

ANTIPSYCHOTICS

KEY POINTS

- Antipsychotics are effective in approximately one in five dementia patients for short-term management of significant agitation, aggression and psychosis.
- Antipsychotics are less effective for some types of behavioural problems, for example, wandering, calling out, urinating in inappropriate places and hypersexuality.
- Non-pharmacological therapy is equally or more effective than antipsychotics in many patients with BPSD.
- Antipsychotics may precipitate adverse effects, some of which mimic behavioural and psychological symptoms of dementia, e.g. akathisia).
- Serious adverse effects of antipsychotic agents include falls, increased mortality and increased risk of stroke.
- Some people are more sensitive to the adverse effects of antipsychotic agents, such as those with Parkinson's Disease, Lewy Body Dementia or cardiac damage.
- Most patients on long-term antipsychotics for BPSD can have their antipsychotics ceased, often with an improvement in symptoms.
- Pain in patients with impaired language and dementia may manifest as agitation.

CONTEXT

This guide considers the use of antipsychotic agents in the context of the behavioural and psychological symptoms of dementia (BPSD).

RECOMMENDED DEPRESCRIBING STRATEGY

- Patients with dementia whose behavioural symptoms are unchanged or improving over weeks or months may benefit from a trial of dose reduction or cessation of antipsychotics.
- Patients who no longer have any troublesome BPSD may benefit from a trial of dose reduction or cessation of antipsychotics.
- Patients who have been symptom or target behaviour free for three months or more, should be considered for a trial of cessation of antipsychotics
- Discontinuation of antipsychotics should be gradual, particularly if use has been long term. The longer the medication has been prescribed and the less the concern over current adverse drug reactions, the slower the withdrawal can be.¹
- The Dementia Behaviour Management Advisory Service has developed a BPSD Guide, which is available as a phone or device application.

EFFICACY

Many randomised trials have attempted to demonstrate efficacy of antipsychotic agents in dementia patients with behavioural and psychological symptoms of dementia. Most of these studies have small sample sizes and monitor patients for a maximum of 12 weeks.

First-generation agents have been examined in a systematic review. A meta-analysis covering 12 trials was unable to find any clear evidence for efficacy of conventional antipsychotics, such as perphenazine, thioridazine and haloperidol.²

The Clinical Antipsychotic Trial of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) was a 42-site double-blind placebo-controlled trial of 421 patients with behavioural and psychological symptoms of dementia. BPSD symptoms included psychosis, aggression or agitation. Patients were randomised to a flexible dose regimen of risperidone, quetiapine, olanzapine or placebo for up to 36 weeks. The main outcome was time to discontinuation. No significant differences were found in overall time to discontinuation or in clinical improvement between treatment with antipsychotics and placebo.³

EFFICACY

The study allowed for a change between treatments at the physician's discretion after a 12-week period (termed end of Phase One). An analysis of the Phase One results indicated that antipsychotic agents may be more effective for particular symptoms such as anger, aggression and paranoid ideas.⁴

A 2006 Cochrane review of the use of atypical antipsychotic agents found that risperidone and olanzapine had a beneficial effect on aggression symptoms in approximately 20% of patients.⁵

While some improvement in BPSD may occur during the initial phases of treatment with antipsychotics, there is no evidence that long-term treatment changes outcomes. Some behaviours are not changed by antipsychotics in the intermediate to long term. These include wandering, calling out, urinating in inappropriate places and hypersexuality. Indeed, a study of withdrawal of antipsychotic agents in 102 dementia patients who had been taking antipsychotics – at least 10mg chlorpromazine equivalent or 0.5mg risperidone – for BPSD for three months or more found that cessation did not impact significantly on neuropsychiatric index.⁶

A Cochrane review of withdrawal vs continuation of chronic antipsychotic drugs for BPSD in older people with dementia was published in 2013.⁷ They found that overall, in seven of nine trials, antipsychotics could be withdrawn without a significant effect on most outcomes. In particular, behavioural symptoms, as measured by the neuropsychiatric index were not influenced in most people.⁷ They found some evidence that patients with more severe BPSD (as indicated by a neuropsychiatric index score over 14) could benefit from continuing antipsychotic treatment. They also found that some patients who previously had psychotic features or severe agitation may relapse after discontinuation.⁷

