



# Pharmacological treatment of behavioural problems in dementia

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## Summary

**Dementia is commonly associated with distressing behavioural problems that warrant intervention. A general medical assessment of the patient is needed before assessing whether specific treatment is required. Both non-pharmacological and pharmacological interventions can be considered. The best available evidence is for the use of low-dose antipsychotic medication in patients with agitated or aggressive behaviour with or without associated psychotic symptoms. There is less evidence to support the use of antidepressants, anticonvulsants and cholinesterase inhibitors in patients whose dementia is complicated by behavioural problems. When psychotropic medication is prescribed to people with dementia, it should be regularly reviewed with a view to stopping it or assessing the patient after a trial off the medication.**

Keywords: antipsychotics, antiepileptics, antidepressants.

(*Aust Prescr* 2005;28:67–70)

## Introduction

Dementia is a clinical syndrome usually characterised by progressive cognitive impairment, neuropsychiatric symptoms, impaired capacity to undertake activities of daily living, and behavioural disturbance. It affects approximately 6% of Australians aged 65 years and over and is the second greatest cause of years of life lost due to disability in Australia. More than 160 000 Australians suffer from dementia and many other family members and friends are indirectly affected. The commonest cause of the dementia syndrome in Australia is Alzheimer's disease.

## Behavioural and psychological symptoms of dementia

A number of terms are used interchangeably to refer to the behavioural or psychological symptoms of dementia. These include neuropsychiatric symptoms of dementia, non-cognitive

symptoms of dementia, behavioural and psychological symptoms of dementia and behavioural disturbance in dementia.

Neuropsychiatric symptoms such as apathy, anxiety, agitation, depression, delusions and hallucinations occur commonly in older people with dementia. These symptoms are a major cause of personal distress to patients and their families and place a substantial burden on the healthcare system. Neuropsychiatric symptoms are more important predictors of caregiver burden than cognitive impairment and are associated with admission to a nursing home. The prevalence of behavioural symptoms in hostel and nursing home populations is much greater than in older people living in the community.

The best available estimates of the prevalence of neuropsychiatric symptoms in an epidemiologically derived sample of older people with dementia living in the community come from the US Cache County Study.<sup>1</sup> Across all categories of severity, 61% of patients had one or more neuropsychiatric symptoms and 32% had severe symptoms. The most prevalent individual symptoms were apathy (27.4%), depression (20.1%), irritability (20.4%), aggression/agitation (23.7%) and delusions (18.5%).

## Important assessment and management principles

Take a personal history from the patient and an informant to better understand their symptoms in the context of their previous experiences. Before embarking on symptomatic treatment for behavioural problems in people with dementia, it is important to assess the patient's general health. There may be an underlying remediable cause for the symptoms.

## Other illnesses

The development of acute agitation in people with dementia is often due to delirium, which is commonly precipitated by intercurrent illness or polypharmacy. Common causes of delirium include infections of the urinary tract, respiratory tract or skin, overzealous use of drugs with anticholinergic properties, and inappropriate use of hypnotosedatives. Treatment should be directed towards the underlying cause, although short-term symptomatic treatment for the behavioural symptoms may be required.

In some patients with moderate or severe dementia, the development of agitated behaviour may indicate unreported pain from conditions such as osteoarthritis. If the doctor suspects this possibility, a time-limited therapeutic trial of simple

analgesia such as regular paracetamol should be considered. Although case series have reported the use of narcotic analgesics in this situation, there is insufficient evidence to recommend this approach.

In some older people with dementia, the development of a comorbid depressive, anxiety or psychotic disorder may present with abnormal behaviour. The diagnosis of such conditions in the presence of more than mild dementia can pose a clinical challenge.

