Deprescribing cholinesterase inhibitors and memantine in dementia: guideline summary

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Abstract

Introduction: Cholinesterase inhibitors (ChEIs) and memantine are medications used to treat the symptoms of specific types of dementia. Their benefits and harms can change over time, particularly during long term use. Therefore, appropriate use of ChEIs and memantine involves both prescribing these medications to individuals who are likely to benefit, and deprescribing (withdrawing) them from individuals when the risks outweigh the benefits. We recently developed an evidence-based clinical practice guideline for deprescribing ChEIs and memantine, using robust international guideline development processes.

Main recommendations: Our recommendations aim to assist clinicians to:

- identify individuals who may be suitable for a trial of deprescribing ChEIs and memantine (such as those who do not have an appropriate indication, those who have never experienced a benefit, those who appear to be no longer benefitting, and those who have severe or end-stage dementia); and
- taper treatment and monitor individuals during the deprescribing process.

Changes in management as a result of the guideline:

- Deprescribing ChEIs and memantine through shared decision making with individuals and their caregivers by:
  - determining their treatment goals;
  - discussing benefits and harms of continuing and ceasing medication, from the start of therapy and throughout; and
  - engaging them in monitoring after discontinuation, while informing carers that the individual will continue to decline after discontinuation.
- This approach may reduce adverse drug reactions and medication burden, leading to improved quality of life in people with dementia.

Dementia describes a syndrome that is characterised by a progressive loss of cognition, function and behaviour.[1] Two classes of medications are currently available to treat the cognitive symptoms of specific types of dementia (such as Alzheimer disease): cholinesterase inhibitors (ChEIs: donepezil, rivastigmine and galantamine) and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine.[2] Use of ChEIs and memantine has been growing in Australia and internationally.[2,3] However, about one-third of use is potentially inappropriate; that is, the likely harms outweigh the likely benefits to the individual.[4–7]

Clinicians have cited a lack of evidence-based deprescribing guidelines as a barrier to optimising medication use in older adults.[8,9] Deprescribing is the process of withdrawing (or reducing the dose of) inappropriate medications with the aim of optimising medication use and patient outcomes.[10,11] ChEIs have been identified as a medication class for which an evidence-based deprescribing guideline would be of significant benefit to clinicians.[12] We have developed a guideline for deprescribing ChEIs and memantine, which provides specific advice on when and how to deprescribe.[13] This article summarises the guideline. The primary target audience for the guideline is clinicians involved in the care of adults prescribed a ChEI or memantine, including but not limited to general practitioners, specialist physicians, nurses and pharmacists.

Methods

We followed the process developed by the Bruyère Research Institute Deprescribing Guidelines in the Elderly project,[14] which was based on a comprehensive checklist for successful guideline development (Guideline 2.0),[15] the GRADE approach[16] and the AGREE II criteria.[17] We also followed the requirements for Australian National Health and Medical Research Council (NHMRC) external guideline approval.[18]

The guideline development team (GDT) comprised 10 clinicians (geriatrician/clinical pharmacologist, geriatric psychiatrist, GP, GPs with aged care accreditation, registered nurse and pharmacists) from Australia and Canada with experience in caring for people with dementia, research expertise in deprescribing, and methodological skills in guideline development. The GDT also included two consumer representatives (a person with mild dementia and a carer of a person with dementia).

After establishing the scope of the guideline and the clinical questions, the GDT conducted a systematic review and meta-analysis of the outcomes of deprescribing ChEIs and memantine. We followed the GRADE method to convert the evidence to recommendations.[16] This involved consideration of the results of the systematic review, the quality of the evidence, the benefits and harms of these medications, consumer preferences and resource implications.

Following external clinical and methodological review and public consultation, final guideline recommendations were approved by the NHMRC and published in February 2018.[13]

Recommendations

Box 1 outlines the recommendations, identifying those with the least potential for harm from discontinuation and the greatest potential for benefit, with advice on how to discontinue treatment. Recommendations were informed by the findings of our systematic review on the outcomes of discontinuation, coupled with reviews of the potential benefits and harms of treatment, consumer preferences and resource implications. The

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1 Recommendations for deprescribing cholinesterase inhibitors (ChEIs) and memantine*

