
Recommendations for the Management of Behavioral and Psychological Symptoms of Dementia

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ABSTRACT: Background: The behavioral and psychological symptoms of dementia (BPSD) are common, serious problems that impair the quality of life for both patient and caregiver. In order to provide recommendations based upon the best available evidence, a qualitative literature review was performed. **Methods:** A search of the English language medical literature published between 1966 and 2000 was performed. The quality of the studies was assessed by considering the subjects, trial design, analysis and results. Final recommendations were based upon the quality of available evidence. **Results:** The management of BPSD begins with a thorough assessment to search for underlying causes of behaviour change. Concomitant medical illness should be treated and sensory impairment ameliorated. Nonpharmacological approaches should be instituted prior to medication use. These interventions include music, light, changes in level of stimulation and specific behavioral techniques. Antipsychotics are the best studied pharmacological intervention for agitation and aggression and have demonstrated modest but consistent efficacy. Antidepressants such as trazodone and selective serotonin re-uptake inhibitors, as well as anticonvulsants such as carbamazepine and valproic acid have also demonstrated efficacy. Benzodiazepines can be used for short-term treatment as p.r.n. agents when necessary. Pharmacotherapy must be monitored closely for both effectiveness and side effects, with consideration of medication withdrawal when appropriate. **Conclusion:** The management of BPSD can significantly improve the quality of life for the patient and caregiver. Their assessment and management are essential components of the treatment of dementia.

RÉSUMÉ: Recommandations pour la prise en charge des symptômes comportementaux et psychologiques de la démence. Introduction: Les symptômes comportementaux et psychologiques de la démence (SCPD) sont des problèmes fréquents et sérieux qui altèrent la qualité de vie du patient et de l'aidant. Une revue qualitative de la littérature a été effectuée afin de fournir des recommandations basées sur les données scientifiques disponibles. **Méthodes:** Une recherche de la littérature médicale de langue anglaise publiée entre 1966 et 2000 a été effectuée. La qualité des études a été évaluée en considérant les sujets, le plan de l'étude, l'analyse et les résultats. Les recommandations finales ont été fondées sur la qualité des observations disponibles. **Résultats:** La prise en charge des SCPD commence par une évaluation minutieuse pour rechercher les causes sous-jacentes du changement de comportement. Les maladies concomitantes devraient être traitées et les déficits sensoriels améliorés. Des approches non pharmacologiques devraient être instituées avant de prescrire une médication. Ces interventions incluent la musicothérapie, la photothérapie, les changements dans le niveau de stimulation et l'utilisation de techniques comportementales spécifiques. Les antipsychotiques constituent l'intervention pharmacologique la mieux étudiée pour traiter l'agitation et l'agressivité. Ils ont démontré une efficacité modeste mais constante. Les antidépresseurs tels le trazodone et les inhibiteurs sélectifs de la recapture de la sérotonine de même que des anticonvulsifs tels la carbamazépine et l'acide valproïque sont également efficaces. Les benzodiazépines peuvent être utilisées à court terme, p.r.n. La pharmacothérapie doit être surveillée étroitement tant au point de vue de son efficacité que de ses effets secondaires, avec réévaluation de sa pertinence. **Conclusion:** La prise en charge des SCPD peut améliorer significativement la qualité de vie du patient et des aidants. Leur évaluation et leur prise en charge sont des composantes essentielles du traitement de la démence.

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The behavioral and psychological symptoms of dementia (BPSD) include delusions, hallucinations, misidentifications, agitation, wandering, pacing, restlessness, disinhibition, apathy, negativism, emotional lability, depression, anxiety, sleep disturbance and sexually inappropriate behaviours.¹ While not included as diagnostic criteria for dementia by DSM-IV² or the NINCDS-ADRDA,³ behaviours such as paranoia, depression, euphoria and apathy were recognized by Alzheimer in the initial description of the illness that bears his name.⁴ Historically, the focus on BPSD began only recently, prompted by an early study by Rabins et al.,⁵ who interviewed caregivers of patients with dementia. While these behaviours were noted in 50-90% of patients, caregivers considered physical aggression the most

serious problem that they encountered, rating it more frequently as a serious problem than the memory disturbance itself. The significance of BPSD was recently endorsed by both the United States Alzheimer's Association⁶ and the International Psychogeriatric Association¹ as research priorities.