## **Drugs**

Although drugs are often used in the management of behavioural problems in older people with dementia, it is important to review the medications they already take before adding more. Sometimes behavioural problems are caused by sub-acute delirium or other types of toxicity due to prescribed medication. Drugs that are particularly prone to cause behavioural problems in older people include those with anticholinergic properties (tricyclic antidepressants such as amitriptyline, phenothiazine antipsychotics such as chlorpromazine, and anti-Parkinsonian drugs such as benzotropine), benzodiazepines such as diazepam, and narcotic analgesics such as tramadol. It is often possible to cease some medications in older people without adverse consequences. In residential aged-care settings a review of the patient's medication in consultation with a clinical pharmacist may be useful.

## **Environment**

The prudent prescriber assesses the patient's environment and the capacity of the patient's caregivers to cope with the behavioural problem. Abnormal behaviour in people with dementia often comes to clinical attention because of a mismatch between the patient, their environment and the characteristics of the caregivers. Sometimes a change in the environment or caregiver behaviour will result in substantial improvement in the patient's behaviour or a better match between the patient's needs and the capacity for those needs to be met. The use of psychotropic medication may then be unnecessary.

A change in environment may be something as straightforward as changing from bathing to showering, or changing from showering in the morning to showering in the evening, or changing to a different person assisting with showering. It is useful to place familiar objects around people with dementia in an attempt to make the unfamiliar seem familiar.

## **Impact of behaviour**

It is worth considering whether the behavioural disturbance is causing the patient obvious distress or making it difficult for others to care for them. If there is no underlying reversible

cause and the behaviour is not particularly problematic, it might be worth considering a further period of observation without treatment. Hallucinations are one example of a symptom that does not always warrant treatment. The routine prescription of psychotropic medication in the absence of good general care of patients with dementia is likely to lead to further agitation and complications like confusion and falls.

## **Non-pharmacological approaches**

A wide range of non-pharmacological interventions has been tested in behaviourally disturbed people with dementia. Many of the trials have had significant methodological limitations. Nevertheless, a recent systematic review found that there was evidence to support the efficacy of activity programs, music, behaviour therapy, light therapy, carer education and changes to the physical environment.<sup>2</sup> In well-run residential aged-care facilities some of these techniques are in routine use.

Interventions for patients with dementia and behavioural problems should be individualised. Specific discussion of this complex issue is contained in a report to the Commonwealth Department of Health and Ageing on the psychosocial approaches to challenging behaviour in dementia.<sup>3</sup>

## **Pharmacological approaches**

When non-pharmacological approaches are insufficient to manage the patient's behaviour, drugs can be added to their treatment. It is important to consider the likely benefits against the likelihood of adverse effects and drug interactions.

## **Antipsychotics**

There is some evidence for the efficacy of both typical (e.g. haloperidol) and atypical (e.g. risperidone<sup>4</sup>, olanzapine<sup>5</sup>) antipsychotic drugs in the treatment of psychotic symptoms in people with dementia. There is also some evidence for the use of these drugs in people with dementia who are aggressive or agitated but who do not have overt psychotic symptoms.

Although the so-called atypical antipsychotic medications (risperidone, olanzapine, quetiapine, amisulpride, aripiprazole) have safer adverse effect profiles than typical antipsychotic medications, most of them are not subsidised by the Pharmaceutical Benefits Scheme (PBS) for people with dementia in the absence of schizophrenia. The best evidence is for low-dose risperidone, which has been approved for the management of behavioural disturbance in dementia. The usual starting dose of risperidone in older people with dementia is 0.25–0.5 mg daily, with the final dose generally 1–2 mg per day.

A Cochrane review found that haloperidol was useful for aggression, but not for other aspects of agitation in people with dementia.<sup>6</sup> If haloperidol is to be used in the treatment of either psychotic symptoms or agitation/aggression, it is important to use the lowest effective dose. The usual starting dose of

haloperidol in older people is 0.5 mg daily, with the final daily dose generally 1–2 mg per day.

If either haloperidol or an atypical antipsychotic drug is used, it is important to titrate the dose slowly and check the patient frequently for adverse effects. The most important adverse effects in older patients are Parkinsonism, confusion and postural hypotension. Parkinsonism can develop after several weeks of treatment and may present with falls. At these doses, akathisia is a much less frequent problem than when higher doses are used.