For individuals taking a ChEI for Alzheimer disease, dementia of Parkinson disease, Lewy body dementia or vascular dementia for > 12 months, we recommend trial discontinuation if: • cognition and/or function has significantly worsened over the past 6 months (or less, as per the individual); • no benefit (improvement, stabilisation or decreased rate of decline) was seen at any time during treatment; or • the individual has severe or end-stage dementia (characteristics include dependence in most activities of daily living, inability to respond to environment and/or limited life expectancy)	Consensus-based recommendation: strength: strong; level of evidence: low†
For individuals taking a ChEI for an indication other than Alzheimer disease, dementia of Parkinson disease, Lewy body dementia or vascular dementia, we recommend trial discontinuation	Consensus-based recommendation: strength: strong; level of evidence: low†
For individuals taking memantine for Alzheimer disease, dementia of Parkinson disease or Lewy body dementia for > 12 months, we recommend trial discontinuation if: • cognition and/or function has significantly worsened over the past 6 months (or less, as per the individual) • no benefit (improvement, stabilisation or decreased rate of decline) was seen at any time during treatment • the individual has severe/end-stage dementia (characteristics of this stage include dependence in most activities of daily living, inability to respond to their environment and/or limited life expectancy)	Consensus-based recommendation: strength: strong; level of evidence: very low†
For individuals taking memantine for indications other than Alzheimer disease, dementia of Parkinson disease or Lewy body dementia, we recommend trial discontinuation	Consensus-based recommendation: strength: strong; level of evidence: very low†
Deprescribing a ChEI or memantine should be a trial discontinuation, with close periodic monitoring (eg, every 4 weeks) and re-initiation of the medication if the individual shows clear worsening of condition after withdrawal	Practice point‡
The dose of the ChEIs or memantine should be tapered prior to discontinuation by halving the dose (or by stepping down through available dose formulations) every 4 weeks to the lowest available dose, followed by discontinuation	Practice point‡
Other situations in which trial deprescribing of CHEIs or memantine can be considered include: • a decision by a person with dementia and/or their family/carer to discontinue the medication • a person with dementia's refusal or inability to take the medication • non-adherence that cannot be resolved • drug–drug or drug–disease interactions that make treatment risky • severe agitation/psychomotor restlessness and non-dementia terminal illness	Practice point‡

* These recommendations apply to adults (aged ≥ 18 years) prescribed a ChEI (donepezil, rivastigmine, galantamine) or memantine, in any care setting (community, residential care, inpatient, outpatient). † Consensus-based recommendations are recommendations that result from the systematic review of the evidence when the quality of the evidence is low or very low. While the recommendations are classified as consensus, they are still formulated based on evidence (the term "consensus" recognises that, where there is low quality evidence, some expert/consensus input is required to formulate the recommendations).[18] Strength of recommendation and level of evidence are determined using the GRADE approach.[16] ‡ Practice points are not a direct result of the systematic review; they essentially function to support users to apply and execute the consensus-based recommendations. ◆

recommendations were developed with high value placed on minimising the potential for medication-induced harm in a vulnerable population.

Clinicians should:

- consider these recommendations within the context of the individual, and implement them using a shared decision making approach;
- base decisions on the goals, values and preferences of the person with dementia and their family or carer; and
- discuss the potential benefits and harms of both continuation and discontinuation, and the evidence and uncertainties of the benefits and harms; such discussions should occur when starting medication and throughout therapy.

Tapering and monitoring

We recommend tapering (Box 1) based on the potential for severe adverse drug withdrawal reactions (identified in case reports),[43–45] ability to identify the lowest effective dose (where the medication cannot be completely discontinued), and the possibility of reducing the effect of return of symptoms (if they do occur) and increasing individual and family or carer comfort.[46]

As part of this process:

- monitor the individual every 4 weeks (ie, with each dose reduction as well as after discontinuation) (Box 1), based on the half-lives of the medications, and allowing an appropriate period for assessment of change (or no change) in condition (rather than day-to-day fluctuations);
- ask the family or carer to monitor how the individual's overall condition (including cognition, function, quality of life and behaviour) has changed over the 4-week period;
- alter the tapering process if necessary to suit the individual and their family or carer. For example, if it is believed that the medication is causing a severe or concerning adverse drug reaction (eg, seizures, severe bradycardia) then abrupt cessation may be appropriate, with more frequent monitoring for potential adverse drug withdrawal reactions (such as altered level of consciousness, hallucinations, delusions, insomnia, increased anxiety and agitation, and altered mood);
- ensure that the individual and their family or carer are aware of what to monitor and what to do if the condition changes; this may differ depending on how long it has been since the medication was discontinued. When deprescribing because of progression of the condition, inform carers that the person with dementia will continue to decline after discontinuation; and
- throughout tapering and monitoring after discontinuation, assess for other possible causes of any change in condition (such as dehydration or infection leading to delirium), and rule these out before restarting the medication (Box 2).

