A GUIDE TO

deprescribing

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CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

ANTIPSYCHOTICS

KEY POINTS

Most patients with dementia have BPSD. Most BPSD will subside spontaneously within 6 months. The first-line treatments for these symptoms are not medication, but behavioural and psychological interventions.[1]

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 (e.g. wandering, calling out, sexual inhibition, urinating in inappropriate places).

Serious adverse effects of antipsychotic agents may include falls and increased risk of strokes and mortality. These risks are evident within weeks of commencing treatment.

Antipsychotics may precipitate a number of other 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 BPSD can have their antipsychotics ceased, often without any worsening of BPSD.

Discontinuation of antipsychotics should be gradual, particularly if use has been long term.

RECOMMENDED DEPRESCRIBING STRATEGY

- 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.
- Consideration may be given to a trial of cessation of antipsychotics if a person has been symptom/target behaviour free for 3 months or more.
- People who no longer have any troublesome BPSD 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.
- Consensus-based deprescribing guidelines that address antipsychotic use for BPSD were published by a Canadian group in 2018 (see **Figure 1**).[54]
- One method, combining the Canadian approach with that described by Miarons et al.,[52] is as follows:
  - **Step 1.** Identify and assess causal and contributing factors that lead to BPSD.
  - **Step 2.** Reduce the antipsychotic dose by 25-50% if possible in cases when there are other causes of behavioural disorders or when there is no evidence of recent BPSD and the antipsychotic has been used for more than 6 weeks.
  - **Step 3.** Assess the patient for symptoms suggesting that dose reduction has not been well tolerated. If such symptoms are absent, reduce the antipsychotic dose by 25-50% every 2 weeks until the antipsychotic is fully discontinued.

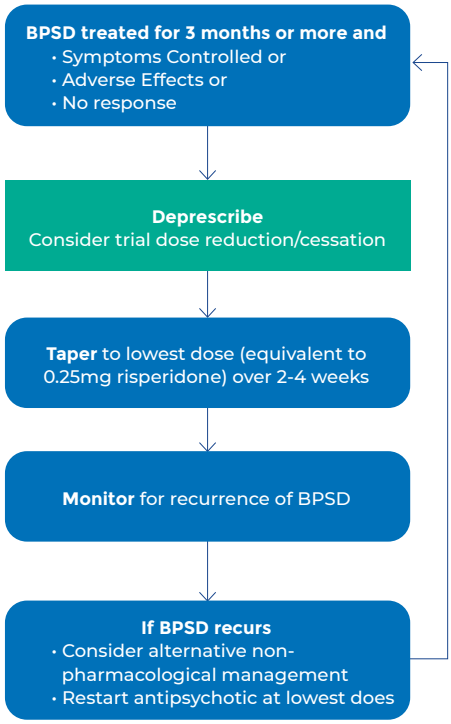
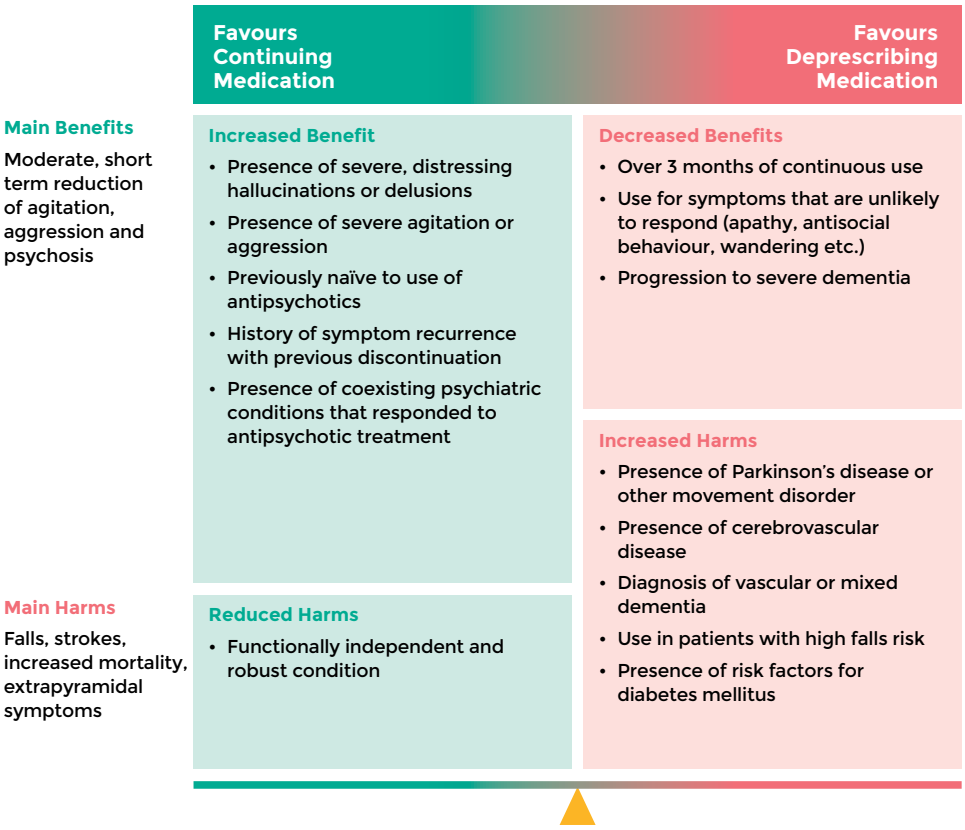