The phenomenology and prevalence of BPSD have been

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documented in numerous studies,⁷⁻¹² with estimates of frequency of up to 90% of patients at some point during the course of the illness.⁶ While likely most common in long-term care institutions,¹³⁻¹⁵ they occur frequently in outpatient populations and community samples as well.^{8,16} Many of these behaviours are most prevalent during the moderate and moderately severe stages of dementia,⁸ though symptoms such as agitation, apathy and aberrant motor behaviour may continue to increase with progressive cognitive decline.^{17,18} BPSD are common in both Alzheimer's disease (AD)¹⁹⁻²² and vascular dementia,²³ and may occur even more frequently and earlier in the course of the frontotemporal dementias²⁴ and dementia with Lewy bodies (DLB).²⁵ Besides representing a primary source of stress for caregivers,⁶ behaviours such as agitation and aggression can contribute to the institutionalization of demented patients.^{26,27} Conversely, even modest improvements in these behaviours can result in significant improvements in the quality of life for both patient and caregiver.²⁸

METHODS

A comprehensive search of the medical literature using Medline (1996-2000) and Embase (1974-2000) databases was conducted. Key words included: dementia, behavior, behavior therapy, drug therapy, antipsychotic agent and antidepressant agent. Manual cross-referencing of bibliographies from all papers and recent reviews was also done. The quality of the studies was assessed by considering the subjects, trial design, analysis and results. Final recommendations were based upon best available evidence utilizing criteria developed by the Canadian Task Force on the Periodic Health Examination.²⁹ An earlier version of this paper served as a source document for the Canadian Consensus Conference on Dementia.³⁰ These recommendations do not include the management of depression and depressive symptoms which have been dealt with in another paper in this series.

Management

Assessment

The management of BPSD requires a multifaceted plan which includes assessment and diagnosis, ensuring the safety of the patient, caregiver and co-residents, choosing and monitoring target symptoms, instituting environmental and behavioral interventions and initiating and monitoring pharmacotherapy if necessary. Because patients with dementia are highly susceptible to delirium, the assessment of new onset BPSD must include a physical examination and appropriate laboratory investigations to rule out concomitant medical illness (for example, urinary tract infections). Even chronic medical conditions (for example, arthritis) should be optimized, as stimuli such as pain, constipation and shortness of breath may cause agitation, restlessness and aggression. Optimization should also include hearing and vision, as sensory impairment can lead to behaviours such as agitation and paranoia.^{31,32} The importance of considering sensory impairment was recently highlighted in a study comparing AD patients with and without visual hallucinations.³³ Visual acuity was significantly more impaired in patients with hallucinations and none of the patients who presented with visual hallucinations had normal acuity. When

vision was improved by refraction in a portion of those patients with visual hallucinations, most of these were free of hallucinations on follow-up. A review of concomitant medications is essential as at least one study has suggested that 16% of demented patients who presented to a regional psychogeriatric service with agitation, aggression, confusion, or disorientation had causes that were attributable to medications.³⁴

As part of the initial assessment, safety issues must be considered. BPSD can increase the risk of suicide as well as physical aggression and violence. While caregiver and co-resident safety need to be assessed, behaviours such as perseverative screaming and intrusive wandering may place the patient at risk from physical harm by other residents whom they disturb. Finally, while wandering out of a safe, protected environment is potentially dangerous, wandering can also increase the risk of falls, particularly when there is a pre-existing gait disturbance, or the environment contains dangerous obstacles such as throw rugs, poor lighting or low tables.

The choice and characterization of target symptoms is a frequently overlooked but important aspect of management. Along with the caregiver, the clinician should document the nature, intensity, frequency, precipitants and consequences of each behaviour.³⁵ While numerous scales for BPSD have been designed, all have relative strengths and weaknesses,³⁶ and there is no single scale that has attained the almost universal acceptance of the Mini Mental State Examination³⁷ for cognition. Several useful scales with documented validity and reliability include the Behavioral Pathology in Alzheimer's Disease Rating Scale,⁸ the Neuropsychiatric Inventory,³⁸ and the Cohen-Mansfield Agitation Inventory.^{39,40} The systematic documentation of behaviours provides for a more accurate assessment of the effectiveness of interventions, as well as engages the caregiver in the management plan even prior to initiation of therapy. The value of systematic behavioral assessments has also been demonstrated in a study by Nilsson et al.⁴¹ In an attempt to demonstrate the reliability and validity of a newly designed scale to measure aggression in the elderly, these investigators asked staff on long-term psychogeriatric wards to use the scale for six weeks. The scale required staff to document the nature of the aggression, the antecedents and the consequences.⁴² The number of aggressive incidents decreased from 91 at baseline to 16 at week six, without any other changes in management. This structured approach to observation likely allowed the staff to recognize, anticipate and avoid provocative events.

Nonpharmacological interventions

Nonpharmacological interventions for BPSD include a variety of treatments such as environmental modifications, light therapy, music therapy, pet therapy, activity therapy (for example, exercise, dancing, social interaction, etc.) and specific behavioral techniques.⁴³ Extensive clinical experience with these techniques support their use, with some investigators describing them as possibly more effective and better tolerated than pharmacological approaches.⁴⁴ Unfortunately, there are almost no large, randomized, controlled trials of these techniques, though numerous, small studies with intrasubject designs do exist.^{35,45} A recent systematic review of the psychosocial approaches to BPSD found 43 studies which included at least

some measure of behavior pre- and postintervention.⁴⁶ There were only five randomized controlled trials and only one study which was rated as having strong validity. Weakness of study design included small numbers of subjects, poorly characterized study participants, inadequate data collection, high drop-out rates and insufficient statistical analysis. As an example, the only study rated as having strong validity utilized a behavior management program to modify repetitive verbalizations in community-dwelling patients with AD.⁴⁷ This well-designed, carefully documented study included only seven subjects and seven controls. The only large, randomized trial examined a multimodal treatment approach for 89 nursing home residents, which included a daily, structured activities program, as well as staff education and guidelines for psychotropic use. Following six months of these interventions, 29% of treatment subjects exhibited behavioral problems compared with 51% of controls. While subjects in both groups received psychotropics, controls were more than twice as likely to receive antipsychotics or be physically restrained compared with subjects in the treatment group.⁴⁸

