

# ANTIPSYCHOTICS

## KEY POINTS

- Non-pharmacological therapy, particularly person-centred interventions that address the precipitants of the symptoms, is often equally or more effective than antipsychotics in the majority of people with BPSD.
- Antipsychotics are effective in approximately one in five people with dementia for short term management of significant agitation, aggression and psychosis.
- Antipsychotics are considerably less effective for some types of behavioural problems than others (e.g. wandering, calling out, sexual disinhibition, urinating in inappropriate places).
- Serious adverse effects of antipsychotic agents may include falls, increased mortality and increased risk of stroke. The risk of several of these is evident within weeks of commencing treatment.
- Antipsychotics may precipitate a number of adverse effects, particularly akathisia, some of which may mimic BPSD.
- Certain groups of people are more sensitive to the adverse effects of antipsychotic agents (e.g. those with Parkinson's disease, Lewy body dementia, or cardiac disease).
- Most people on long term antipsychotics for behavioural and psychological symptoms of dementia can have their antipsychotics ceased, often without any decline in BPSD.
- Discontinuation of antipsychotics should be gradual, particularly if use has been long term.

## CONTEXT

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

## RECOMMENDED DEPRESCRIBING STRATEGY

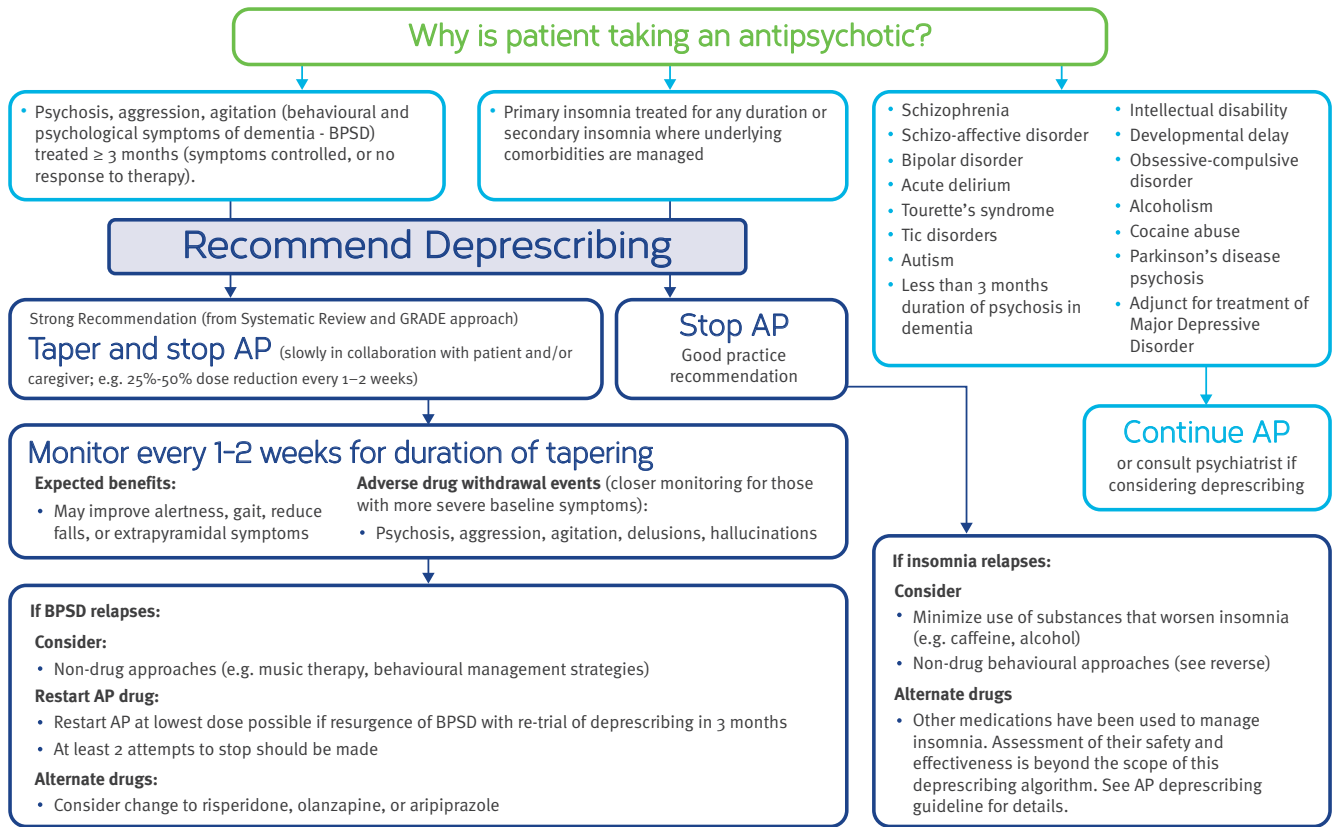
- Consensus-based deprescribing guidelines that address antipsychotic use for BPSD were published by a Canadian group in 2018 (see **Figure 1, Page 2**).
- Consideration may be given to a trial of cessation of antipsychotics if a person has been symptom/target behaviour free for three months or more.
- People whose BPSD are unchanged or improving over several weeks or months may benefit from a trial of dose reduction and/or cessation of antipsychotics.
- The provision of person-centred interventions that address the precipitants of BPSD should be maintained throughout the provision of care.

## BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
<p><b>Main Benefits</b></p> <ul style="list-style-type: none"> <li>➤ Moderate, short term reduction of agitation, aggression and psychosis</li> </ul>	<p><b>Increased Benefit</b></p> <ul style="list-style-type: none"> <li>➤ Presence of severe, distressing hallucinations or delusions</li> <li>➤ Presence of severe agitation or aggression</li> <li>➤ Previously naive to use of antipsychotics</li> <li>➤ History of symptom recurrence with previous discontinuation</li> <li>➤ Presence of coexisting psychiatric conditions that responded to antipsychotic treatment</li> </ul>	<p><b>Decreased Benefits</b></p> <ul style="list-style-type: none"> <li>➤ Over 3 months of continuous use</li> <li>➤ Use for symptoms that are unlikely to respond (apathy, antisocial behaviour, wandering etc.)</li> <li>➤ Progression to severe dementia</li> </ul>
<p><b>Main Harms</b></p> <ul style="list-style-type: none"> <li>➤ Falls, strokes, increased mortality, extrapyramidal symptoms</li> </ul>	<p><b>Reduced Harms</b></p> <ul style="list-style-type: none"> <li>➤ Functionally independent and robust condition</li> </ul>	<p><b>Increased Harms</b></p> <ul style="list-style-type: none"> <li>➤ Presence of Parkinson's Disease or other movement disorder</li> <li>➤ Presence of cerebrovascular disease</li> <li>➤ Diagnosis of vascular or mixed dementia</li> <li>➤ Use in patients with high falls risk</li> <li>➤ Presence of risk factors for diabetes mellitus</li> </ul>



deprescribing.org | Antipsychotic (AP) Deprescribing Algorithm



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Bjere LM, Farrell B, Hogel M, Graham L, Lemay G, McCarthy L, et al. Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: Evidence-based clinical practice guideline. *Can Fam Physician* 2018;64:17-27 (Eng), e1-e12 (Fr).



Figure 1: Antipsychotic (AP) deprescribing algorithm <sup>39</sup>

**BACKGROUND**

The term “behavioural and psychological symptoms of dementia” (BPSD) describes a constellation of non-cognitive phenomena frequently observed in people with dementia, particularly in the latter stages of the disease. Behavioural symptoms include agitation, aggression, walking without purpose and vocalisation; psychological symptoms include hallucinations, delusions, depression and psychosis.

BPSD are presumed to occur due to multiple interacting factors, including pathological changes in the brain, the person's lived experience, unmet needs, environment, emotions, and altered clinical circumstances (e.g. pain, constipation or infection). Consequently, the most appropriate strategy to support a person with dementia who has BPSD is to identify and address as many precipitants as possible. Such measures frequently mitigate the need to use pharmacological measures, and avoids the risk of adverse effects associated with medication use. Nonetheless, the use of antipsychotic agents for BPSD is particularly common.