The Dementia Behaviour Management Advisory Service provides a comprehensive guide to non-pharmacological and pharmacological management of specific behaviours commonly encountered in dementia. The BPSD Guide was developed to provide guidance for clinicians in their role of assisting residential aged care facility staff, community care staff and family members caring for persons living with dementia, who present with behavioural and psychological symptoms. The guide is now available as a phone/device application. The app provides summary information relevant to the most commonly presenting behavioural and psychological symptoms of dementia (<http://dbmas.org.au/resources/bpsd-guide-app/>) (<http://dbmas.org.au/resources/bpsd-guide-app/>)⁸

One important factor to consider is the role of inadequately managed pain in patients with dementia. Pain in patients with impaired language and dementia may manifest as agitation. More effective treatment of undiagnosed pain may contribute to the overall management of agitation in patients with dementia.^{9,10,11}

ADVERSE EFFECTS

Antipsychotics have a range of metabolic, cardiac, movement and CNS adverse effects. Metabolic adverse effects include weight gain, diabetes and the development of metabolic syndrome. Many antipsychotic agents also prolong the QT interval and can exacerbate or precipitate arrhythmias and syncope. Movement disorders that can result from, or be exacerbated by, antipsychotics include a range of extrapyramidal symptoms from acute dystonic reactions, akathisia, parkinsonism and tardive dyskinesia. CNS adverse effects can be variable, with somnolence, cognitive worsening and occasionally abnormal gait and seizures.

Akathisia is an extrapyramidal syndrome that may be induced by antipsychotic and other anti dopaminergic agents. It is characterised by an "inner restlessness" that makes the patient feel anxious, agitated and is often associated with an urge to move, manifesting as pacing, leg movements or leg rubbing. This adverse effects typically commences 3-8 weeks after initiation or dose increase of an antipsychotic agent.

In addition to these adverse effects, there are serious concerns regarding the use of antipsychotics in patients with dementia in terms of increased mortality, strokes and falls.

INCREASED MORTALITY

In 2005, the United States Food and Drug Administration (FDA) analysed 17 trials of atypical antipsychotic use in dementia (some of which were unpublished) and showed an increased relative risk of death of approximately 54-70% (an absolute increased risk of 1-2% per year; NNH 50-100).¹² The increased mortality was mainly due to vascular or infectious causes.

The FDA warning was subsequently extended to cover all antipsychotics (including the older agents) following retrospective population-based studies that demonstrated that typical antipsychotics also showed a similar increased risk of death.^{13,14} A recent retrospective cohort study using national data from the US Department of Veterans Affairs for patients ≥65 years old with dementia, beginning outpatient treatment with an antipsychotic (risperidone, olanzapine, quetiapine, or haloperidol) or valproic acid examined mortality.¹⁵ They found:

- Haloperidol: 45.8 deaths per 100 person years: RR 1.54 (95%CI 1.38-1.73)
- Risperidone: 27.5 deaths per 100 person years : RR 1.00 (reference)
- Olanzapine: 27.1 deaths per 100 person years : RR 0.99 (95%CI 0.89-1.10)
- Valproate: 21.0 deaths per 100 person years : RR 0.91 (95%CI 0.78-1.06)
- Quetiapine: 18.6 deaths per 100 person years : RR 0.73 (95%CI 0.67-0.80)

Mittal et al. reviewed the evidence relating to antipsychotic associated cerebrovascular events and mortality risk.¹⁶ The increase in mortality was 1.2-1.6 fold higher when antipsychotics were used. Older age, male gender, severe dementia and functional impairment were all associated with a higher risk of death.¹⁶

Long-term mortality follow-up data from the DART-AD study indicated that discontinuation of antipsychotics was associated with reduced mortality at 12, 24, and 36 months.¹⁷

INCREASED RISK OF STROKE

The evidence regarding increased stroke risk associated with the use of atypical antipsychotic drugs is conflicting. While several studies have reported such a link,^{2,18,19,20} others have not.^{21,22,23}

A Cochrane review of five studies of risperidone use in dementia patients found a rate of stroke of 37/1175 (3.1%) for risperidone in 13 weeks of treatment compared to 8/779 (1%) for placebo. (OR 3.64 [95%CI 1.72-7.69]; ARI 2.1% NNH 47).²⁴