Changes to the level of stimulation can have varying effects on patients with dementia and disturbed behaviour. While studies examining methods to increase stimulation by use of activity groups, exercise and social interaction have demonstrated positive results,^{43,48} other studies suggest reduced stimulation may decrease agitation and other problematic behaviours.⁴⁹ Increasing the level of stimulation may occasionally have adverse effects. In a small, case-control study, when subjects with dementia participated in twice weekly group sessions aimed at increasing emotional and intellectual stimulation, improvements on some measures of cognition were noted but there was also a significant increase in restlessness in the treatment group.⁵⁰

Other environmental manipulations include the use of sound and light. Several studies suggest that a variety of music interventions can decrease agitation.⁵¹⁻⁵⁴ Similarly, audio tapes of environmental "white noise" (sounds of gentle oceans and mountain streams) can also significantly reduce agitation.⁵⁵ Finally, several studies have suggested that interventions with bright light might improve sleep-wake cycle disturbances and other behaviours.^{56,57} For example, a recent study administered one hour of bright light every morning using a 10,000 lux full spectrum lamp at three feet. These patients were seated in front of the lamp in a quiet room, with a nurse who reminded them to keep their eyes open for the entire treatment period. Only eight of 15 patients could complete the full four week treatment period but the average number of nocturnal sleep hours increased significantly from 6.4 to 8.1 hours/night. No other changes in behavior could be documented.⁵⁸

Behavioral techniques have been defined as interventions that require clinical problems to be operationalized, emphasize learning experience to modify behaviour, require empirical treatment evaluation, are directive and active in nature and involve use of another person to help achieve therapeutic change.⁴⁵ After systematically documenting behaviours, their antecedents and consequences as described previously, caregivers intervene with a variety of techniques such as differential reinforcement of other behaviours, extinction and time-out.^{43,59} Preliminary studies suggest these techniques can

effectively decrease aggression and disruptive behaviours.^{60,61} While all these interventions are promising, well-designed and controlled trials are required to clearly document their efficacy.⁶²

Pharmacotherapy

General principles

The use of psychotropic medications for the treatment of BPSD can be extremely helpful, especially when patients have failed to respond to environmental and behavioral interventions.^{63,64} While pharmacotherapy should not be considered a "treatment of last resort", there is growing concern that these medications are over-used, misused and administered by staff who are unaware of their expected benefits and potential side effects.⁶⁵ Psychotropic medications for BPSD are used frequently in hospitals,⁶⁶ long-term care facilities^{65,67,68} and the community.⁶⁹ In the United States, concerns about over-use and misuse has led to the enactment of the Omnibus Reconciliation Act (OBRA-87), which established guidelines for the appropriate use of these medications.^{70,71}

There are numerous age-associated changes that affect the pharmacokinetics and pharmacodynamics of psychotropic medications.⁷² For many psychotropics, it will take longer to reach steady state, half-life will be lengthened and elimination will take longer. Elderly patients often require lower dosages and are most susceptible to side effects. Co-morbid illness may increase the potential for adverse events and concomitant medications may increase the potential for drug interactions. A specific concern involves the anticholinergic effects of many psychotropics such as antipsychotics and some antidepressants. In elderly patients with dementia, anticholinergic effects can worsen confusion,⁷³ precipitate delirium,⁷⁴ exacerbate pre-existing cardiac disease and lead to urinary retention in patients with prostatic hypertrophy. Psychotropic medications with anticholinergic properties may also counteract therapy with cognitive enhancers such as cholinesterase inhibitors and acetylcholine agonists.

Following documentation of specific target behaviours and choosing a psychotropic medication with the caveats noted previously, therapy should be initiated at low dosages with increases every three to seven days if necessary. Besides monitoring for effectiveness, adverse effects on cognition, function and gait, as well as excess sedation and changes in blood pressure (orthostatic hypotension) should be documented. The appropriate minimum length of a pharmacotherapeutic trial has not been established but range from two to four weeks for certain medications (for example, antipsychotics, benzodiazepines) to four to eight weeks for others (for example, beta blockers, anticonvulsants, antidepressants). Once patients have responded to a pharmacotherapy, periodic attempts to reduce or withdraw the medications are recommended, though the specific timing of such withdrawal attempts is not supported by data from clinical trials. While a number of antipsychotic discontinuation studies have been published,^{70,75-80} none were randomized, placebo-controlled, outcome was often insufficiently documented and duration of follow-up was short. These studies suggest, however, that at least for some patients, antipsychotic discontinuation is possible and can result in improvements in mood, cognition and functioning. Similar results have also been