Dementia Support Australia (DSA) provides a comprehensive guide to non-pharmacological and pharmacological management of specific behaviours commonly encountered in dementia. The guide is available in several formats at <https://www.dementia.com.au/resources/library>.

 EFFICACY

Many randomised trials have evaluated the efficacy of antipsychotic agents for BPSD. As most of these studies had small sample sizes, monitored participants for a maximum of 12 weeks, and a number had methodological limitations, the applicability of their findings to practice is somewhat limited.<sup>1</sup> Furthermore, the rate of response to treatment with placebo in several studies was around 30%.

The evidence regarding older agents (conventional or “typical” antipsychotics) is particularly limited. These medications were evaluated in a systematic review and meta-analysis that involved two previous meta-analyses of 12 trials, and two additional studies.<sup>2</sup> This review reported that there was no clear evidence for efficacy for alleviating BPSD in any of the conventional antipsychotics included in the analysis (such as haloperidol, trifluoperazine and thioridazine). A 2002 Cochrane review of haloperidol for agitation in dementia found some benefit for aggression, but not for other BPSD including agitation.<sup>3</sup>

Newer, “atypical” antipsychotics have been evaluated somewhat more thoroughly. The CATIE-AD was a 42 site, double blind, placebo controlled trial of 421 people with BPSD. BPSD symptoms included psychosis, aggression, and agitation; participants were randomised to a flexible dose regimen of risperidone, quetiapine, olanzapine or placebo for up to 36 weeks.<sup>4</sup> 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.<sup>4</sup> 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.<sup>5</sup>

A 2006 Cochrane review of the use of atypical antipsychotic agents found that risperidone and olanzapine had a beneficial effect on aggression in approximately 20% of people.<sup>6</sup> A 2016 systematic review of 10 meta-analyses involving atypical antipsychotics for BPSD concluded that risperidone, olanzapine and aripiprazole modestly improve BPSD, with psychosis, aggression, agitation and more severe symptoms the most responsive to atypical antipsychotic treatment.<sup>7</sup> The same review reported that there is no evidence that quetiapine is of benefit for BPSD.

Whilst improvement in some behaviours may occur during the initial phases of treatment with antipsychotics, there is minimal evidence of efficacy in the long term (i.e. more than 3 months). Some behaviours are not improved by antipsychotics in the intermediate to long term, such as wandering, undressing, urinating inappropriately, shadowing staff or calling out (see **Table 1**).

A study of withdrawal of antipsychotic agents in 102 people with dementia who had been taking antipsychotics (at least 10mg chlorpromazine equivalent or 0.5mg risperidone daily) for BPSD for 3 months or more found that cessation did not significantly affect symptom severity, as measured by the Neuropsychiatric Inventory (NPI).<sup>8</sup>

A Cochrane review that assessed ten studies that investigated withdrawal versus continuation of chronic antipsychotic drugs for BPSD was published in 2018.<sup>9</sup> Whilst it was not possible to meta-analyse data from all ten trials due to a high level of heterogeneity, the review found that, in general, **antipsychotic discontinuation appeared to make minimal to no difference in overall BPSD** as measured by the NPI. In fact, there was some evidence that antipsychotic discontinuation reduced agitation in people with less severe BPSD at baseline. Conversely, those with more severe BPSD (as indicated by a NPI score >14) may have benefited from continuing antipsychotic treatment, particularly people who previously had psychotic features or severe agitation.<sup>9</sup> Similarly, Patel et al reported that people with severe hallucinations at baseline were significantly more likely to relapse with the cessation of risperidone, compared to those with mild or no hallucinations (HR 2.96, 95% CI 1.52 to 5.76).<sup>10</sup>

ANTIPSYCHOTICS MAY HELP TO MANAGE SYMPTOMS OR BEHAVIOURS LIKE:	ANTIPSYCHOTICS DO NOT HELP TO MANAGE SYMPTOMS OR BEHAVIOURS LIKE:
✔ Hallucinations (hearing voices, seeing things/people)	✘ Apathy or not being social with others
✔ Delusions (paranoia or severe suspicion)	✘ Inappropriate behaviour (urinating inappropriately, sexual advances, removing clothes)
✔ Severe Agitation (screaming, severe irritability, sleep disturbances)	✘ Perseveration (repeating actions or words over and over)
✔ Aggression (shouting, kicking/biting/hitting)	✘ Wandering or restlessness
	✘ Hoarding/hiding items

Table 1: Symptoms likely or unlikely to respond to antipsychotics



## 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 between approximately 54 and 70% (an absolute increased risk of 1-2% per year; NNH 50-100)<sup>11</sup>. The increased mortality was mainly due to vascular or infectious causes. A boxed warning was issued at this time.