When starting an antipsychotic drug in older people with dementia, it is important to have a stopping rule. Prescribe treatment for no longer than 3–6 months before tapering the dose and undertaking a trial of ceasing the medication. Patients should be regularly reviewed because their behavioural problems may abate as their dementia progresses.

Recently, concern has arisen about an increased risk of cerebrovascular adverse effects when risperidone or olanzapine are used to treat psychotic or behavioural symptoms in older patients with dementia. Although no prospective studies have been designed specifically to examine this outcome, pooled secondary analyses of randomised controlled trials suggest that both drugs are associated with a small but significantly increased risk of cerebrovascular adverse effects.<sup>78</sup> In contrast, a retrospective cohort study did not find a statistically significant increased risk of stroke when risperidone and olanzapine were compared with conventional antipsychotic medications in older people with mixed diagnoses.<sup>9</sup> It is not known whether haloperidol, quetiapine, amisulpride or aripiprazole are also associated with cerebrovascular adverse effects. Nor is it known whether the observed increased risk of cerebrovascular adverse effects also affects older patients with psychotic disorders but no dementia. It is therefore important to recognise that there is an increased risk in prescribing antipsychotics in these situations, so the harms and benefits should be clearly identified and discussed in as much detail as possible with the patient and their carers.

### **Antidepressants**

Depression and anxiety symptoms occur commonly in people with dementia. Sometimes these symptoms are short-lived and do not require specific treatment. However, if the person with dementia develops a clinically significant depressive or anxiety disorder they should be treated.

Modern antidepressant medication is effective against both depressive and anxiety disorders, although the evidence base in patients with dementia is weak. The adverse effect profiles of sertraline, citalopram, escitalopram and moclobemide make them suitable for use in older people, including those with dementia. Evidence is best for sertraline, for which the usual starting dose in this patient group is 25 mg daily.<sup>10</sup> Treatment,

if effective, should usually continue for about 12 months, or longer if there is a history of recurrent depression.

There is a risk of hyponatraemia with antidepressants in older people.<sup>11</sup> The prescriber should check the patient's serum sodium before and approximately one week after starting treatment with an antidepressant. However, hyponatraemia can occur several weeks into therapy, so a high index of suspicion should be maintained. Increasing confusion is a common symptom of hyponatraemia in older patients. Hyponatraemia seems to be more common in women, in patients with cerebrovascular disease, and in patients on diuretics.

### **Anticonvulsants**

Carbamazepine and sodium valproate have been used in the management of agitated behaviour in people with dementia. The evidence base is rather weak for both drugs, although does tend to favour carbamazepine<sup>12</sup>, despite its relatively greater propensity for adverse effects, including drug-drug interactions. Like antipsychotic treatment, anticonvulsants should only be prescribed for a limited time.

### **Cholinesterase inhibitors**

There are preliminary data showing that some patients with dementia-related behavioural disturbance benefit from treatment with cholinesterase inhibitors. These data are based mainly on subsidiary analyses of studies designed for other purposes. Prescribers should be aware, however, that cholinesterase inhibitor treatment is sometimes associated with deterioration in behaviour. Also, there are no independent head-to-head studies comparing donepezil, rivastigmine and galantamine in the treatment of neuropsychiatric or behavioural symptoms in dementia.

### **Benzodiazepines**

Benzodiazepines should be avoided in older people with dementia. Benzodiazepines impair cognition (particularly memory), gait (leading to falls) and, like all sedatives, may also worsen the common clinical problem of constipation. If a benzodiazepine is prescribed for severe anxiety, it should not be continued for more than two weeks. Benzodiazepines should not be used to treat insomnia in people with dementia.

### **Management of aggression**

Physical aggression is common in dementia, particularly towards caregivers. Sometimes aggression can be managed by modifying the behaviour of the caregiver or by modifying the environment in some other way. However, pharmacological intervention is often required, particularly when there is a risk of physical injury to the patient or their carer.