noted with benzodiazepine discontinuation.⁸¹ Finally, the specific target symptoms for which pharmacotherapy was prescribed may ultimately determine when, and if, to attempt taper and withdrawal. In a large, naturalistic observational study of mild to moderate AD, Devanand et al⁸² prospectively followed 235 patients over five years. Wandering and agitation were the most persistent problems, delusions and hallucinations were intermediate and depression was rarely persistent. Physical aggression was infrequent (likely due to the mild to moderate nature of the illness in this population) but the authors caution this behaviour not only increased in frequency throughout the observation period but may also become more persistent in the moderate to severe stages of the illness.

There are several popular treatment algorithms for the pharmacotherapy of BPSD that are purportedly based upon a “rational” approach to management.⁸³⁻⁸⁵ For example, Yudofsky et al⁸⁵ have recommended the use of antipsychotics for aggression associated with psychotic symptoms, carbamazepine for aggression with seizures, lithium for aggression with mood symptoms, buspirone for aggression with anxiety and beta blockers for chronic aggression. While such recommendations appear “rational”, there are insufficient data from clinical trials in patients with dementia to support the use of such algorithms. Studies have rarely been designed to examine the differential effects of pharmacotherapy on specific behaviours but more commonly have focussed on broader symptom complexes such as “agitation.” Recommendations from this review will therefore be derived from an evidence-based approach to literature.

Antipsychotics

The best studied pharmacological intervention for BPSD is typical antipsychotic (neuroleptic) medication^{63,64} (Table 1). In a

meta-analysis of well-designed controlled trials published until 1997, these medications attained significantly better improvement rates of 61% compared with 34% for placebo.⁸⁶ Since that review, only one further randomized, placebo-controlled trial has been published.⁸⁷ In that study “standard” dose haloperidol (2-3 mg/day) was significantly better than “low” dose haloperidol (0.5-0.75 mg/day) or placebo for the treatment of psychosis and psychomotor agitation in AD. Response rates ranged from 55-60% with standard doses, 25-35% with low doses of haloperidol, to 25-30% with placebo. While these studies demonstrate consistent but often modest improvement in behaviour, typical antipsychotics are unfortunately associated with prominent side effects including sedation, orthostatic hypotension, anticholinergic effects and extrapyramidal effects. A recent study confirmed the significant risk for developing parkinsonism in patients with dementia, even when treated with very low dosages of typical antipsychotics.⁸⁸ There is also some concern that typical antipsychotics may increase the rate of cognitive decline in patients with AD⁸⁹ and hasten mortality in patients with LBD.⁹⁰

The available atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine) offer significant theoretical advantages over typical antipsychotics in view of their tendency to produce fewer extrapyramidal effects. There are several small case series describing the use of clozapine for BPSD, though significant side effects including falls, bradycardia, delirium and possibly an increased risk for the development of leukopenia limit its usefulness.⁹¹⁻⁹³ Several case reports suggest that olanzapine, in doses between 2.5 and 10 mg/day, can improve a variety of behaviors including agitation, aggression and psychosis in patients with AD and LBD.^{94,95} These reports, however, raise concerns about the precipitation of delirium and worsened

Table 1: Selected Antipsychotics for BPSD^a

Type	Dose Range (mg/day) ^b	Optimal Dosage (mg/day) ^b	Comments
<i>Typical Antipsychotics:</i>			
chlorpromazine	10 - 200		significant sedation, anticholinergic symptoms and orthostatic hypotension
trifluoperazine	1 - 15		significant extrapyramidal effects
thioridazine	10 - 200		significant sedation, anticholinergic symptoms and orthostatic hypotension
thiothixene	1 - 15		–
haloperidol	0.25 - 4	1.0 - 3.0	significant extrapyramidal effects
loxapine	5 - 50		–
perphenazine	2 - 24	4.0 - 8.0	–
<i>Atypical Antipsychotics:</i>			
clozapine	6.25 - 200		significant sedation, anticholinergic symptoms, postural hypotension, leukopenia
risperidone	0.25 - 2.0	1.0	orthostatic hypotension, sedation
olanzapine	2.5 - 10.0	5.0	possible anticholinergic effects
quetiapine	25 - 200		sedation

a - Table modified from Herrmann N, Lanctôt K, Naranjo C. Behavioural disorders in demented elderly patients: current issues in pharmacotherapy. CNS Drugs 1996; 6(4):280-30. Reprinted with permission.

