

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 than others (eg. wandering, calling out, sexual disinhibition, urinating in inappropriate places).
- Non-pharmacologic therapy is equally or more effective than antipsychotics in many patients with behaviours associated with dementia.
- Antipsychotics may precipitate a number of adverse effects, some of which may mimic behavioural and psychological symptoms of dementia.
- Serious adverse effects of antipsychotic agents may include falls, increased mortality and increased risk of strokes.
- Certain patient groups are more sensitive to the adverse effects of antipsychotic agents (Parkinson's Disease, Lewy Body Dementia, cardiac damage)
- Most patients on long term antipsychotics for behavioural and psychological symptoms of dementia can have their antipsychotics ceased, often with an improvement in symptoms.
- Discontinuation of antipsychotics should be gradual, particularly if use has been long term.

CONTEXT

This guide covers the use of antipsychotics in the context of behavioural and psychological symptoms of dementia (BPSD). Other drug classes eg. anticonvulsants, antidepressants and anxiolytics have also been prescribed in BPSD, thus care is required to ascertain the original indication for each medication.

RECOMMENDED DEPRESCRIBING STRATEGY

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| 1 | Patients with dementia whose behavioural symptoms are unchanged or improving over several weeks or months may benefit from a trial of dose reduction and/or cessation of antipsychotics. |
| 2 | Patients who no longer have any troublesome behavioural and psychological symptoms of dementia may benefit from a trial of dose reduction and/or cessation of antipsychotics. |
| 3 | Consideration may be given to a trial of cessation of antipsychotics if a person has been symptom/target behaviour free for three to six months. |
| 4 | Withdrawal should be considered no less than annually in all cases. |
| 5 | Withdrawal of antipsychotics should be done gradually. For example, reducing the dose by 50% every two weeks and ceasing after two weeks on the minimum dose. |

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 the majority monitor patients for a maximum of 12 weeks. Older 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 (eg perphenazine, thioridazine, haloperidol).¹ 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 and patients were randomised to a flexible dose regimen of risperidone, quetiapine, olanzapine or placebo for up to 36 weeks.² 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.²

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 the metabolic syndrome. Many antipsychotic agents also prolong QT interval and can exacerbate or precipitate arrhythmias and syncope. Movement disorders include a range of extrapyramidal symptoms from acute dystonic reactions, through akathisia, parkinsonism and tardive dyskinesia. CNS symptoms 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, increased strokes and increased falls.

INCREASED MORTALITY

In 2005, the United States Food and Drug Administration 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).⁸ 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.^{9,10} 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.¹¹ 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)

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.¹²

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,^{13, 14, 15, 16} others have not.^{17, 18, 19}

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).²⁰

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%.

A number of reviews and studies have indicated that cessation of antipsychotic agents is associated with a reduction in risk of falls.^{21, 22, 23, 24}

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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.³

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.⁴

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, 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 3 months or more found that cessation did not impact on neuropsychiatric index significantly.⁵

A Cochrane review of withdrawal vs continuation of chronic antipsychotic drugs for BPSD in older people with dementia was published in 2013.⁶ 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.⁶ 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.⁶

The Dementia Behaviour Management Advisory Service provides a comprehensive guide to non-pharmacological and pharmacological management of specific behaviours commonly encountered in dementia.⁷



DISCONTINUATION SYNDROMES

Most studies have found that many individuals can have antipsychotics safely discontinued without worsening of behavioural symptoms.^{4,12} Predictors of successful discontinuation antipsychotics include lower daily doses of antipsychotics and lower baseline severity of behavioural and psychological symptoms of dementia.

The 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.²⁷



FACTORS TO CONSIDER BEFORE DEPRESCRIBING

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 with Parkinson's Disease
- ✓ Patients with Lewy Body Dementia²⁵
- ✓ Patients with previous stroke or TIA history
- ✓ Patients with existing prolonged QT syndromes
- ✓ Patients taking agents that prolong QT syndrome (TCAs, macrolides)
- ✓ Patients with existing cardiac damage and electrolyte disorders (esp. hypokalaemia, hypomagnesaemia).²⁶
- ✓ 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.

RESOURCES

- ☒ QUICK REFERENCE GUIDE
- ☒ ANTIHYPERTENSIVES GUIDE
- ☒ ANTIPLATELET AGENTS GUIDE
- ☒ ANTIPSYCHOTICS GUIDE
- ☒ BENZODIAZEPINES GUIDE
- ☒ BISPHOSPHONATES GUIDE
- ☒ STATINS GUIDE
- ☒ VITAMIN D & CALCIUM GUIDE



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