For non-pharmacological management and ongoing care of people with dementia after deprescribing, including behavioural and psychological symptoms, Australian guidelines are

2 Guidance on management of change in condition following discontinuation*

Timing of symptoms after dose reduction/ cessation	Types of symptoms	Action to be taken by family/nurses/ care staff	Possible cause†
< 1 week	Severe symptoms, including agitation, aggression, hallucinations or reduced consciousness	Restart previous dose immediately and contact responsible health care professional as soon as possible	Adverse drug withdrawal event
2 to 6 weeks	Worsening of cognition, behavioural or psychological symptoms or function	Contact responsible health care professional and consider restarting previous dose and/or make an appointment to see responsible health care professional at the next available time	Re-emergence of symptoms that were being treated by cholinesterase inhibitor/memantine
6 weeks to 3 months	Worsening of cognition, behavioural or psychological symptoms or function	Contact responsible health care professional at the next available time to make an appointment	Likely progression of condition or possible re-emergence of symptoms that were being treated by cholinesterase inhibitor/memantine
> 3 months	Any	Usual care	Progression of condition

* Originally published in Reeve et al;[13] permission to reproduce table within this article was given by the copyright authors. † After exclusion of other acute, reversible causes such as delirium due to dehydration or infection. ◆

available at http://sydney.edu.au/medicine/cdpc/resources/dementia-guidelines.php.

Evidence summary of the benefits and harms of ChEIs and memantine

Benefits. In people with specific types of dementia (such as Alzheimer disease, Parkinson disease dementia and Lewy body dementia), the evidence supports a wide range of benefits for ChEIs and memantine, particularly for cognition, function (such as activities of daily living) and neuropsychiatric symptoms (as measured by behavioural scales). However, the evidence shows that their efficacy is limited: benefit size on average is moderate, with not all individuals experiencing a benefit, and little evidence on outcomes important to consumers. There is also very limited unbiased information on their long term efficacy.[2,19,20]

Harms. There is a lack of high quality evidence in representative populations on long term harms. However, the potential adverse drug reactions (such as gastrointestinal problems, insomnia, agitation, somnolence, confusion, headaches, falls, weight loss, urinary incontinence, syncope and bradycardia) may have serious sequelae, especially in older adults living with frailty, and may significantly affect their quality of life.[21] Rare adverse effects of ChEIs include dermatological (eg, Stevens–Johnson syndrome) complications, Pisa syndrome, seizures, gastrointestinal haemorrhage and rhabdomyolysis.

People with dementia may be at a greater risk of adverse drug reactions than those without dementia, and such reactions may go unrecognised, leading to prescribing cascades (for example, urinary incontinence may lead to prescribing an anticholinergic drug to treat this symptom).[22] In fact, ChEIs and memantine may be the greatest contributors to adverse drug reactions in people with dementia.[23]

Evidence summary on discontinuation of ChEIs and memantine

ChEIs. From pooled results of seven randomised controlled trials (RCTs) of discontinuation versus continuation of ChEIs, we found that discontinuation can, on average, lead to worsened cognitive function across various populations of users; it may also increase neuropsychiatric symptoms. However, there appeared to be no significant change in global change outcome measures or in function or quality life (although few studies examined these person-centred outcomes). Most included studies had serious bias and findings could not be generalised.[13]

Based on other studies which reported outcomes of ChEI withdrawal (including retrospective reviews, observational before–after studies, washout of treatment and placebo after completion of an RCT, and crossover studies) where participants had been on long term therapy or had a non-approved indication, there appeared to be minimal clinically significant effects on cognition, activities of daily living, neuropsychiatric symptoms, carer burden, quality of life and mortality following discontinuation.[13]

Memantine. We identified eight studies of memantine discontinuation, including open prospective discontinuation studies, washout of treatment and placebo after completion of RCTs, and a retrospective chart review (none were RCTs of continuation versus discontinuation). Three studies reported that more participants in the discontinuation group had recurrence of symptoms than in the control group (with one of these also finding a significant worsening in global change), and one study reported worse symptom change scores (a score developed for that study). There were no other significant differences in cognitive, functional, global change or neuropsychiatric scores.[13]

