

Professional Practice Guideline 10

Antipsychotic medications as a treatment of behavioural and psychological symptoms of dementia

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General principles

Behavioural and psychological symptoms of dementia (BPSD) have a significant impact on the quality of life for patients and their carers. Such symptoms are almost invariable in terms of frequency, occurring in over 95% of people with dementia at some point (Kales, Gitlin, Lykestos, 2015).

The first-line approach to management of BPSD is a person-centred, psychosocial, multidisciplinary treatment plan, as recommended by expert consensus guidelines.

Pharmacological approaches are considered where symptoms are severe, disabling, or syndromal and where a risk of significant harm exists. Various classes of medications may be of benefit in the treatment of BPSD. These practice guidelines have been prepared to inform clinicians of best practice principles regarding the role of antipsychotic medications in the treatment of BPSD.

Indications for antipsychotic medications in patients with dementia include:

- severe agitation and aggression associated with risk of harm
- delusions and hallucinations
- comorbid pre-existing mental health conditions.

It is important that, in obtaining informed consent, clinicians explain to the patient and their family/carer, the advantages and disadvantages of various treatments. It is not up to the clinician to make the final decision but rather the clinician should assist the patient and their family/carer to do so by providing a full explanation of potential risks and benefits of the relevant treatment.

From the outset, it should be emphasised that behavioural interventions should always be used prior to considering the use of any class of psychotropic medications for BPSD management. As stated by Professor Subee Banerjee in a report to United Kingdom Minister of State for Care Services:

In reviewing the evidence, these drugs appear to have only a limited positive effect in treating these symptoms but can cause significant harm to people with dementia. Clearly, some people do benefit from these medications and there are groups (e.g. where there is severe and complex risk) where trials have not been completed but where there may be particular value in using these medications (Banerjee, 2009).

The benefits and risks of antipsychotic medications

There have been numerous placebo controlled trials and several meta-analyses examining the efficacy of antipsychotic medications to treat BPSD. These studies show a small effect size of 0.13 to 0.20. (Schneider, Dagerman and Insel, 2006). Notably, this effect size is smaller than some non-pharmacological approaches to treatment of BPSD.

The only antipsychotic medication that is listed by the Pharmaceutical Benefit Scheme (PBS; Australia) and the Pharmaceutical Schedule (NZ) for patients showing 'behavioural disturbances in

dementia' is risperidone and this medication has the strongest evidence for its effectiveness (Brodaty et al., 2003).

There are mixed and limited results supporting the use of other atypical antipsychotics such as olanzapine, quetiapine and aripiprazole (Schneider, Dagerman and Insel, 2006). Older conventional antipsychotics, such as haloperidol, while having some efficacy in treating BPSD (Devanand et al., 1998), have a greater propensity to cause extrapyramidal symptoms (Suh, Son, Ju et al., 2004) and this is of particular concern for patients with Lewy Body Dementia.

In general, antipsychotic medications are associated with increased risks of central nervous system adverse events, sedation, exacerbation of existing cognitive impairment and confusion, fractures, falls, urinary tract infections, deep venous thromboses, peripheral oedemas, gait disturbances, akathisia and Q-T prolongation.

In 2004, a pooled analysis by the UK Committee on Safety of Medicines of data from four published and unpublished studies of risperidone pointed to a three-fold risk of 'cerebrovascular events' (3.5% versus 1.2%) versus placebo. These events included non-specific neurological symptoms like dizziness, headaches and 'funny turns' through to transient ischaemic attacks and completed stroke. There was no difference in mortality rates. The Committee presented no data from trials of olanzapine but concluded that it was associated with a similarly increased risk of stroke and a two-fold increase in mortality compared with placebo (CSM, 2004).

In 2005, the US Food and Drug Administration noted that in analyses of 17 placebo-controlled studies of atypical antipsychotics, the mortality rate for elderly patients with dementia was about 1.6–1.7 times that of placebo. Although the causes of death were varied most seemed to be either cardiac related (such as heart failure or sudden death) or from infections (pneumonia; FDA, 2005). Around the same time a meta-analysis of published and unpublished data from five randomised controlled trials of risperidone, five of olanzapine, three of quetiapine and three of aripiprazole, found death rates among the 3353 patients with dementia were 3.5% for those taking the medications versus 2.3% for those on placebo (Schneider, Dagerman and Insel, 2005).

In light of this and other evidence, risperidone is listed in Australia for prescription on the PBS for patients showing 'behavioural disturbances in Alzheimer's disease' for a period not exceeding 12 weeks. The Pharmaceutical Benefits Advisory Committee was 'satisfied that the benefits of risperidone outweighed its risks in this patient group but recommended that a caution relating to the increased risk of stroke be added to the listing' (CSM, 2004). On the Pharmaceutical Schedule in NZ, risperidone is indicated for the treatment of aggression in moderate to severe Alzheimer's dementia unresponsive to non-pharmacological interventions and when there is a risk of harm to self or others.

