the BPSD has been eventually decreasing (59).

There have been not many studies about the typical antipsychotics for the treatment of BPSD. The typical antipsychotic haloperidol was shown to only improve agitation in dementia (80), and in another 6-month RCT, psychosis and hostile suspiciousness factors were decreased with haloperidol (81). Regarding serious side effects, such as cognitive worsening, tardive dys-

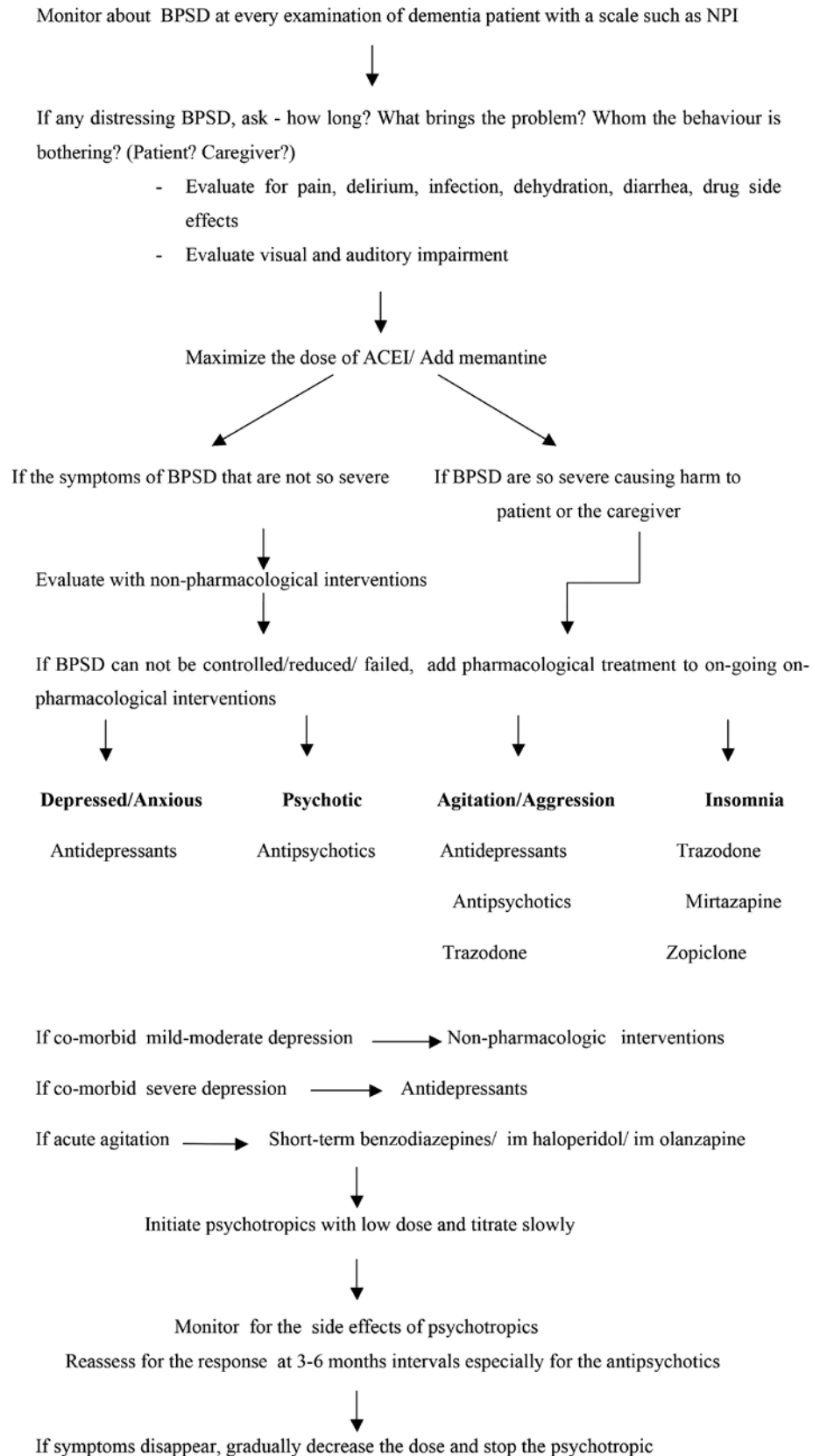


Figure 1. Algorithm for the Diagnosing and Treatment of BPSD (adapted from the references 17,18,19,20)