The FDA warning was subsequently extended in 2008 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.<sup>12,13</sup>

A retrospective cohort study examined mortality using national data from the US Department of Veterans Affairs for people ≥65 years old with dementia, beginning outpatient treatment with an antipsychotic (risperidone, olanzapine, quetiapine, or haloperidol) or valproic acid.<sup>14</sup> They associated the commencement of antipsychotic treatment with the following absolute increases in mortality risk and numbers needed to harm after 180 days:

- Haloperidol: 3.8% (95%CI 1.0 to 6.6%); NNH 26 (95%CI 15 to 99)
- Olanzapine: 2.5% (95%CI 0.3 to 4.7%); NNH 40 (95%CI 21 to 312)
- Quetiapine: 2.0% (95%CI 0.7 to 3.3%); NNH 50 (95%CI 30 to 150)
- Risperidone: 3.7% (95%CI 2.2 to 5.3%); NNH 27 (95%CI 19 to 46)

Mittal et al reviewed the evidence relating to antipsychotic associated cerebrovascular events and mortality risk.<sup>15</sup> The increase in mortality was 1.2 to 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.<sup>15</sup>

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.<sup>16</sup>

## CEREBROVASCULAR EVENTS

There is evidence that antipsychotic use in people with dementia is associated with an increased risk of stroke, however, this has not been reported consistently in trials. While several studies have reported such a link,<sup>17,18,19</sup> others have not.<sup>20,21,22</sup>

A Cochrane review of five studies of risperidone use in people with dementia found a rate of stroke of 3.1% for risperidone after 13 weeks of treatment, compared to 1% for placebo (OR 3.64 [95%CI 1.72-7.69]; NNH 47).<sup>23</sup>

Mittal et al also reviewed the evidence relating to antipsychotic associated cerebrovascular events and mortality risk in people with dementia.<sup>15</sup> They concluded that the risk of cardiovascular events was between 1.3 and 2 times higher in people treated with antipsychotics. No one antipsychotic drug was found to be safer than any other 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 strokes in this group.<sup>15</sup>

In 2015 the Australian Therapeutic Goods Administration (TGA) increased restrictions on the indication for risperidone use in people with dementia to the following:

**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 people with vascular or mixed dementia, compared to Alzheimer's type dementia. The data presented by the TGA in justification of the changed approval was an odds ratio for any cerebrovascular adverse event in people with vascular or mixed dementia being 5.26 (95% confidence interval [CI] 1.18-48.11) in those taking risperidone. The comparative odds ratio for people with Alzheimer's dementia was 2.23 (95% CI 0.85-6.88).<sup>24</sup>

## FALLS

Antipsychotic use in people with dementia has been associated with an increased risk of falls in numerous studies. Multiple meta-analyses of the impact of drugs on falls found increased relative risk of falls associated with antipsychotic/neuroleptic use. In studies that reported an increased risk of falls, the overall increase in risk of at least one fall during trial periods (often 12 weeks or less) ranged between 25 and 79%.<sup>25-29</sup>

There is also evidence associating an increased risk of hip fracture with the use of antipsychotics in people with dementia.

For example, a population based cohort study from the United Kingdom identified a prior event rate ratio of 1.62 (95% CI 1.59 to 1.65) in people using antipsychotics.<sup>30</sup>



## DISCONTINUATION SYNDROMES

Most studies have found that many individuals can have antipsychotics safely discontinued without worsening of behavioural symptoms.<sup>8,16</sup> A 2018 Cochrane review reported that antipsychotic discontinuation may have little or no effect on overall cognitive function, and may not adversely affect quality of life.<sup>9</sup> Predictors of successful discontinuation antipsychotics include lower daily doses of antipsychotics and lower baseline severity of behavioural and psychological symptoms of dementia.

