Approach to the Management of Dementia-Related Behavioural Problems

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The following review uses case studies to illustrate the importance of a biopsychosocial approach to the assessment and management of behavioural and psychological symptoms of dementia (BPSD). Practical BPSD assessment strategies are reviewed, in addition to evidence-based and guideline-supported recommendations for acute and long-term BPSD management.

Key words: *dementia, behaviour, agitation, antipsychotic, memantine*

Introduction

Dementia-related behavioural problems are common and debilitating.[1–3] The assessment and management of these problems can be challenging. As in delirium, the factors underlying behavioural and psychological symptoms of dementia (BPSD) are usually multifaceted. Unlike delirium, these factors are often complex, and BPSD may become chronic and refractory as the background dementia progresses over time. Prompt identification and treatment of BPSD is, therefore, essential. The biopsychosocial assessment and management of BPSD are important throughout the course of illness, and are recommended by the recently published Canadian dementia-treatment guidelines.[4] The following case studies illustrate some commonly observed problems in patients presenting with BPSD. A review of these cases leads to a discussion of guideline-supported recommendations for the management of BPSD.

Case Study 1

Mrs. N was a 90-year-old widow who was legally blind, had moderate Alzheimer-type dementia, and was living in a complex-care facility. Her only son visited her on a weekly basis. She required admission to acute care due to an acute onset of increased confusion, falls, day-night reversal, agitation, and visual hallucinations. She was found to have had a urinary tract infection; this was treated, and her delirium-related problems gradually improved accordingly. Unfortunately, despite the resolution of her acute medical problem, she was not able to walk independently. This was attributed to deconditioning and cranial computed tomography scan findings of lacunar infarcts that were not seen on the imaging from the previous year. She was, therefore, wait-listed for extended-care facility placement.

During the wait in acute care, Mrs. N began to manifest anxiety and verbal agitation with repetitive vocalization, calling out her son's name over and over again for hours at night. This proved to be distressing for the patient, her caregivers, and her roommates in hospital. She was moved to a single-bed room but experienced no improvement in anxiety and verbal agitation. Her facial expression suggested intermittent pain, although her reporting of pain was not consistent, and she was not cooperative with physical examination. Acetaminophen was empirically prescribed for pain and quetiapine 12.5–25 mg b.i.d. p.r.n. was given for agitation. Her son expressed concern about her decreased level of consciousness. As a result, the medications were minimized, but her anxiety and verbal agitation resurfaced.

Nursing staff noticed that Mrs. N showed a more consistent startle response on approach from the left side. On examination, a left-sided hearing impairment was confirmed, and her care plan was updated to ensure approach from the right side at all times. Due to her bilateral visual impairment, her care plan required that staff give clear verbal notification of arrival and intent upon entering her room. Although she was usually calm in her son's presence and, at times, during the day, her repetitive vocalization worsened significantly at night. The team recommended that her son record an audiotape of his voice reading aloud some of her favourite stories and reminiscing about good times from over the years. The audiotape of her son's voice was played to her through headphones during the evening, and her verbal agitation was significantly reduced. Two weeks later, Mrs. N was successfully transitioned to a community care facility.

Case Study 2

Mr. K was a 75-year-old retired executive with moderate Alzheimer-type dementia who was still living at home with his wife. He had worked his way up the corporate ladder and was known as an inspirational business leader and devoted family man. Prior to the formal diagnosis of dementia, he had been making mistakes at work, and colleagues eventually persuaded him to take a less active role with the company. During Mr. K's cognitive workup, his wife reported that

he often abused alcohol to cope with work-related stress. She disclosed that, over the years, he was at times anxious and withdrawn, unable to work for a week or more. These episodes had long been covered up as "impromptu vacations" so as not to raise a suspicion of weakness in a highly competitive work environment.

Police were called to his home late one evening when neighbours became concerned due to his shouting and throwing items around the house. He became even more agitated when paramedics arrived, and he required physical and chemical restraints in the hospital emergency department. Chemical restraint with injectable haloperidol was required for the short-term management of dangerous aggression. Regular dosing of risperidone was started once adherence to oral medication was consistent.

His wife later reported that, over the previous month, Mr. K had been increasingly anxious and agitated. He had been dwelling on work-related stress issues from years ago, becoming angry at his wife for refusing to allow him to call former colleagues late at night. His sleep and appetite were disrupted, and he had lost 2–5 kg in 6 weeks. He had been nonadherent with all of his medications, including a

Table 1: Practical Approaches to the Assessment of BPSD

Antecedents/Behaviour/Consequence (ABC) Approach

Enlist patient and caregivers in the practice of gathering and documenting data on what seemed to trigger behavioural problems (antecedents), on the description of the behavioural problem (behaviour), and on the outcome of the behavioural problem (consequence). Emergent patterns can often suggest underlying problems that are then identified and corrected in this manner.