b - Dosages based upon trials for BPSD

Table 2: Selected Nonantipsychotic Medication for BPSD^a

Type	Dose Range (mg/day) ^b	Optimal Dose (mg/day) ^b	Comments
<i>Antidepressants</i>			
trazodone	25 - 300		Use divided doses; possible sedation and orthostatic hypotension
fluoxetine	5 - 20		Possible gastrointestinal side effects including nausea, diarrhoea, and weight loss, drug interactions
sertraline	25 - 100		Possible diarrhoea
paroxetine	10 - 20		Drug interactions
fluvoxamine	50 - 100		Possible nausea, drug interactions
citalopram	10 - 20		
<i>Anticonvulsants</i>			
carbamazepine	100 - 800	300	Adjust dosage for serum levels 4 to 8 mg/ml; possible sedation, gait unsteadiness
valproic acid	500 - 2500	1500	
<i>Beta-Blockers</i>			
propranolol	10 - 240		May require eight weeks for effect; possible bradycardia and hypotension; contraindicated with COPD
pindolol	10 - 60		
<i>Benzodiazepines</i>			
lorazepam	0.5 - 3		Possible sedation, falls, tolerance, withdrawal reactions
oxazepam	10 - 60		
clonazepam	0.5 - 1.5		
<i>Azipirones</i>			
bupirone	10 - 45	30	Possible nausea

a - Table modified from Herrmann N, Lanctôt K, Naranjo C. Behavioural disorders in demented elderly patients: current issues in pharmacotherapy. *CNS Drugs* 1996; 6(4):280-30. Reprinted with permission.

b -Dose ranges derived from studies listed in text

cognition in a proportion of patients, possibly due to olanzapine's anticholinergic effects which have been documented *in vitro*.⁹⁶ Data from a large randomized placebo-controlled trial of olanzapine for BPSD in AD have recently been published, suggesting that at the optimal dose of 5 mg/day, olanzapine was more effective than placebo treating agitation, delusions and hallucinations, with extrapyramidal symptoms no different compared to placebo.⁹⁷ Of note, at this dose, there was no significant increase in central or peripheral anticholinergic effects compared with placebo. Less data are available on quetiapine, though results from a one year open-label study of 78 patients with AD suggest significant improvements in behaviors such as hostility.⁹⁸ A randomized, placebo-controlled trial of quetiapine for BPSD has also recently been completed.

The best evidence for the use of atypical antipsychotics for BPSD is with risperidone. There is a large number of case series which document its use.⁹⁹⁻¹⁰² In low doses, risperidone appears effective and well-tolerated. Side effects have included sedation, orthostatic hypotension and extrapyramidal symptoms which are clearly dose related. The results of two large, multicentre, randomized, placebo-controlled studies of risperidone for the treatment of BPSD have been published. In a fixed-dose study of

risperidone comparing 0.5 mg, 1 mg and 2 mg per day with placebo in 625 patients with dementia, significantly greater improvement was noted in patients receiving 1-2 mg of risperidone on total behavioral scores, as well as subscales assessing psychosis and aggression. The frequency of side effects was similar to placebo in the group receiving 1 mg per day, with increased extrapyramidal symptoms in the group receiving 2 mg per day.¹⁰³ In a second study of 344 patients with dementia, a flexible dose of risperidone was compared with placebo as well as an active control, haloperidol. At an average dose of 1.1 mg per day, risperidone was significantly better than placebo at reducing total behavioral scores and aggression. The efficacy of risperidone was equal to that of 1.2 mg per day of haloperidol, though extrapyramidal side effects were significantly more frequent in the haloperidol-treated patients.¹⁰⁴

While controlled trials, such as those described previously, are beginning to document the expected benefit of lower acute extrapyramidal symptoms with atypical antipsychotics, their potential lower association with tardive dyskinesia may be even more impressive. Randomized controlled trials of long-term use are not yet available, however a prospective nine-month longitudinal study of elderly outpatients, many with dementia,

compared the incidence of emergent tardive dyskinesia in a group treated with risperidone (median dose 1.0 mg) and haloperidol (median dose 1.0 mg). Over 30% of the haloperidol-treated patients developed tardive dyskinesia compared with less than 5% in the risperidone-treated group, even though the latter had significantly more extrapyramidal symptoms at baseline.¹⁰⁵ Given the well-documented risk factors for tardive dyskinesia, which include older age, female gender and neurodegenerative disorders,¹⁰⁶ this potential advantage appears clinically significant.

In summary, antipsychotics are the best studied medication for the treatment of BPSD, appear modestly but consistently effective and have significant potential side effects. The newer, atypical antipsychotics, especially risperidone and olanzapine, in low doses appear equally effective but better tolerated with a lower risk of tardive dyskinesia compared with the older typical antipsychotics and should therefore be considered first-line therapies for agitation, particularly in the presence of aggression and psychosis.

Antidepressants

Antidepressants (Table 2) have been studied for a variety of indications in patients with dementia, including the treatment of agitation, aggression, depression and cognitive enhancement. The treatment of depression and cognitive enhancement is covered by other guidelines and will not be dealt with here.

