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; Rosom et al., 2010; Huybrechts et al., 2012) that are dose-related (Rosom 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


Resources

Disclaimer
This information is intended to provide a general guide to practitioners, and should not be relied on as a substitute for proper assessment with respect to the merits of each case and the needs of the patient. The RANZCP endeavours to ensure that information is accurate and current at the time of preparation, but takes no responsibility for matters arising from changed circumstances, information or material that may have become subsequently available.

Revision Record Footer

<table>
<thead>
<tr>
<th>Date</th>
<th>Version</th>
<th>Approver</th>
<th>Description</th>
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</tr>
</tbody>
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