S-M-A-R-T Approach[62]

Safety	Ensure safety of patient, staff, and other residents
Medical	Workup to treat reversible causes; reduce toxic medication load
Assess competency	Address issues regarding consent for personal care, financial, and driving decisions; protect assets
Rest	Review other causes of agitation, e.g., eyes, ears, teeth, mouth, bowels, bladder, skin, feet, nutrition, hydration, pain, ambulation, environmental temperature, noise level, etc.
Trial of medication	Pharmacological risk-benefit assessment; involve substitute decision-maker if patient incapable of providing informed consent

P.I.E.C.E.S. Approach[63]

Consider the following 6 factors:

Physical problem/discomfort

Intellectual/cognitive changes

Emotional problems

Capabilities

Environment

Social/cultural

Ask the following 3 questions:

What has changed?

What are the risks to the patient and possible causes of the change?

What are the necessary interventions (acute and long-term)?

Use the Dementia Observation Scale.[64]

BPSD = behavioural and psychological symptoms of dementia.

cholinesterase inhibitor and memantine, asking at times, "What's the point in taking all of these pills?"

The cholinesterase inhibitor and memantine were restarted in hospital. An antidepressant medication was also started. Six weeks later, his anxiety and agitation gradually resolved, allowing for the risperidone to be tapered and discontinued. Mr. K was discharged back home with enhanced home support, seniors' day programming, and regular respite for his wife.

Assessment

No problem can be solved without an accurate definition of the key components requiring analysis. When it comes to an assessment of BPSD, the traditional approach of history-taking and physical examination requires adaptation

Table 2: Strategies for Acute Pharmacological Management of BPSD

Medication Class	Medication	Dosing Strategies* and Comments
Atypical antipsychotics	Risperidone	0.125–0.5 mg daily or b.i.d., increasing by 0.125–0.25 mg/d every week as tolerated and as needed
		Rapid-dissolve tablet and oral liquid options available
		Long-term IM depot option available but small doses may not be possible due to reconstitution requirements
	Olanzapine	1.25–2.5 mg daily or b.i.d., increasing by 2.5 mg/d every week as tolerated and as needed
		Rapid-dissolve tablet option available
		Short-acting IM option available
	Quetiapine	6.25–12.5 mg b.i.d.–q.i.d., increasing by 12.5–25 mg/d as tolerated and as needed
		Conversion to once-daily XR preparation possible at doses over 50 mg daily
	Aripiprazole	1–5 mg daily, increasing to 10 mg daily as tolerated and as needed
		Rapid dissolve tablet and oral liquid options available
		Short-acting IM option available
Conventional antipsychotics	Haloperidol	0.125–0.5 mg multiroute q.2–4h. as needed
		Oral liquid option available
		Conversion to b.i.d.–t.i.d. regular dosing for brief periods (days) may be required
	Loxapine	1.25–2.5 mg multiroute q.2–4h. as needed
		Oral liquid option available
		Conversion to b.i.d.–t.i.d. regular dosing for brief periods (days) may be required
	Zuclopenthixol	Option for persistent dangerous BPSD in nonadherent patient
		6.25–12.5 mg Acuphase™ IM depot (2–3 day duration)
		Conversion to 12.5–25 mg long-acting decanoate IM depot (2 week duration) for brief periods (weeks–months) may be required
Benzodiazepine	Lorazepam	0.125–0.5 mg multiroute q.4–6h. as needed
		Regular dosing precare may be required
Antidepressant	Trazodone	12.5–25 mg b.i.d.–t.i.d., increasing to total daily dose of 100–400 mg as tolerated and as needed

BPSD = behavioural and psychological symptoms of dementia; IM = intramuscular; XR = extended release. *For divided daily dose options, it is generally recommended to give a higher dose in the evening to promote nocturnal rest and preserve daytime wakefulness.