Trazodone is a triazolopyridine antidepressant, the use of which in the treatment of BPSD has been described in multiple case series and case reports. Reviewing the early reports, Schneider and Sobin¹⁰⁷ noted nine of 23 dementia patients improved with dosages of 150 to 500 mg per day, with side effects such as sedation and orthostatic hypotension common. In several more recent uncontrolled trials and series, high rates of improvement were noted in agitation, restlessness, anxiety, irritability and emotional lability at a variety of dosages, including doses as low as 25 mg t.i.d. and 50 mg q.h.s.¹⁰⁸⁻¹¹¹ Unfortunately, there are only two, randomized, controlled trials, the design of which do not allow for definitive conclusions about the role of trazodone for BPSD. In a small, placebo-controlled, double-blind, crossover trial, ten AD patients were treated with trazodone (maximum dose 50 mg t.i.d.), buspirone, or a placebo.¹¹² Trazodone-treated patients had small but significant improvements compared with buspirone and placebo, though some could not tolerate 150 mg per day because of excess sedation. In a recent, randomized, double-blind trial of 28 patients with dementia, half were treated with trazodone (average dose 218 mg) and half with haloperidol (average dose 2.5 mg).¹¹³ While both groups improved equally as measured by changes in an agitation scale, adverse events and dose reductions occurred in 14% and 29% of trazodone patients compared with 50% and 57% of haloperidol-treated patients. Lack of a placebo control group limits definitive statements about the results of this study.

The use of selective serotonin re-uptake inhibitors (SSRIs) for the treatment of BPSD has received increasing attention with some investigators even recommending them as first-line agents.¹¹⁴ In a series of 10 AD patients treated with fluoxetine, there was significant improvement in irritability, anxiety, fear and mood lability.¹¹⁵ While fluoxetine was well-tolerated in that

series, another description of five patients suggested that fluoxetine was ineffective and caused significant side effects, including confusion, agitation, dizziness, nausea, anorexia, weight loss and insomnia.¹¹⁶ In a recent series of 20 patients (19 treated with sertraline 50 mg, one treated with paroxetine 20 mg), 15 patients were rated as moderately or markedly improved. The medication was well-tolerated with only one patient requiring discontinuation due to diarrhoea.¹¹⁷ In a double-blind, placebo-controlled trial of fluvoxamine in 46 patients with dementia, there were no statistically significant differences, though trends were noted favouring the fluvoxamine for improvement on a variety of behavioral symptoms.¹¹⁸ In a large, well-designed, double-blind, placebo-controlled trial of citalopram in 98 dementia patients, significant improvement was noted in symptoms such as confusion, irritability, anxiety, fear and restlessness in the citalopram group.¹¹⁹ Because the patients in this study were only mildly disturbed, Pollack et al¹²⁰ have recently attempted to replicate these results in an open study of 16 patients with moderate to severe psychosis or other behaviour problems. Patients received 20 mg of citalopram with marked improvement noted in nine and significant reduction in symptoms such as disinhibition, agitation, hostility and suspicion. Finally, in a group of patients carefully selected to fulfil criteria for frontotemporal dementia, fluoxetine, sertraline or paroxetine were used to treat a variety of characteristic behavioral disturbances.¹²¹ Disinhibition and depressive symptoms improved in 67%, compulsions improved in 64% and carbohydrate craving improved in 56% of subjects.

While irreversible mono-amine oxidase inhibitors (MAOIs) and selective MAO-A inhibitors have been examined for the treatment of depression in dementia, selegiline, a selective MAO-B inhibitor, has been reported to improve a variety of other behaviours in dementia as well. A number of case series¹²²⁻¹²⁴ have demonstrated modest improvements in some behaviours and mild but significant improvements in BPSD were noted in three of four double-blind, placebo-controlled trials.¹²⁵⁻¹²⁸ Unfortunately, almost all of these studies used patients with very mild behavioral disturbances and therefore the utility of selegiline in more severely disturbed patients awaits clarification.

In summary, while antidepressants such as trazodone and the SSRIs appear to be well-tolerated and helpful with BPSD such as irritability, anxiety, agitation, aggression and some disinhibition symptoms, randomized, placebo-controlled studies with more severely behaviorally disturbed patients are required.

Anticonvulsants

A number of case reports, series and uncontrolled trials suggest carbamazepine is useful for the treatment of BPSD (Table 2). In doses of 100-1000 mg per day, a significant percentage of patients responded within two to four weeks and tolerated the medication well.¹²⁹⁻¹³³ While an early, double-blind, placebo-controlled trial failed to demonstrate efficacy,¹³⁴ this study suffered from numerous methodological problems, which could account for the negative results.⁶⁴ Three placebo-controlled trials of carbamazepine have all been positive.¹³⁵⁻¹³⁷ In the most recent study, 51 nursing home residents with significant agitation scores (tension, hostility, uncooperativeness and/or excitement items) were randomized to receive carbamazepine

(modal doses 300 mg/day) or placebo.¹³⁷ The investigators attempted to reach an optimal carbamazepine dosage with target serum levels of 5–8 µg/ml, similar to the suggested guidelines for the use of carbamazepine in elderly bipolar patients.¹⁰⁷ Global improvement was noted in 77% of carbamazepine-treated patients compared with 21% of those taking placebo, with positive changes in agitation and aggression. While side effects were more common in the carbamazepine-treated patients, there was only one dropout due to side effects. The authors noted that anecdotally there appeared to be more ataxia and disorientation in the carbamazepine group, though no side effect occurred significantly more often compared with placebo.