kinesia, and anticholinergic and cardiovascular side effects in the elderly, haloperidol is not recommended as the first choice. In harmful conditions, such as acute agitation/aggression and when the patient refuses oral forms, intramuscular haloperidol could be recommended only in low doses.

For the atypical antipsychotics, the latest meta-analysis including 16 RCTs, searching olanzapine, quetiapine, risperidone, clozapine, aripiprazole, and ziprasidone, reported a significant improvement in psychosis with risperidone and a significant improvement in aggression with risperidone and olanzapine treatment compared to placebo (82).

The effect of antipsychotics for cognition in dementia is another area for research. In a small RCT, compared to rivastigmine, quetiapine was associated with cognitive deterioration, even in low doses, such as 25-50 mg per day in a 26-week duration (83). But, the effect of atypical antipsychotics on cognition is still to be proven (84).

Both the typical and the atypical antipsychotics have been significantly increasing the mortality rates in dementia patients (79,85). Haloperidol was associated with the highest mortality rates (relative risk=1.54, 95% confidence interval [CI]=1.38-1.73), followed by risperidone, olanzapine (relative risk=.99, 95% CI=.89-1.10), and quetiapine (relative risk=.73, 95% CI=.67-.80) (85). The mortality rates with haloperidol were highest during the first 30 days and decreased significantly over time in dementia out-patients. The mortality risk was also higher for haloperidol compared to risperidone in dementia patients residing in nursing homes (86). The mortality risk increases with higher doses of antipsychotics (86). Some studies have demonstrated contrary findings; a 5-year retrospective study with data from 89,000 veterans showed that lower doses of atypical antipsychotics (olanzapine<2.5 mg/d, quetiapine<50 mg/d, and risperidone <1 mg/d) did not increase the mortality rates, but not haloperidol, even in low doses (87).

Besides increased mortality rates, antipsychotics have other serious side effects in dementia patients. Typical antipsychotics and risperidone have increased extrapyramidal side effects, and tardive dyskinesia risk. Atypical antipsychotics, but especially risperidone and olanzapine, have increased risk of stroke, myocardial infection, venous thrombo-emboli, and pneumonia. (19,39,88,89).

Regarding the treatment of severe agitation/aggression and/or psychosis, most of the clinical practice guidelines recommend risperidone, olanzapine, and haloperidol if non-pharmacological approaches fail or fail in combination with both groups of anti-dementia drugs (17). However, antipsychotics are not yet approved for the treatment of BPSD in patients with dementia by the US Food and Drug Administration (FDA), and also, the FDA has warned about the risk of increased mortality and stroke with all antipsychotics in people with dementia. But, only risperidone is licensed for persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological interventions and when there is a risk of

harm to self or others for the short-term treatment up to 6 weeks in the United Kingdom (90).

Because of the serious side effects of antipsychotics in dementia, the duration of antipsychotic treatment is still a question. As shown by some studies, such as DART-AD, discontinuing antipsychotics had no difference in the NPI scores and functional status than continuing the antipsychotic for the 6- and 12-month follow-up. The only significant deterioration in neuropsychiatric symptoms was seen in the patients with more severe behavioral symptoms (NPI scores>14) in the DART-AD study. But, the longer-term use of antipsychotics in the study was associated with increased mortality rate versus placebo in the follow-up (91). Another study investigated the relapse rates after discontinuation of risperidone for agitation/aggression and psychosis against placebo in AD for 16 weeks. The study showed that relapse rates were higher for the group that was switched from risperidone to placebo than for the group continuing risperidone (48% vs. 15%; $P=.02$; hazard ratio: 4.88; 95% CI: 1.08 to 21.98; $P=.02$) (92). Also, earlier discontinuation of risperidone increased the risk of relapse (92). Newly released Cochrane meta-analysis results declared that patients having BPSD can be withdrawn from chronic antipsychotics without deteriorating effects on BPSD, but it remains uncertain whether withdrawal is beneficial for cognition or psychomotor status (93).