Table 3: Strategies for Longer-Term Pharmacological Management of BPSD

Medications	Applications and Comments
Cholinesterase inhibitors	Multiple randomized controlled trials Can improve agitation, mood, anxiety, apathy, and psychotic symptoms Especially effective in patients with Lewy body dementia Gastrointestinal side effects can limit tolerability
Galantamine (8–24 mg daily) Donepezil (5–10 mg daily) Rivastigmine (3–9 mg daily [capsules], 4.6 mg/24 h–9.5 mg/24 h [transdermal])	
NMDA-glutamate receptor antagonist	Multiple randomized controlled trials Small to moderate effect size Can stabilize cognition, function, and agitation Possible antipsychotic sparing effect May worsen agitation or psychotic symptoms in some patients
Memantine (10–20 mg daily)	
Antidepressants	Multiple randomized controlled trials Selective serotonin reuptake inhibitors are the most effective and best-tolerated antidepressants Target agitation resulting from comorbid depressive disorders May reduce agitation via enhancement of frontal serotonin neurotransmission Monitor for SIADH-related hyponatremia and movement disorders
Citalopram (10–40 mg daily) Sertraline (25–200 mg daily) Trazodone (12.5–400 mg daily)	
Anticonvulsants	Fair evidence base Valproic acid has conflicting evidence Carbamazepine use may be complicated by numerous side effects and hepatic autoinduction Gabapentin dosing must be reduced in patients with renal impairment
Valproic acid (250–1,500 mg daily) Carbamazepine (100–600 mg daily) Gabapentin (200–2,700 mg daily)	
Analgesics	Poor evidence base Use when pain is suspected as a factor contributing to agitation
Acetaminophen (up to 4 g daily) NSAIDs/COX-2 inhibitors Narcotic analgesics SNRI antidepressants Gabapentin/pregabalin	
Cannabinoid receptor agonists	Poor evidence base May improve anorexia and agitation

Table 3 continued: Strategies for Longer-Term Pharmacological Management of BPSD

Medications	Applications and Comments
	Possible neuroprotective and disease-modifying properties Possible cholinesterase inhibition properties
Nabilone (0.5–1 mg daily)	
Dronabinol	
Hormonal treatments	Poor evidence base Antiandrogen agents may reduce sexual disinhibition/aggression in men with agitation Melatonin may reduce nocturnal agitation/insomnia
Antiandrogen agents (cyproterone, leuprolide, estrogen, goserelin)	
Melatonin (3–9 mg evening)	
Ginkgo biloba extract (EGb 761)	Poor evidence base May increase risk of bleeding

BPSD = behavioural and psychological symptoms of dementia; COX-2 = cyclo-oxygenase 2; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug; SIADH = syndrome of inappropriate antidiuretic hormone.
Source: Adapted from Passmore MJ et al., 2008.[65]

because the patient is often not able to participate in a reliable or meaningful way. Individual history-taking thus becomes group data gathering. Codified behavioural charting by caregivers can yield essential clues as to which target signs and symptoms might respond to particular interventions. An accurate definition of the problem(s) is the first step toward the successful management of BPSD. Once the problems are accurately defined, it becomes possible to identify and correct upstream factors contributing to target signs and symptoms. Examples can include sensory impairment, as with Mrs. N, or an underrecognized mood disorder, as with Mr. K. Some practical BPSD assessment strategies are outlined in Table 1.