Mittal et al. also reviewed the evidence relating to antipsychotic associated cerebrovascular events and mortality risk.¹⁶ They concluded that the risk of cardiovascular events was 1.3-2 times higher in patients treated with antipsychotics. No one drug was found to be safer than others in terms of the cerebrovascular risk. They also concluded that higher doses, older age of patient, presence of vascular dementia and presence of atrial fibrillation all increased the risk of stroke.¹⁶

The Therapeutic Goods Administration in Australia recently limited the indication for risperidone in dementia patients and restricted its use to short-term management. The updated dementia-related indication for risperidone is: treatment (up to 12 weeks) of psychotic symptoms, or persistent agitation or aggression unresponsive to non-pharmacological approaches in patients with moderate to severe dementia of the Alzheimer type.

This change was based on the increased risk of stroke being more prominent in patients with vascular or mixed dementia, compared to Alzheimer's type dementia. The odds ratio for any cerebrovascular adverse event in patients with vascular or mixed dementia taking risperidone was 5.26 (95% confidence interval [CI] 1.18-48.11). The comparative odds ratio for Alzheimer's dementia patients was 2.23 (95% CI 0.85-6.88).²⁵

INCREASED RISK OF FALLS

Antipsychotics are associated with an increased risk of falls. Multiple meta-analyses of the impact of drugs on falls found increased relative risk of falls associated with antipsychotic/neuroleptic use. These were reviewed recently and an overall increase in risk of at least one fall during the reported trial periods (often 12 weeks or less) was between 25-79%.^{26,27,28,29,30}

A number of reviews and studies have indicated that cessation of antipsychotic agents is associated with a reduction in risk of falls.^{31,32}

FACTORS TO CONSIDER

IN FAVOUR OF DEPRESCRIBING

- ✔ Any patients with overt or suspected adverse effects will be more likely to benefit from dose reduction or cessation of the antipsychotic agent.
- ✔ Some patients may be at higher risk of adverse effects from antipsychotics and these agents should be reconsidered regularly in such patients. These include patients taking agents that prolong QT syndrome (TCAs, macrolides) and patients with:
 - Parkinson's Disease
 - Lewy Body Dementia³⁴
 - previous stroke or TIA history
 - existing prolonged QT syndromes
 - existing cardiac damage and electrolyte disorders (esp. hypokalaemia, hypomagnesaemia).³⁵
- ✔ Patients whose dementia has progressed and whose previous behaviours of concern have ceased or lessened are less likely to relapse into worsening behaviours if the antipsychotic is ceased.

AGAINST DEPRESCRIBING

- ✘ Patients with more severe behavioural and psychological symptoms of dementia, for example violent aggression or distressing agitation may be more likely to worsen behaviour if dose reduction or cessation is attempted.
- ✘ Patients with a pre-dementia history of psychosis or other psychiatric disorder requiring antipsychotics may worsen their underlying psychiatric condition by reducing or ceasing antipsychotics.

DISCONTINUATION SYNDROMES

Most studies have found that many individuals can have antipsychotics safely discontinued without worsening of behavioural symptoms.^{5,17} Predictors of successful discontinuation antipsychotics include lower daily doses of antipsychotics and lower baseline severity of behavioural and psychological symptoms of dementia.

The Royal Australian New Zealand College of Psychiatrists recommends that withdrawal of antipsychotics should be done gradually, for example by reducing the dose by 50% every two weeks then stopping after two weeks on the minimum dose. They also recommend monitoring for recurrence of target symptoms or behaviours or emergence of new ones. They state that the longer the medication has been prescribed, no matter at what dose, and the less the concern over current adverse drug reactions, the slower the withdrawal can be.³³

RESOURCES

 QUICK REFERENCE GUIDE

 GENERAL INFORMATION

 ALLOPURINOL

 ANTIHYPERTENSIVES

 ANTIPLATELET AGENTS

 ANTIPSYCHOTICS

 BENZODIAZEPINES

 BISPHOSPHONATES

 CHOLINESTERASE INHIBITORS

 GLAUCOMA EYE DROPS

 NSAIDS

 OPIOIDS

 PROTON PUMP INHIBITORS

 STATINS

 SULPHONYLUREAS

 VITAMIN D AND CALCIUM

AUTHORSHIP

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