Figure 1: Antipsychotic deprescribing Algorithm

BENEFIT VERSUS HARM



BACKGROUND

The term "behavioural and psychological symptoms of dementia" (BPSD), also called neuropsychiatric symptoms of dementia, 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, and depression.

BPSD are presumed to occur due to multiple interacting factors, including pathological changes in the brain, the person's lived experience, unmet needs, environmental unsuitability, emotions, and altered clinical circumstances (e.g. pain, constipation or infection). Behaviours should be seen as symptoms that have an underlying cause. Consequently, the most appropriate strategy to support a person with dementia who has BPSD is to identify and address as many precipitants as possible.[1] Such measures frequently mitigate the need to use pharmacological measures, and avoid the risk of adverse effects associated with medication use.

However, in practice, the widespread use of non-pharmacological strategies is hindered by difficulties, including a lack of trained personnel, limited knowledge on the efficacy of non-pharmacological interventions, staff opinions and preferences, and an expectation of quick resolution of symptoms. In addition, in the case of severe agitation, or other emergency situations where patients may be endangering themselves or others, pharmacological intervention has priority.[2]

The continued use of antipsychotic agents for BPSD is common, despite a high adverse effect burden and limited evidence of efficacy.[1,3] A proportion of antipsychotic prescribing occurs in the 3 months before someone enters aged care. It then increases markedly in the 3 months after admission.[1,4]

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 clinical guidelines recommend the use of non-pharmacological methods as the first course of action, and that pharmacotherapy should only be used as a secondary option or when there is severe presentation of symptoms.[1,2,5-9] If behaviour is adequately assessed and its cause is promptly addressed, pharmacological management is unnecessary for most patients with dementia who experience symptoms of agitation, aggression or psychosis.[5]

Clinical trial data indicate that the atypical antipsychotics show at best modest benefit against BPSD.[2] Furthermore, the rate of response to treatment with placebo in some studies was around 30%, in part reflecting the high rate of spontaneous remission of symptoms within 3 months.[1,10]

The behaviours for which antipsychotics may have some benefit are limited to psychosis, agitation and aggression. However, apart from psychosis, the mechanism of action is unclear, so the effects may also represent non-specific sedation and essentially serve as a form of chemical restraint.[1,2]

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, and agitation being the most responsive to atypical antipsychotic treatment.[11] The same review reported that there was no evidence that quetiapine is of benefit for BPSD.

A recent Cochrane review addressed the efficacy and safety of antipsychotics for the treatment of agitation and psychosis in people with Alzheimer's disease and vascular dementia.[12] It was concluded that there is some evidence that first generation/ typical antipsychotics (e.g. haloperidol) might decrease agitation and psychosis slightly in patients with dementia. Atypical antipsychotics reduce agitation in dementia slightly, but their effect on psychosis in dementia is negligible.

The apparent effectiveness of the drugs seen in daily practice may be explained by a favourable natural course of the symptoms, as observed in the placebo groups.[12]

Symptoms such as agitation, aggression, hallucinations, and delusions may be especially distressing and dangerous to patients and caregivers; the judicious short-term use of pharmacologic agents may be warranted when symptoms are dangerous and/or severely distressing.[13]

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 (or may be paradoxically worsened) by antipsychotics in the intermediate to long term, such as wandering, undressing, urinating inappropriately, shadowing staff or calling out (see **Table 1**).