Behavioural and Environmental Management

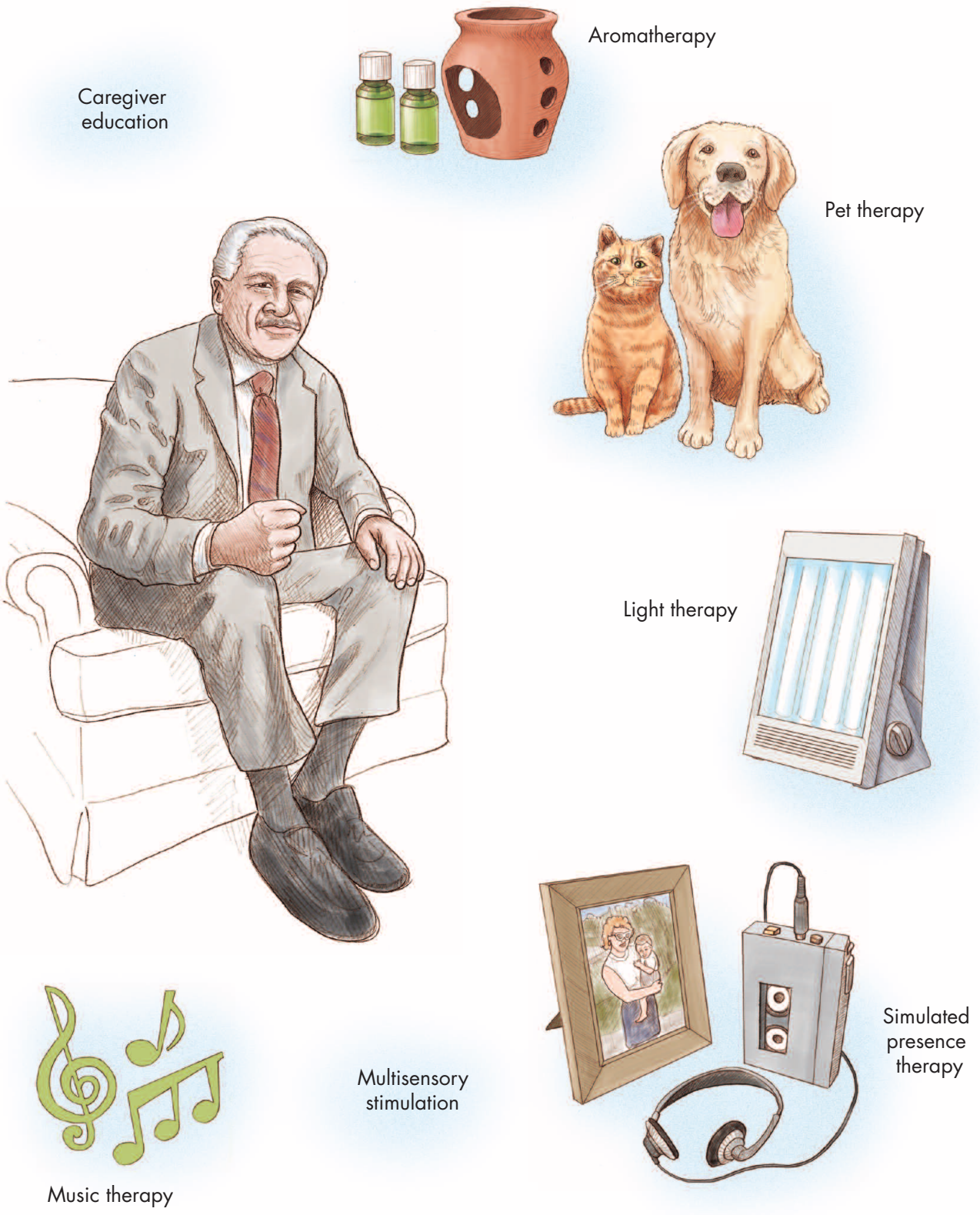
Despite inconsistent results from studies of behavioural and environmental interventions for the management of BPSD, individually tailored nonpharmacological approaches may be helpful and are not likely to be harmful. They are, therefore, first-line therapy recommendations in recently published treatment guidelines (Figure 1).[4,5] The evidence base for specific nonpharmacological strategies is not robust. These interventions include light therapy,[6] music therapy,[7] pet therapy,[8] aromatherapy,[9] caregiver education,[10,11] multisensory stimulation,[12] and simulated presence therapy,[13] as in the case of Mrs. N when exposure to audiotapes of her son's voice reduced her importuning behaviour.

Acute Pharmacological Management

The efficacy of certain atypical antipsychotics (particularly risperidone and olanzapine) for the management of BPSD is supported by numerous randomized controlled trials.[14–17] The effectiveness of atypical antipsychotics for the management of mild to moderate BPSD in outpatients was called into question by initial results from the Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD) trial.[18] The CATIE-AD extension report indicated that atypical antipsychotic use was associated with specific improvements in anger, aggression, and paranoid ideas.[19] In practice, the potential benefits of antipsychotic use for BPSD management have to be carefully weighed against possible risks including stroke,[20,21] pneumonia,[22] and death.[23] As in the case of Mr. K, antipsychotic use in patients with dementia should be limited to the acute management of severe, dangerous agitation, aggression, or psychosis.

For patients who cannot take regular tablets orally, risperidone and olanzapine are available in a rapidly dissolving tablet form, and risperidone is available in liquid form. For patients requiring parenteral antipsychotic administration, low-dose conventional antipsychotics such as haloperidol or loxapine are most often used. A brief-acting intramuscular preparation of olanzapine is available and was shown to be more efficacious than lorazepam or placebo in the control of acute dementia-related agitation.[24] A long-acting intramuscular depot preparation of risperidone is available, although the low doses often required for older adults may be difficult to achieve due to specific reconstitution requirements before administration, as outlined in the product monograph.[25] Low-dose zuclopenthixol may be a useful option when an intramuscular depot antipsy-

Figure 1: Nonpharmacological Strategies for Managing Dementia-Related Behavioural Problems



Key Points

- Behavioural and psychological symptoms of dementia (BPSD) are usually complex and multifactorial.
- Biopsychosocial BPSD assessment strategies are essential.
- Behavioural and environmental BPSD management strategies are first-line recommendations in current consensus treatment guidelines.
- Acute, dangerous BPSD may require short-term management with an antipsychotic or benzodiazepine.
- Options for prevention and/or medium to long-term BPSD management include cholinesterase inhibitors, memantine, and/or SSRI antidepressants.

chotic is required for the management of persistently dangerous BPSD in a nonadherent patient.