Tapering and monitoring. Limited evidence was available to inform the process of discontinuation of ChEIs and memantine, particularly tapering and monitoring. Both abrupt discontinuation and dose reduction before cessation (tapering) were employed in deprescribing trials. However, owing to the large variation in populations, settings and study types, we were unable to determine if one approach was safer or more effective than another.[13]

Consumer values and preferences

Previous research has shown that most older adults, their carers, and people with dementia would be willing to have a medication deprescribed if their doctor said it was possible.[24–26] Carers have reported multiple reasons for considering discontinuation of ChEIs and memantine, including limited observed benefit, progression of dementia, considerations of cost, dependence in all activities of daily living, and a rapid decline in physical health.[27–31] However, carers have also expressed fear regarding

withdrawal of therapy (eg, in case this triggers a rapid decline or even precipitates death).[27,28]

Considering the potential benefits and harms of deprescribing ChEIs and memantine in the context of what most carers and people with dementia report to be important (quality of life and function, with less emphasis on the improvement of objective measures of cognition),[29,30] it is likely that when provided with this information, with the knowledge that discontinuation is a trial, most would be open to the possibility of deprescribing.

Resource implications and cost-effectiveness

Numerous cost-effectiveness studies conclude that prescription of ChEIs and memantine are cost-effective (within approved indications) from both a health and societal perspective.[33–35] However, there are many limitations to these studies; data on benefits often come from pharmaceutical company-sponsored studies of short duration (6 months or less), inability to account for the complexity in the progression of dementia, variability in service use, limited data on costs and important outcome measures (such as institutionalisation), and indirect data on quality of life (ie, based on modelled predictions or ratings of utility by people without dementia).[33–35] Additionally, international evidence suggests ChEIs and memantine are used for longer periods and outside of indications assessed in cost-effectiveness studies.[2,3,7]

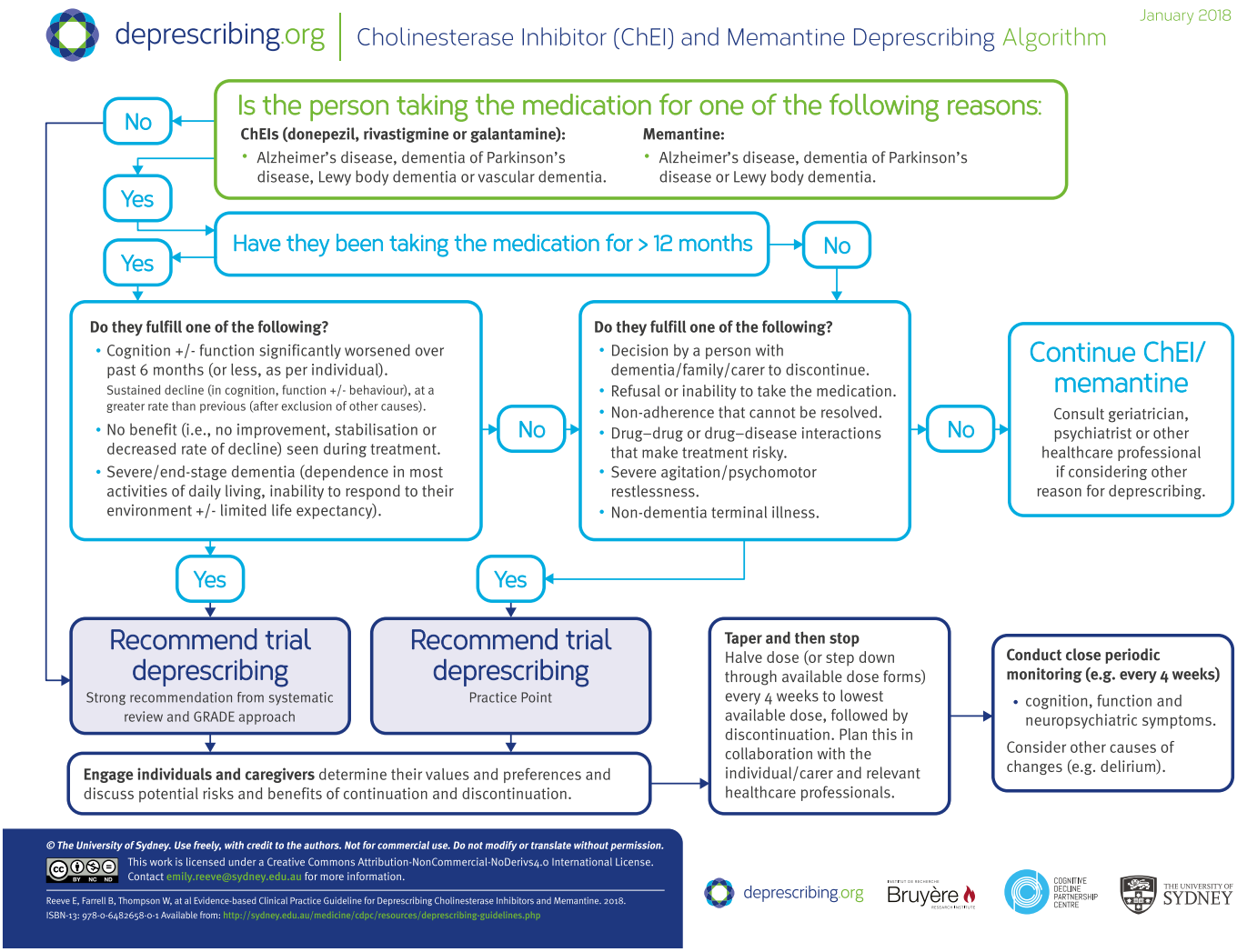
Because of the elimination of medication costs, it is anticipated that there will be a cost benefit to deprescribing medications.[36] Cost-effectiveness may be reliant, however, on the ability to identify individuals who are suitable for deprescribing; that is, those who will experience more benefit than harm after medication withdrawal.[37]