There is little evidence to guide the most appropriate dose reduction strategy. Withdrawal schedules from randomised controlled studies have varied from abrupt cessation to dose tapering over a number of weeks.

A number of withdrawal effects are possible, such as the following:

- autonomic symptoms such as nausea, vomiting, anorexia, rhinorrhoea, diarrhoea, diaphoresis, myalgia and paraesthesia
- anxiety, agitation, insomnia and restlessness (although these may also be BPSD not directly related to the initial symptom for which the antipsychotic was originally prescribed)
- neuroleptic malignant syndrome, which is very rare but extremely severe

It is possible that tapering withdrawal schedules reduce the likelihood of these effects occurring. Canadian deprescribing guidelines recommend a 25-50% dose reduction every 1-2 weeks to cessation.<sup>38</sup> Australian guidelines recommend 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.<sup>39</sup>

During withdrawal, it is important to monitor for recurrence of target symptoms or behaviours, or emergence of new ones.



## FACTORS TO CONSIDER

Most Australian and international guidelines recommend that antipsychotics should only be used short-term for BPSD, if at all. The severity of most BPSD can be effectively reduced with appropriate person-centred interventions that address the precipitants of such symptoms. Whenever an antipsychotic is commenced for BPSD, there should be an intention of eventual dose reduction and cessation.

The natural history of most BPSD is a waxing and waning of severity in response to precipitants (clinical and environmental factors), and disease progression.<sup>31</sup> A 2017 antipsychotic deprescribing study by Brodaty et al reported that 76% of participants remained off antipsychotic treatment 12 months after cessation, with minimal change in measures of BPSD severity 6 months after cessation.<sup>32</sup>

## IN FAVOUR OF DEPRESCRIBING

- ✔ Any person with overt or suspected adverse effects will be more likely to benefit from dose reduction or cessation of the antipsychotic agent. Some people may be at higher risk of adverse effects from antipsychotics and these agents should be reconsidered regularly in such people. These include people:
  - three months of ongoing antipsychotic use
  - with Parkinson's disease
  - with Lewy body or vascular dementia<sup>33</sup>
  - with previous stroke or TIA history
  - with existing prolonged QT syndromes
  - taking agents that prolong QT syndrome (in particular, tricyclic antidepressants and macrolide antibiotics)
  - with risk factors for arrhythmias, including existing cardiac pathology and/or electrolyte disorders (esp. hypokalaemia, hypomagnesaemia).<sup>34</sup>
- ✔ People whose dementia has progressed and whose previous BPSD have ceased or lessened are less likely to relapse if the antipsychotic is ceased.
- ✔ For many people with dementia, any benefit from antipsychotic treatment occurs shortly after its commencement. A post-hoc analysis of the CATIE-AD study reported that a lack of response 2 weeks after the commencement of an antipsychotic was associated with a lack of response at 8 weeks.<sup>35</sup>
- ✔ There is some evidence that cessation of antipsychotic agents is associated with a reduction in risk of falls.<sup>36</sup>

- ✔ Stopping antipsychotics may also reduce the risk of death (NNT = 4 at 2 years), with minimal effect on BPSD.<sup>37</sup>

## AGAINST DEPRESCRIBING

- ✘ People with more severe BPSD, for example severe hallucinations, physically violent aggression or distressing agitation may be more likely to relapse or experience worsening of symptoms if dose reduction or cessation is attempted.
- ✘ People with a history of psychosis or other psychiatric disorders requiring antipsychotics prior to them developing dementia may experience worsening of their underlying psychiatric condition by reducing or ceasing antipsychotics.



RESOURCES

- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERGLYCAEMICS
- ANTIHYPERTENSIVES
- ANTIPSYCHOTICS
- ASPIRIN
- BENZODIAZEPINES
- BISPSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- VITAMIN D AND CALCIUM

AUTHORSHIP

This guide was updated by Dr Andrew Stafford, Dr David Dunbabin and Dr Peter Tenni from a document developed in consultation with the Deprescribing Reference Group.

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