Because of the modest efficacy of antipsychotics, their benefits often still outweigh their risks in patients with BPSD. In the absence of other effective agents for BPSD, using antipsychotics cautiously and for the possible short term, after informing the patients and the families, is recommended. There should be an ongoing assessment of benefits versus harms, and consideration for withdrawing the medications should be made periodically, such as every 3 to 6 months (17,18,19,20) (Figure 1).

Anticonvulsants: There have been only 2 RCTs with divalproex sodium (94,95), 1 RCT with carbamazepine (96), and 1 RCT with oxcarbazepine (97). One Cochrane meta-analysis about divalproex sodium examining agitation did not find any efficacy and also found higher adverse events versus placebo, such as sedation, falls, infection, and gastrointestinal disorders (98). One multi-center RCT using divalproex sodium did not delay emergence of agitation or psychosis or slow cognitive decline in patients with moderate Alzheimer disease for 24 months and was also associated with hippocampal and whole-brain volume atrophy (99). Recently, a small study with only 7 patients showed that low-dose gabapentin could be used for aggressive behaviors in vascular and Alzheimer dementia without adverse reactions (100).

One more review for mood stabilizers in BPSD (101) showed that CBZ is effective for BPSD at 300-600 mg per day for 6-8 weeks, especially for aggression and hostility. But, having serious adverse effects, such as fatal skin reactions, and also drug-drug interactions limits the use of CBZ for the BPSD. There has been scarce evidence for the other anticonvulsants. Nonethe-

less, the guidelines have not addressed the anticonvulsants in the management of BPSD, and the use of anticonvulsants must be avoided with the emerging data about the side effects and significant toxic effects on the brain (17,102).

Benzodiazepines: Although reported to be effective for aggression in dementia in former studies (103), serious side effects, such as daytime sedation, cognitive deterioration, and increased risk of falls in the elderly, restrained the use of benzodiazepines, especially the short- and intermediate-acting ones, for the demented and also for the healthy elderly (104).

According to a systematic appraisal of guidelines of management of BPSD, benzodiazepines are solely recommended in dementia guidelines when a patient with dementia has agitation/aggression and/or psychosis but only for the short term (17). One RCT showed that intramuscular (im) lorazepam was effective for excitation in dementia only for 2 hours but not for 24 hours; im olanzapine had a sustained positive effect for 24 hours (105).

In daily clinical practice, when agitation/aggression or psychosis can not be controlled with non-pharmacological interventions and psychotropics, benzodiazepines with less inactive metabolites, such as lorazepam (.5-1 mg/day), could be prescribed as a p.r.n. agent for a short time (Table 3). Benzodiazepine use should be limited to only brief stressful episodes, such as change in residence or an anxiety-provoking event. At the same time, the continuing antipsychotic should be exchanged with a more potent one, or the dose of antipsychotic should be increased to a more effective dose.

Treatment of psychiatric and behavioral disturbances in dementia is complex and may require several interventions as part of a comprehensive care plan. The treatment of BPSD should be personalized for each patient to improve the neuropsychiatric symptoms and quality of life of the patient and also the caregiver.

Because of the modest efficacy of antipsychotics, their benefits often still outweigh their risks in patients with BPSD. In the absence of other effective agents for BPSD, using antipsychotics cautiously and for the possible short term, after informing the patients and the families, is recommended. There should be an ongoing assessment of benefits versus harms, and consideration for withdrawing the antipsychotics should be made periodically, such as every 3 to 6 months.

At present, the best strategy for the treatment of BPSD seems to be non-pharmacological interventions first, and if they do not work out, they can be combined with appropriate pharmacological interventions. Further investigations are needed for more effective and safer pharmacological treatment options, besides encouraging non-pharmacological interventions.

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