Based on experience with elderly bipolars which suggests valproic acid is better tolerated and less likely to cause drug interactions than carbamazepine, this agent has recently been examined for use in the treatment of BPSD. In four early case series of 31 patients with dementia and agitation, nine improved significantly and eight others experienced slight or temporary improvements.^{138–141} In a retrospective review of 25 patients with BPSD, valproic acid was either used alone or was added to ongoing neuroleptic treatment.¹⁴² Fifty-six per cent of patients were rated as responders and the medication was well-tolerated except for reversible sedation. In a prospective, open study of 16 patients with severe BPSD, significant reductions in agitation scores were noted, with four patients rated at least much improved and four patients as minimally improved.¹⁴³ Valproic acid was generally well-tolerated; adverse events included mild sedation with the medication being discontinued in only one patient because of diarrhoea. These studies utilized divalproex sodium in doses ranging from 500 to 2500 mg per day (average dosages approximately 1500 mg per day), with serum levels of approximately 50 mg/L.

Finally, with the availability of several newer anticonvulsants, drugs such as gabapentin, lamotrigine, clobazam and topiramate will likely be investigated for treatment of BPSD. To date, there are only case reports of patients with BPSD treated with gabapentin.^{144–148} In an open label prospective series, 12 patients were treated with gabapentin for up to eight weeks with an average dose of 900 mg/day. In this antipsychotic-refractory group of mixed dementias there were no significant changes in behavioral scale scores overall, though two patients were rated as much improved and three as minimally improved.¹⁴⁹ Gabapentin was generally well-tolerated.

In summary, there is increasing interest in the use of anticonvulsants as an alternative to antipsychotics for the treatment of agitation and aggression. At the present time, there are several randomized controlled trials that suggest carbamazepine is effective and well-tolerated but no published controlled trials with other anticonvulsants including valproic acid. Despite the dearth of evidence, a recent survey of North American experts recommended divalproex for the treatment of aggression in dementia and “only modest support” for the use of carbamazepine.¹⁵⁰

Beta blockers

The use of propranolol and pindolol to treat BPSD has been reported in several case series and controlled trials (Table 2).^{151–156} While methodological problems, including crossover designs, small numbers and mixed age samples, limit interpretation of

results, approximately 67% of patients appear to respond.¹⁵⁷ Specific contraindications for the use of beta blockers include congestive heart failure and chronic obstructive pulmonary disease and adverse effects include bradycardia and hypotension (possibly with lesser frequency when using pindolol). These studies have tended to use high dosages (200–800 mg per day for propranolol, 40–60 mg per day for pindolol) with improvement noted in two to four weeks,¹⁵⁷ though up to eight weeks may be required for full effect.⁸⁵ In contrast to these recommendations, however, a recent small uncontrolled trial of low dose propranolol (10–80 mg per day) demonstrated effectiveness in 67% of patients, often within the first two weeks of treatment.¹⁵⁸

Benzodiazepines

Several early, large, placebo-controlled trials of oxazepam demonstrated efficacy greater than placebo, though lack of standardized diagnostic criteria and outcome measures limit interpretation of these results.^{159–161} More recently, several studies have compared the efficacy of a variety of benzodiazepines to neuroleptics.^{162–165} Because of concerns regarding the potential for the development of dependence and tolerance with long-term use, as well as side effects including excessive sedation and falls, clinical recommendations for the use of benzodiazepines has generally been limited to short-term and p.r.n. use for specific sedation, for example, when undergoing a procedure (for example, CT scan, dental work),¹⁶⁶ though these recommendations are not yet supported by randomized trials. Other recommendations have included using short-acting benzodiazepines (for example, lorazepam, oxazepam),^{59,85,166} though several case reports suggest that the long half-life benzodiazepine, clonazepam, may also be helpful.^{167–169}

Buspirone

Buspirone, a nonbenzodiazepine anxiolytic, was first suggested to be useful in the treatment of BPSD in a single case report.¹⁷⁰ Three uncontrolled trials suggested significant improvements in some patients using dosages of 20–40 mg per day.^{171–173} Buspirone was extremely well-tolerated in these trials with only occasional mild sedation and nausea noted. Two randomized, controlled trials have demonstrated opposite results. A small, placebo-controlled, crossover trial of 10 patients was unable to show buspirone 30 mg per day to be better than placebo.¹¹² A recent, randomized, double-blind study of buspirone 15 mg per day versus haloperidol 1.5 mg per day in 26 patients demonstrated equal and significant efficacy over a 10-week period.¹⁷⁴ Given the lack of a placebo control in this study, definitive statements about the efficacy of buspirone cannot be made. In both these trials, however, buspirone was well-tolerated. While these results raise questions about the efficacy of buspirone for the treatment of BPSD, its benign side effect profile and minimum tendency to interact with other medications argues for further investigation.