Common dosing strategies are outlined in Table 2. Canadian treatment guidelines recommend that clinicians reassess the need for ongoing antipsychotic use within 3 months of behavioural control.[4] Gradual dosage reduction or discontinuation of an antipsychotic medication may be possible without symptom re-emergence. The Dementia Antipsychotic Withdrawal Trial (DART-AD) showed no significant difference in BPSD outcome scores at 6 and 12 months following a switch from an antipsychotic to a placebo versus continued antipsychotic use.[26]

Benzodiazepine use in older adults is associated with increased risks of confusion, falls, and fractures.[27,28] If necessary, short-term use of brief half-life benzodiazepines may reduce dementia-related anxiety or agitation, particularly in the context of comorbid alcohol or benzodiazepine-withdrawal agitation. Benzodiazepine use may be required to facilitate brief interventions such as medical or nursing procedures or the provision of hands-on care. This is often the case for bed-bound individuals with severe dementia who cannot cooperate at all with caregivers. Lorazepam can be a practical option owing to its multiroute administration, brief half-life, and extrahepatic metabolism. Common dosing strategies are outlined in Table 2. In patients who become oversedated on lorazepam, the ultrabrief half-life benzodiazepine midazolam may be a useful alternative, although the risk of respiratory depression is a potential concern.[29]

Trazodone is a sedating antidepressant with serotonergic properties that make it a useful and likely safer alternative to oral antipsychotics or benzodiazepines in patients with BPSD who require more acute anxiolysis or sedation. The evidence base supporting trazodone for the management of BPSD is inconsistent.[30,31] A randomized controlled trial in patients with frontotemporal dementia found that trazodone was helpful in the management of behavioural problems.[32] Trazodone is sometimes associated with postural hypotension in older adults, and patients may occasionally exhibit paradoxical agitation owing to variable cytochrome P-450 2D6 activity and the consequent accumulation of an anxiogenic active metabolite (m–CPP).[33]

Medium and Long-Term Pharmacological Management

Cholinesterase inhibitors can play a role in the management of BPSD. Various levels of evidence suggest that galantamine,[34] rivastigmine,[35–37] and donepezil[38–40] can have a positive impact on BPSD-related outcome measures. A randomized trial of donepezil failed to show significant reduction in agitation after only 12 weeks.[41] This suggests that cholinesterase inhibitor–mediated effects on BPSD may evolve gradually, after the first 3–6 months of treatment. Rivastigmine use has been associated with a decreased rate of antipsychotic initiation.[42] By perhaps reducing the risk of BPSD emergence, cholinesterase inhibitors may spare certain patients from requiring risky treatment with an antipsychotic medication. Behavioural and psychological symptoms of dementia associated with Lewy body dementia may be particularly responsive to cholinesterase inhibitor therapy.[43] The rivastigmine transdermal patch may be a useful option for agitated patients who are frequently nonadherent to oral medication. Dosing strategies are summarized in Table 3.

Memantine is an N-methyl-D-aspartate (NMDA)-glutamate receptor antagonist approved for the treatment of moderate to severe Alzheimer's disease. A recent pooled analysis of three randomized trials for agitation/aggression or psychosis in the context of moderate to severe Alzheimer's disease found a statistically significant treatment advantage for memantine over placebo.[44] A recent analysis showed that memantine pre-

Clinical Pearls

Factors underlying behavioural and psychological symptoms of dementia (BPSD) are usually multifaceted, requiring biopsychosocial assessment and management.

While antipsychotics are often effective for short-term control of dangerous BPSD, their ongoing use should be re-evaluated every 3 months. Cholinesterase inhibitors, memantine and/or SSRI antidepressants are viable medium to long-term BPSD management options.

scription was associated with stabilization in the rate of antipsychotic prescription.[45] The Cochrane Collaboration review states, "Slightly fewer patients with moderate to severe Alzheimer's disease taking memantine develop agitation, but there is no evidence either way about whether it has an effect on agitation which is already present."[46] Canadian treatment guidelines suggest that in patients with severe Alzheimer's disease, modest improvements in behaviour can occur with a cholinesterase inhibitor and/or memantine.[4] Dosing strategies are summarized in Table 3. In the case of Mr. K, nonadherence to cholinesterase inhibitor and memantine treatment may have been a factor in the emergence of BPSD, and the reinstitution of treatment with both medications was, therefore, indicated.