With specific reference to risperidone, a review concluded "Given the current evidence on the clinical effectiveness and safety of risperidone in the management of BPSD, its use should be restricted to patients with severe symptoms (aggression, agitation, or psychosis) who fail to respond adequately to non-pharmacological treatments. In this case, a low dose (0.25-2 mg daily) and short treatment duration (6-12 weeks) must be favoured. Moreover, risperidone must be avoided in patients with a history of stroke or TIA or with risk factors for stroke. Clinicians should also monitor patients for parkinsonism and risk of falls, using a fall rating scale. Risperidone should be stopped after 12 weeks if the risk of adverse events increases, or no benefit is observed."[14]

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.[10,15,16] Metabolic adverse effects include weight gain, and the development of diabetes or the metabolic syndrome. Many antipsychotic agents also prolong the QT interval and can exacerbate or precipitate arrhythmias and syncope. Movement disorders, which can result from or be exacerbated by antipsychotics, include a range of extrapyramidal symptoms from acute dystonic reactions, akathisia, parkinsonism and tardive dyskinesia. These movement disorders are more common with the first generation/typical agents, but can also occur with the atypical antipsychotics. 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 antipsychotics and other anti-dopaminergic agents. It is characterised by an "inner restlessness" that makes the person feel anxious, agitated and is often associated with an urge to move, manifesting as pacing, leg movements or leg rubbing. This adverse effect typically commences 3-8 weeks after initiation or dose increase of an antipsychotic agent.

In addition to these adverse effects, there are serious well-established concerns regarding the use of antipsychotics in people with dementia in terms of increased mortality, and the risk of strokes, falls and pneumonia.[10,15,16]

INCREASED MORTALITY

A meta-analysis of 20 studies involving over 350,000 patients by Ralph and Espinet concluded that there was consistent evidence that:[17]

- the relative risk (RR) for all-cause mortality of patients prescribed antipsychotic drugs is close to 2 (95%CI 1.9-2.19);
- the danger period for elevated risk of mortality is highest from the outset over the initial 6 months after starting their use;
- risks of all-cause mortality are dose-related, increasing with greater doses;
- little difference exists in risks when using either the typical or atypical antipsychotic drugs; and
- risk of mortality is significant and similarly high for all users, including dementia and non-dementia patients alike.

These findings were very similar to an earlier meta-analysis.[18]

A recent Danish study used nationwide registry data to examine rates of death within 180 days after the initiation of antipsychotic treatment in patients with a registered diagnosis of dementia.[19] After adjustment for potential confounders, patients exposed to antipsychotics had a significantly higher adjusted risk of death (hazard ratio [HR] 1.35, 95CI 1.27-1.43) than unexposed patients. Relative risk of mortality was elevated irrespective of a history of cardiovascular disease or diabetes.

Long-term mortality follow-up data from a deprescribing study indicated that discontinuation of antipsychotics was associated with reduced mortality at 12, 24, and 36 months.[20]

INCREASED RISK OF STROKE

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.[21-25] In case-control studies, the probability of strokes in elderly users of antipsychotics, irrespective of indication, compared with non-users was in the range of 1.3- to 2-fold greater.[22] However, the risk among patients with dementia appears to be lower than this.[25] The highest risk of stroke appears to be during the first weeks of treatment, and risk factors may include older age, cognitive impairment and vascular illness.[21,22]

In a study including 70,718 community-dwelling people with Alzheimer's disease in Finland, Koponen et al. recently assessed whether antipsychotic initiation increases the risk of stroke and whether there is a difference in stroke risk between risperidone and quetiapine.[26] People with previous strokes were excluded. After matching and adjusting for potential confounders, compared with non-use, antipsychotic use was associated with an increased risk of stroke within 60 days of antipsychotic initiation (HR 1.73, 95%CI 1.32-2.28). There was no difference in stroke risk between risperidone and quetiapine.

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 change was an odds ratio for any cerebrovascular adverse event in people with vascular or mixed dementia of 5.26 (95%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).[27]

INCREASED RISK OF FALLS

Antipsychotic use in people with dementia has been associated with an increased risk of falls in numerous studies.[28,29] 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%.[30-34]

There is also evidence associating an increased risk of hip fracture with the use of antipsychotics in people with dementia.[35] Torstensson et al. investigated the association between individual antipsychotics and fractures (hip, pelvis or upper extremities) in elderly persons.[36] The nationwide register-based study included all Danish individuals aged ≥65 who had not been treated with an antipsychotic in the year before inclusion. Almost 100,000 initiated treatment with antipsychotics and were followed for a mean of 9.6 years. During follow-up, 246,057 (16%) experienced a fracture. For all antipsychotics the associations with fracture were highest in the initial treatment period (0-30 days) with relative incidence rates for risperidone of 1.97 (95%CI 1.70-2.28), olanzapine 2.31 (95%CI 1.96-2.73), quetiapine 2.09 (95%CI 1.73-2.52), zuclopenthixol 2.19 (95%CI 1.82-2.63), flupenthixol 1.43 (95%CI 1.06-1.93), and haloperidol 2.98 (95%CI 2.57-3.45), compared with the background population.[36]