Since these studies, there have been a number of observed associations between mortality and the use of both conventional and atypical antipsychotics (Gerhard et al., 2014; Kales et al., 2012; Rossom et al., 2010; Huybrechts et al., 2012) that are dose-related (Rossom et al., 2010) and reveal a greater mortality risk associated with conventional antipsychotics than with atypical antipsychotics, a finding that remained robust even when adjusted for terminal illness (Park et al., 2015).

In summary, the use of antipsychotics in patients with dementia is associated with an increased risk of cerebrovascular events (including stroke) and death due to any cause. The potential mechanisms leading to stroke and death are not clear, but could include orthostatic hypotension, anticholinergic side effects, Q-T prolongation, platelet aggregation effects and venous thromboembolism (Wang et al., 2005).

The presence of cardiovascular disease and vascular risk factors (e.g. stroke history, hypertension, diabetes), QTc interval on electrocardiogram, electrolytic imbalances, family history of torsades des pointes, concomitant treatments and use of other drugs which lengthen QTc may

confer additional risk. A thorough history should be obtained before commencement of pharmacological treatments.

Using antipsychotic medications in patients with BPSD

1. Targeting Symptoms

Use of antipsychotic medications are recommended when BPSD are psychotic in nature, unresponsive to psychosocial interventions or there is a severe and complex risk of harm (Burns et al., 2012). Conversely, antipsychotic medications are not recommended and are unlikely to be effective in certain symptoms such as wandering, undressing, inappropriate voiding, verbal aggression or screaming.

When considering the use of antipsychotic medications, the clinician should target specific symptoms. The use of antipsychotics should be reserved for those patients experiencing significant agitation, aggression or psychosis as manifestations of their BPSD. Mental disorders comorbid with dementia such as major depression require specific and appropriate pharmacotherapy.

2. Choosing an antipsychotic

Antipsychotics differ with respect to efficacy and side effects. The decision regarding which antipsychotic to use is a clinical one based on a careful risk–benefit analysis for each patient. Before deciding to prescribe an antipsychotic drug, clinicians should consider the following factors:

- Risperidone is the only oral medication approved in Australia and New Zealand for use in behavioural disturbances associated with Alzheimer's type dementia.
- Other antipsychotics such as quetiapine, olanzapine or aripiprazole if used for BPSD are off label and should only be considered if risperidone is not tolerated or is not appropriate (RANZCP, 2016).
- Olanzapine is the only antipsychotic approved for parenteral (intramuscular) use in Australia for patients with BPSD. It is noted that this medication is intended for patients who are orally non-compliant or in an acute emergency setting.
- Consider alternative medications – there is some evidence supporting the efficacy of citalopram, cholinesterase inhibitors (ChEIs) and memantine in the management of psychotic symptoms in dementia (Burns et al., 2012).

3. Consent

When prescription of a medication is being considered, informed consent is essential. Therefore, it is necessary that information about the risks and benefits of prescribing a medication to a person with dementia is conveyed to the person or their substitute decision maker, and that this is understood.

4.1. Acute situations

In an acute situation, when the safety of the patient or significant others are at risk, the common law principle of necessity allows a doctor to act in an emergency in the best interests of a patient unable to provide valid consent to their own treatment. In such circumstances, treatment should be initiated quickly and targeted appropriately with the object of minimising distress and injury. Informed consent from the appropriate individual(s) should then be obtained as soon as practicable if treatment is to be continued. Local guardianship or mental health legislation may also offer guidance.

4.2. Non-acute situations

In non-acute situations, informed consent for the use of antipsychotics should always be obtained from the person themselves where possible. The person with dementia should receive an explanation of suggested treatments offered in such a way as to maximise his/her understanding of what is involved. Commonly, the person with dementia is unable to consent but is not objecting

to the treatment and informed consent should then be obtained from either the 'person responsible' or a legal guardian.

Where the person with dementia is unable to provide informed consent and is objecting to taking antipsychotic medication, management should follow local guardianship or mental health legislative guidelines.

5. Monitoring treatment

The use of an instrument designed to rate and monitor BPSD symptoms such as the Neuropsychiatric Inventory, the Behave-AD or the Cohen–Mansfield Agitation Inventory is a useful strategy (Cummings et al., 1994).

Clinical guidelines suggest that when psychotropic medications are indicated, the start low, go slow strategy should be used and there is a need for systematic, sequential trialling of one drug at a time with side effects being monitored regularly and with the drug ceased immediately if significant adverse effects are noted. It is recommended that doses of up to a maximum of 2mg should be prescribed for this population.

Since the natural history of BPSD is variable (symptoms may be intermittent and may settle spontaneously), it is recommended that the use of such agents is time limited and reviewed for their potential discontinuation at least three-monthly (NSW Ministry of Health, 2013).

References

Banerjee S (2009) The use of antipsychotic medication for people with dementia: Time for action. Available at: www.aph.gov.au/DocumentStore.ashx?id=48340346-1dbd-4e37-920b-0e724229047b (accessed 22 August 2016).