Antidepressants can be helpful for the management of BPSD, particularly when signs and symptoms may be related to a comorbid mood or anxiety disorder. In the case of Mr. K, numerous clues suggesting the presence of a latent mood disorder emerged from the collateral history provided by his wife, from the subacute evolution of neurovegetative problems, and from consideration of behaviours such as medication nonadherence and pessimistic comments suggesting helplessness and hopelessness. Even in the absence of a suspected mood or anxiety disorder, antidepressants can help reduce BPSD. Dementia-related behavioural problems may relate in part to dysfunctional frontal serotonin systems.[47,48] Selective serotonin reuptake inhibitor (SSRI) antidepressants usually confer the most favourable risk-benefit profile in patients with BPSD. A few controlled trials support the use of citalopram[49,50] and sertraline,[51] in particular. An analysis of data from the CATIE-AD trial found a 60% reduction in irritability and apathy scores in patients switched from placebo to citalopram.[52] Positive effects from SSRIs are not usually seen until after 2–4+ weeks, and lower-than-usual starting dosages with a more gradual upward dosage titration are worthwhile considerations when treating older adults (see Table 3).

Anticonvulsant mood stabilizers have been studied as potential treatment options for BPSD. Valproic acid may be a interesting option, particularly in light of recent neuropathological research suggesting disease-modifying effects and a positive impact on behaviour in an animal model of Alzheimer's disease.[53] Earlier valproic acid studies for BPSD management were promising,[54–56] although recent controlled trials and a subsequent Cochrane review were disappointing.[57–59] Carbamazepine may be helpful in the treatment of BPSD,[60,61] but side effects and pharmacokinetic drug interactions secondary to its enzyme-inducing effect can complicate long-term therapy. A variety of other medication types have been identified in case reports and case series to have been helpful for patients with BPSD (see Table 3). The evidence base for the use of these medications is not robust, although individual patient factors may lead clinicians to consider a trial. As always, discussion with and documentation of informed consent given by the patient or substitute decision-maker is advised with any medication trial for BPSD management.

Conclusion

Assessment and management of BPSD is usually complex and challenging. A logical, stepwise approach incorporating input and action from clinical team members and family members is essential. The identification and correction of potentially reversible underlying factors is important. Environmental and behavioural management strategies are considered first-line interventions.[4,5] Antipsychotic use should be limited to short-term management of acute, dangerous agitation, aggression, or psychosis, with a re-evaluation of the need for ongoing antipsychotic use at least every 3 months.[4] For medium to long-term BPSD management, an increasingly robust evidence base supports the use of cholinesterase inhibitors, memantine, and/or SSRI antidepressants.

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References

1. Cohen-Mansfield J, Werner P, Watson V, et al. Agitation among elderly persons at adult day-care centers: the experiences of relatives and staff members. Int Psychogeriatr 1995;7:447–58.
2. Margallo-Lana M, Swann A, O'Brien J, et al. Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. Int J Geriatr Psychiatry 2001;16:39–44.
3. Phillips VL, Diwan S. The incremental effect of dementia-related problem behaviors on the time to nursing home placement in poor, frail, demented older people. J Am Geriatr Soc 2003;51:188–93.
4. Herrmann N, Gauthier S. Diagnosis and treatment of dementia: 6. Management of severe Alzheimer disease. CMAJ 2008;179:1279–87.
5. Salzman C, Jeste DV, Meyer RE, et al. Elderly patients with dementia-related symptoms of severe agitation and aggression: consensus statement on treatment options, clinical trials methodology, and policy. J Clin Psychiatry 2008;69:889–98.
6. Riemersma-van der Lek RF, Swaab DF, Twisk J, et al. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. JAMA 2008;299:2642–55.
7. Vink AC, Birks JS, Bruinsma MS, et al. Music therapy for people with dementia. Cochrane Database Syst Rev 2006;(1):CD003477.
8. Perkins J, Bartlett H, Travers C, et al. Dog-assisted therapy for older people with dementia: a review. Australas J Ageing 2008;27:177–82.
9. Nguyen QA, Paton C. The use of aromatherapy to treat behavioural problems in dementia. Int J Geriatr Psychiatry 2008;23:337–46.
10. Javadpour A, Ahmadzadeh L, Bahredar MJ. An educative support group for female family caregivers: impact on caregivers psychological distress and patient's neuropsychiatry symptoms. Int J Geriatr Psychiatry 2009;24:469–71.
11. Senanarong V, Jamjumras P, Harmphadungkit K, et al. A counseling intervention for caregivers: effect on neuropsychiatric symptoms. Int J Geriatr Psychiatr 2004;19:781–8.
12. Milev RV, Kellar T, McLean M, et al. Multisensory stimulation for elderly with dementia: a 24-week single-blind randomized controlled pilot study. Am J Alzheimers Dis Other Demen