Cholinergic medications

There is increasing evidence and opinion about the relationship between cholinergic dysfunction and BPSD.¹⁷⁵ In three large, placebo-controlled trials of tacrine, a cholinesterase inhibitor,^{176–178} no improvement was noted in BPSD. A more recent, open study of tacrine, however, did demonstrate

significant reductions in behavioral disturbances.¹⁷⁹ In a double-blind, crossover trial of two patients with AD, physostigmine, another cholinesterase inhibitor, decreased hallucinations, agitation and delusions to a greater degree than haloperidol, with fewer side effects.¹⁸⁰ In a randomized, controlled trial, xanomeline, a direct cholinergic agonist, was compared with placebo in 343 patients with mild to moderate AD.¹⁸¹ While designed primarily as a cognitive enhancement trial, results indicated dramatic, dose-dependent reductions in such behaviours as shouting, agitation, delusions and hallucinations. In several open-label studies, donepezil treated AD patients demonstrated improvements on a variety of behavioral measures and specific behaviors such as delusions, agitation, anxiety, aggression and disinhibition.^{182,183} Donepezil may also provide significant benefit for patients with LBD, especially for behaviors such as hallucinations, agitation and apathy, though certain side effects such as worsening of parkinsonism and sedation may be more common than in patients with AD.^{184,185} Finally, in a large randomized placebo-controlled trial of the cholinesterase inhibitor metrifonate for mild to moderate AD, total behavioral scores improved with a significant improvement in hallucinations.¹⁸⁶

In summary, while cholinergic therapy appears to be a promising treatment for a variety of behavioral disturbances in AD, the studies published to date have either been case series, or randomized controlled trials with only mildly behaviorally disturbed patients. Recommendations for their use await randomized trials with patients entered specifically with behavioral target symptoms of moderate to marked severity. The role of cholinergic therapy for patients with LBD should also be further explored.

Other somatic treatments

A large variety of other somatic therapies have been proposed for BPSD, though there has been little research to support widespread use. Lithium carbonate has demonstrated poor effectiveness in the case reports published to date,¹⁰⁷ though low doses and serum levels may have acted to limit effectiveness. A small number of individual case reports have suggested a variety of hormonal treatments may be effective for sexually aggressive and disinhibited behaviors as well as agitation, including medroxyprogesterone,¹⁸⁷ conjugated estrogens, diethylstilbestrol,¹⁸⁸ cyproterone,¹⁸⁹ and leuprolide.^{190,191} In a recent small randomized, placebo-controlled study, conjugated estrogens were more effective than placebo at reducing aggressive behaviour in 14 male and female patients with moderate to severe dementia.¹⁹² Benefits were noted as early as the first week of treatment with 0.625 mg and the medication was well-tolerated. Larger studies appear warranted. Ondansetron, a selective 5HT₃ antagonist, significantly decreased hallucinations, delusions and agitation in two, open-label trials of patients with dementia and Parkinson's disease.^{193,194} In a small, placebo-controlled, crossover study, dronabinol, a chemical component of marijuana, increased body weight in anorexic patients and decreased severity of disturbed behaviour in 15 Alzheimer's patients.¹⁹⁵ There are two case reports of ECT used for the treatment of screaming as well as agitation in patients with dementia.^{196,197} Controlled trials with these interventions are required.

SUMMARY AND RECOMMENDATIONS

The behavioral and psychological symptoms of dementia are common, serious problems that impair the quality of life for both patient and caregiver. After appropriate assessments to rule out intercurrent medical illness, adverse drug reactions and other conditions which might cause BPSD, concomitant illness should be optimized and sensory impairment treated, if possible. The safety of the patient and those around him/her must be considered. Target symptoms should be chosen and documented with attention to antecedents and consequences. Nonpharmacological interventions include use of music, light, changes in level of stimulation and behavioral techniques. While large controlled trials of nonpharmacological interventions are lacking, these techniques should usually be attempted prior to initiation of pharmacotherapy. When pharmacotherapy is necessary, choosing the appropriate medication requires consideration of age-related changes that make elderly dementia patients susceptible to adverse effects. Effectiveness should be measured and patients must be monitored for side effects. Medications should be tapered and withdrawn periodically when and if appropriate. Atypical antipsychotics should be considered first-line therapy in view of their well-documented efficacy. Other useful agents that may be effective and better tolerated than antipsychotics include the antidepressant trazodone and the SSRIs, as well as anticonvulsants such as carbamazepine and valproic acid. Trazodone could be considered when a sleep disturbance is the target symptom. Short-term treatment with benzodiazepines such as lorazepam or oxazepam can be considered for use as p.r.n. agents when there are infrequent episodes of agitation or when sedation for a procedure is required. Other pharmacological interventions with medications such as cholinergic medications, conjugated estrogens, beta-blockers and buspirone require further research to elucidate their benefits and risks.

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