Brody H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, Lee E, Lyons B, Grossman F (2003) A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *Journal of Clinical Psychiatry* 64(2): 134–43.

Brody H, Arasaratnam C (2012) Meta-analysis of non-pharmacological interventions for neuropsychiatric symptoms of dementia. *American Journal of Psychiatry* 169(9): 946–53.

Burns K, Jayasinha R, Tsang R, Brody H (2012) Behaviour management a guide to good practice: managing behavioural and psychological symptoms of dementia. Available at: www.dementiaresearch.com.au/images/dcrc/output-files/328-2012_dbmas_bpsd_guidelines_guide.pdf (accessed 22 August 2016).

Chenoweth L, King MT, Jeon YH, Brody H, Stein-Parbury J, Norman R, Haas M, Luscombe G (2009) Caring for aged dementia care resident study (CADRES) of person-centred care, dementia-care mapping, and usual care in dementia: a cluster-randomised trial. *The Lancet Neurology* 8(4): 317–325.

Committee on Safety of Medicines (2004) Atypical antipsychotic drugs and stroke. Available at: <http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019488.pdf> (accessed 22 August 2016).

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 44: 2308–2314.

Devanand DP, Marder K, Michaels KS, Sackeim HA, Bell K, Sullivan MA, Cooper TB, Pelton GH, Mayeux R (1998) A randomized, placebo-controlled, dose-comparison trial of haloperidol treatment for psychosis and disruptive behaviors in Alzheimer's disease. *American Journal of Psychiatry* 155: 1512–1520.

- Food and Drug Administration (2005) Deaths with antipsychotics in elderly patients with behavioural disturbances. Available at: www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171 (accessed 22 August 2016).
- Gerhard T, Huybrechts K, Olfson M, Schneeweiss S, Bobo WV, Doraiswamy DP (2014) Comparative mortality risks of antipsychotic medications in community-dwelling older adults. *British Journal of Psychiatry* 205: 44–51.
- Husebo BS, Ballard C, Sandvic R, Nilssen OB, Aarsland D (2011) Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomized clinical trial. *British Journal of Medicine* 343: d4065.
- Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin J, Lucas JA, Schneeweiss S (2012) Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population cohort study. *British Medical Journal* 344: e977.
- Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, Cunningham F, Schneider LS, Blow FC (2012) Risk of mortality among individual antipsychotics in patients with dementia. *American Journal of Psychiatry* 169: 71–79.
- Kales HC, Gitlin LN, Lykestos CG (2015) Assessment and Management of BPSD. *British Medical Journal* 350: 369.
- McAuliffe L, Nay R, O'Donnell M, Fetherstonhaugh D (2009) Pain assessment in older people with dementia: literature review. *Journal of Advanced Nursing* 65: 2–10.
- National Prescribing Service (2005) Risperidone (Risperdal) for behavioural disturbances in dementia. *Rational Assessment of Drugs and Research* April 2005: 1–6.
- NSW Ministry of Health (2013) Assessment and management of people with behavioural and psychological symptoms of dementia: a handbook for NSW clinicians. Available at: www.ranzcp.org/Files/Publications/A-Handbook-for-NSW-Health-Clinicians-BPSD_June13_W.aspx (accessed 22 August 2016).
- Park Y, Franklin JM, Schneeweiss S, Levin R, Crystal S, Gerhard T, Huybrechts KF (2015) Antipsychotics and mortality: adjusting for mortality risk scores to address confounding by terminal illness. *Journal of the American Geriatrics Society* 63(3): 516–23.
- Royal Australian and New Zealand College of Psychiatrists (2016) Professional Practice Guideline 4: 'Off-label' prescribing in psychiatry. Available at: www.ranzcp.org/Files/Resources/College_Statements/Practice_Guidelines/PPG-4-Off-label-prescribing-in-psychiatry-Feb-2016.aspx (accessed 22 August 2016).
- Rossom RC, Rector TS, Lederle FA, Dyksen MW (2010) Are all commonly prescribed antipsychotics associated with greater mortality in elderly male veterans with dementia? *Journal of American Geriatric Society* 58: 1027–1034.
- Schneider LS, Dagerman K, Insel PS (2006) Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomised, placebo-controlled trials. *American Journal of Geriatric Psychiatry* 14: 191–210.
- Suh GH, Son HG, Ju YJ, Jcho KH, Yeon BK, Shin YM, Kee BS, Choi SK (2004) A randomized, double-blind, crossover comparison of risperidone and haloperidol in Korean dementia patients with behavioural disturbances. *American Journal of Geriatric Psychiatry* 12: 509–516.

Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, Brookhart A (2005) Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *New England Journal of Medicine* 353: 2335–2341.

Resources

Burns K, Jayasina R, Tsang R, Brodaty H (2012) *Behaviour Management – A Guide to Good Practice: Managing Behavioural and Psychological Symptoms of Dementia*. New South Wales: Dementia Collaborative Research Centre – Assessment and Better Care (DCRC-ABC).

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