2008;23:372–6.
13. Zetteler J. Effectiveness of simulated presence therapy for individuals with dementia: a systematic review and meta-analysis. Aging Ment Health 2008;12:779–85.
14. Suh GH, Son HG, Ju YS, et al. A randomized, double-blind, crossover comparison of risperidone and haloperidol in Korean dementia patients with behavioral disturbances. Am J Geriatr Psychiatry 2004;12:509–16.
15. Katz I, de Deyn PP, Mintzer J, et al. The efficacy and safety of risperidone in the treatment of psychosis of Alzheimer's disease and mixed dementia: a meta-analysis of 4 placebo-controlled clinical trials. Int J Geriatr Psychiatry 2007;22:475–84.
16. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry 2000;57:968–76.
17. Mintzer JE, Tune LE, Breder CD, et al. Aripiprazole for the treatment of psychoses in institutionalized patients with Alzheimer dementia: a multicenter, randomized, double-blind, placebo-controlled assessment of three fixed doses. Am J Geriatr Psychiatry 2007;15:918–31.
18. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525–38.
19. Sultzer DL, Davis SM, Tariot PN, et al; CATIE-AD Study Group. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. Am J Psychiatry 2008;165:844–54.
20. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev 2006;(1):CD003476.
21. Sacchetti E, Trifirò G, Caputi A, et al. Risk of stroke with typical and atypical antipsychotics: a retrospective cohort study including unexposed subjects. J Psychopharmacol 2008;22:39–46.
22. Knol W, van Marum RJ, Jansen PA, et al Antipsychotic drug use and risk of pneumonia in elderly people. J Am Geriatr Soc 2008;56:661–6.
23. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–43.
24. Meehan KM, Wang H, David SR, et al. Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. Neuropsychopharmacology 2002;26:494–504.
25. Janssen-Ortho Inc. RisperdalTM ConstaTM product monograph. Toronto (ON): Janssen-Ortho Inc, 2008; http://www.janssen-ortho.com/JOI/pdf_files/Risperdal_E.pdf Site accessed May 18, 2009.
26. Ballard C, Lana MM, Theodoulou M, et al; Investigators DART AD. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). PLoS Med 2008;5:e76.
27. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults. Results of a US consensus panel of experts. Arch Intern Med 2003;163:2716–24.
28. van der Hooft CS, Schoofs MW, Ziere G, et al. Inappropriate benzodiazepine use in older adults and the risk of fracture. Br J Clin Pharmacol 2008;66:276–82.
29. Passmore MJ, Sheldon L, Lax S, et al. Oral midazolam for dementia-related response agitation. J Am Geriatr Soc 2009;57:561–2.
30. Martinon-Torres G, Fioravanti M, Grimley EJ. Trazodone for agitation in dementia. Cochrane Database Syst Rev 2004;(4):CD004990.
31. Sultzer DL, Gray KF, Gunay I, et al. A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. Am J Geriatr Psychiatry 1997;5:60–9.
32. Lebert F, Stekke W, Hasenbroekx C, et al. Frontotemporal dementia: a randomised, controlled trial with trazodone. Dement Geriatr Cogn Disord 2004;17:355–9.
33. Kast R. Are we done with trazodone? The potential for damage by m-CPP—a metabolite of trazodone. Acta Neuropsychiatrica 2007:19:220–1.
34. Herrmann N, Rabheru K, Wang J, et al. Galantamine treatment of problematic behavior in Alzheimer disease: post-hoc analysis of pooled data from three large trials. Am J Geriatr Psychiatry 2005;13:527–3.
35. Figiel G, Sadowsky C. A systematic review of the effectiveness of rivastigmine for the treatment of behavioral disturbances in dementia and other neurological disorders. Curr Med Res Opin 2008;24:157–66.
36. Cummings JL, Koumaras B, Chen M, et al; Rivastigmine Nursing Home Study Team. Effects of rivastigmine treatment on the neuropsychiatric and behavioral disturbances of nursing home residents with moderate to severe probable Alzheimer's disease: a 26-week, multicenter, open-label study. Am J Geriatr Pharmacother 2005;3:137–48.
37. Gauthier S, Juby A, Rehel B, et al. EXACT: rivastigmine improves the high prevalence of attention deficits and mood and behaviour symptoms in Alzheimer's disease. Int J Clin Pract 2007;61:886–95.
38. Cummings JL, McRae T, Zhang R; Donepezil-Sertraline Study Group.Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. Am J Geriatr Psychiatry 2006;14:605–12.
39. Barak Y, Bodner E, Zemishlani H, et al. Donepezil for the treatment of behavioral disturbances in Alzheimer's disease: a 6-month open trial. Arch Gerontol Geriatr 2001;33:237–41.
40. Paleacu D, Mazeh D, Mirecki I, et al. Donepezil for the treatment of behavioral symptoms in patients with Alzheimer's disease. Clin Neuropharmacol 2002;25:313–7.
41. Howard RJ, Juszczak E, Ballard CG, et al; CALM-AD Trial Group. Donepezil for the treatment of agitation in Alzheimer's disease. N Engl J Med 2007;357:1382–92.
42. Narayanan S, Beusterien KM, Thomas SK, et al. Antipsychotic drug use among nursing home residents taking rivastigmine. J Am Med Dir Assoc 2006;7:12–6.
43. Simard M, van Reekum R. The acetylcholinesterase inhibitors for treatment of cognitive and behavioral symptoms in dementia with Lewy bodies. J Neuropsychiatry Clin Neurosci 2004;16:409–25.
44. Wilcock GK, Ballard CG, Cooper JA, et al. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. J Clin Psychiatry 2008;69:341–8.
45. Vidal JS, Lacombe JM, Dartigues JF, et al. Evaluation of the impact of memantine treatment initiation on psychotropics use: a study from the French national health care database. Neuroepidemiology 2008;31:193–200.
46. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev 2006;(2):CD003154. DOI: 10.1002/14651858.CD003154.pub5.
47. Schneider LS, Severson JA, Chui HC, et al. Platelet tritiated imipramine binding and MAO activity in Alzheimer's disease patients with agitation and delusions. Psychiatry Res 1988;25:311–22.
48. Senanarong V, Cummings JL, Fairbanks L, et al. Agitation in Alzheimer's disease is a manifestation of frontal lobe dysfunction. Dement Geriatr Cogn Disord 2004;17:14–20.
49. Pollock BG, Mulsant BH, Rosen J, et al. A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. Am J Geriatr Psychiatry 2007;15:942–52.
50. Pollock BG, Mulsant BH, Rosen J, et al. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in