PNEUMONIA

Other significant safety concerns with the use of antipsychotics in the elderly include the increased risk of community-acquired pneumonia.[37-39]

FACTORS TO CONSIDER

The natural history of most BPSD is a waxing and waning of severity in response to precipitants (clinical and environmental factors), and disease progression.[1,40]

Most Australian and international guidelines recommend that antipsychotics should only be used short term for BPSD, if at all.[1,2,5-9] BPSD may resolve with time, and 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 a clear plan for review, with an intention of eventual dose reduction and cessation.

A Cochrane review assessed 10 studies that investigated withdrawal versus continuation of chronic antipsychotic drugs for BPSD.[41] Whilst it was not possible to meta-analyse data from all 10 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. 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 may have benefited from continuing antipsychotic treatment, particularly people who previously had psychotic features or severe agitation.[11,41] 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).[42]

A systematic review examined clinical outcomes from 12 studies directed at reducing antipsychotic use in aged care facilities; behavioural and psychological symptoms remained stable or improved in 10 of the studies.[43]

The clinical outcomes of the Australian Reducing Use of Sedatives (RedUSe) project were recently published.[44] RedUSe was a multi-strategic program comprising psychotropic medication audit and feedback, staff education, and interdisciplinary case review in 150 aged care facilities.[45] During the 6-month intervention, the proportion of residents prescribed regular antipsychotics significantly declined from 21.6% (95%CI 20.4-22.9%) to 18.9% (95%CI 17.7-20.1%), and the mean chlorpromazine equivalent dose declined from 22.9 mg/resident/day (95%CI 19.8-26.0) to 20.2 mg/resident/day (95%CI 17.5-22.9; P < 0.001). There was no evidence that deprescribing or dose reduction were associated with deterioration in neuropsychiatric symptoms, as measured with a battery of psychometric measures.[44] In fact, dose reduction was associated with small, albeit non-statistically significant, improvements in behaviour, particularly less physically non-aggressive behaviour.

Furthermore, antipsychotic reduction was associated with non-statistically significant improvements in quality of life and social withdrawal.[44]

A smaller Australian antipsychotic deprescribing study reported that 76% of 125 participants remained off antipsychotic treatment 12 months after cessation, with minimal change in measures of BPSD severity 6 months after cessation.[46] In the same study, it was found that nursing staff were the most common drivers of re-prescribing, followed by family members. Increased agitated and aggressive behaviours were the most commonly reported reasons for re-prescribing, even though these changes were not identified over time on objective measures.[47]

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 use of these agents should be reconsidered regularly in such people. These include people:

- with 3 months of ongoing antipsychotic use
- with Parkinson's disease
- with Lewy body dementia
- with previous stroke or TIA history
- with existing prolonged QT syndromes
- taking agents that prolong QT interval (e.g. tricyclic antidepressants and macrolide antibiotics)
- with risk factors for arrhythmias, including existing cardiac pathology and/or electrolyte disorders (esp. hypokalaemia, hypomagnesaemia).

People whose dementia has progressed and whose previous BPSD have ceased or reduced 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.[48]

There is some evidence that cessation of antipsychotic agents is associated with a reduction in risk of falls.[49] Stopping antipsychotics may also reduce the risk of death (NNT = 4 at 2 years), with minimal effect on BPSD.[50]

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. For patients with hallucinations, particularly auditory hallucinations, antipsychotic discontinuation should be approached cautiously because of the high relapse risk.[42]

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.

DISCONTINUATION SYNDROMES

As previously indicated, most studies have found that many individuals can have antipsychotics safely discontinued without worsening of behavioural symptoms.[41,43,44] Predictors of successful discontinuation of antipsychotics include lower daily doses and lower baseline severity of BPSD.

There is limited evidence to guide the most appropriate dose reduction strategy. A number of withdrawal effects are possible, such as the following:

- autonomic symptoms such as nausea, vomiting, anorexia, rhinorrhoea, diarrhoea, diaphoresis, hypotension, 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 over more than one month may reduce the likelihood of these effects occurring and avoid relapse of BPSD.[51-53] Canadian deprescribing guidelines recommend a 25-50% dose reduction every 1-2 weeks to cessation.[54]

During withdrawal, it is important to monitor for recurrence of target symptoms or behaviours, or emergence of new ones. In the case of problems with antipsychotic withdrawal, it is recommended to revert to the previous dose and to reduce the dose by 10% each month.[52]

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