In an emergency, aggressive behaviour in a patient with dementia may need to be treated with antipsychotic medication. If oral treatment is feasible, risperidone or haloperidol should

be tried. If parenteral treatment is required, the short-term use of intramuscular haloperidol or olanzapine is often appropriate. It is particularly important that following the administration of parenteral antipsychotic medication, the patient with dementia is monitored for an extended period. Adverse effects including excessive sedation and extrapyramidal reactions may occur.

The dose of antipsychotic medication should vary according to the size, gender, age and general condition of the patient. Intramuscular haloperidol is often administered in an initial dose of 1–2 mg and intramuscular olanzapine in an initial dose of 2.5 mg. Repeated dosing is sometimes required, but increases the risk of adverse effects.

Although approved for behavioural problems, intramuscular olanzapine is not currently subsidised by the PBS. Droperidol and midazolam are not recommended for use in older people with dementia. A combination of parenteral benzodiazepines with parenteral antipsychotic medication can lead to excessive sedation in older people and is not recommended for routine use.

If physical aggression is more chronic in nature and associated with other agitated behaviour, a trial of anticonvulsant medication, either sodium valproate or carbamazepine, is often appropriate. In this situation, these anticonvulsants may be used as antipsychotic sparing medications.

## Ethical considerations

In most jurisdictions treatment without consent has been dealt with by statute law and a list of substitute decision makers is specified. In certain circumstances referral to a guardianship board (or similar local body) may be prudent, or even required, before treatment without consent can proceed.

In emergencies, particularly where physical violence to self or others is concerned, the doctor's duty of care might override the requirement of informed consent. Although not yet universal, in some jurisdictions patients with dementia are covered by the local Mental Health Act.

*Acknowledgement: Dr David Lie provided valuable comments on an earlier draft of this article.*

## References

1. Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* 2000;157:708-14.
2. Opie J, Rosewarne R, O'Connor DW. The efficacy of psychosocial approaches to behaviour disorders in dementia: a systematic literature review. *Aust N Z J Psychiatry* 1999;33:789-99.
3. Bird M, Llewellyn-Jones R, Smithers H, Korten A. Psychosocial approaches to challenging behaviour in dementia: A controlled trial. Canberra: Commonwealth Department of Health and Ageing. 2002.

<http://www.health.gov.au/internet/wcms/publishing.nsf/Content/ageing-publicat-psychsoc.htm> [cited 2005 May 10]

4. Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry* 2003;64:134-43.
5. Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN, 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.
6. Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. *The Cochrane Database of Systematic Reviews* 2002, Issue 2. Art. No.: CD002852. DOI: 10.1002/14651858.CD002852.
7. Woollorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. *CMAJ* 2002;167:1269-70.
8. Woollorton E. Olanzapine (Zyprexa): increased incidence of cerebrovascular events in dementia trials. *CMAJ* 2004;170:1395.
9. Herrmann N, Mamdani M, Lanctot KL. Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* 2004;161:1113-5.
10. Lyketsos CG, DelCampo L, Steinberg M, Miles Q, Steele CD, Munro C, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Arch Gen Psychiatry* 2003;60:737-46.
11. Furlanos S, Greenberg P. Managing drug-induced hyponatraemia in adults. *Aust Prescr* 2003;26:114-17.
12. Tariot PN, Erb R, Podgorski CA, Cox C, Patel S, Jakimovich L, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry* 1998;155:54-61.

*Dr Byrne has been a member of national advisory committees on donepezil (Pfizer), rivastigmine (Novartis), and galantamine and risperidone (Janssen-Cilag).*

See **Patient Support Organisation: Alzheimer's Australia** on page 72.

## Self-test questions

*The following statements are either true or false (see answers on page 79)*

5. Altered behaviour in a patient with dementia may be the result of an intercurrent illness.
6. If an antipsychotic drug is prescribed to control behaviour problems in a patient with dementia, its use should be reviewed as the dementing condition changes.