hospitalized, demented patients. Am J Psychiatry 2002;159:460–5.
51. Finkel SI, Mintzer JE, Dysken M, et al. A randomized, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. Int J Geriatr Psychiatry 2004;19:9–18.
52. Siddique H, Hynan LS, Weiner MF. Effect of a serotonin reuptake inhibitor on irritability, apathy, and psychotic symptoms in patients with Alzheimer's disease. J Clin Psychiatry 2009 May 5. Epub ahead of print.
53. Qing H, He G, Ly PT, et al. Valproic acid inhibits Abeta production, neuritic plaque formation, and behavioral deficits in Alzheimer's disease mouse models. J Exp Med 2008;205:2781–9.
54. Kunik ME, Puryear L, Orengo CA, et al. The efficacy and tolerability of divalproex sodium in elderly demented patients with behavioral disturbances. Int J Geriatr Psychiatry 1998;13:29–34.
55. Meinhold JM, Blake LM, Mini LJ, et al. Effect of divalproex sodium on behavioural and cognitive problems in elderly dementia. Drugs Aging 2005;22:615–26.
56. Porsteinsson AP, Tariot PN, Jakimovich LJ, et al. Valproate therapy for agitation in dementia: open-label extension of a double-blind trial. Am J Geriatr Psychiatry 2003;11:434–40.
57. Tariot PN, Raman R, Jakimovich L, et al. Divalproex sodium in nursing home residents with possible or probable Alzheimer disease complicated by agitation: a randomized, controlled trial. Am J Geriatr Psychiatry 2005;13:942–9.
58. Herrmann N, Lanctôt KL, Rothenburg LS, et al. A placebo-controlled trial of valproate for agitation and aggression in Alzheimer's disease. Dement Geriatr Cogn Disord 2007;23:116–9.
59. Lonergan ET, Cameron M, Luxenberg J. Valproic acid for agitation in dementia. Cochrane Database Syst Rev 2004;(2):CD003945.
60. Tariot PN, Erb R, Podgorski CA, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. Am J Psychiatry 1998;155:54–61.
61. Olin JT, Fox LS, Pawluczyk S, et al. A pilot randomized trial of carbamazepine for behavioral symptoms in treatment-resistant outpatients with Alzheimer disease. Am J Geriatr Psychiatry 2001;9:400–5.
62. Rabheru K. Take a S-M-A-R-T Approach: Unpredictable course of dementia symptoms can be managed. Can Fam Physician 2003;49:389.
63. P.I.E.C.E.S. Putting the P.I.E.C.E.S. together. Tillsonburg (ON): P.I.E.C.E.S., 2005; http://www.piecescanada.com/index.html# Site accessed May 20, 2009.
64. P.I.E.C.E.S. Dementia Observation Scale. Tillsonburg (ON): P.I.E.C.E.S.; http://www.piecescanada.com/pdf/Resources%20-%20DOS.pdf Site accessed May 20, 2009.
65. Passmore MJ, Gardner DM, Polak Y, et al. Alternatives to atypical antipsychotics for the management of dementia-related agitation. Drugs Aging 2008;25:381–98.