Clinical considerations

The full guideline also discusses:

- how to assess benefit and continued need;
- how to conduct deprescribing (including recommended tapering schedule, monitoring, and whether temporary dose reduction or cessation will cause irreversible harm);

3 Cholinesterase inhibitor and memantine deprescribing algorithm*



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- alternatives to cessation (switching agents or reducing dose);
- when to consult a specialist or other health care professional;
- how to engage people with dementia and their family or carers;
- ethical and legal considerations;
- considerations for Aboriginal and Torres Strait Islander peoples, indigenous Canadians and culturally and linguistically diverse populations;
- medications outside the scope of this guideline (including anticholinergic and sedative medications); and
- non-pharmacological management and ongoing care after deprescribing.

Overcoming barriers to deprescribing

Ideally, clinicians should discuss deprescribing when a medication is first prescribed and throughout therapy, with periodic review of the individual's goals of care, values and preferences. If the person with dementia and their family or carer have discussed situations where they would consider deprescribing, this may reduce carer concern when the person with dementia is no longer able to actively participate in decision making, as they know it is being done in accordance with their loved one's values and preferences.[31] The process of initiating, monitoring and ceasing a medication if there is no benefit is also what many carers expect in making decisions about drug use.[32]

It can be difficult for clinicians and people with dementia and their family or carers to determine the current benefits and harms of a medication that they have been taking for years. Dementia is a progressive, although fluctuating, condition and cognition may not decline at a steady rate, with individuals being highly variable in their progression.[38,39] The decision to deprescribe can be informed by a combination of validated tools for cognitive assessment and input from carers and physicians.[40,41] If clinicians and family or carers notice a sustained or accelerated decline in multiple areas such as cognition, function and behaviour, this may indicate that the medication is no longer of benefit. There is also potential for harm and burden, especially in an individual who is frail, multimorbid and/or taking multiple medications[11,22,42] This highlights the need for regular reassessment and discussion with carers and families, balancing any benefits (or lack thereof) and potential for harm in the context of the individual's care goals.

Implementation

A one-page (double-sided) algorithm has been developed for clinicians to aid in implementation (Box 3; http://sydney.edu.au/medicine/cdpc/resources/deprescribing-algorithm.php).

Gaps in knowledge and future guideline updates

The major gaps in knowledge relate to the limited unbiased, generalisable information on who is suitable for deprescribing of ChEIs and memantine. There was limited evidence on person-centred outcomes (such as quality of life) in deprescribing and the resource cost of deprescribing across different settings (such as time to review appropriateness, communicate with carers and family and other health care professionals, and conduct monitoring and follow-up). Outcomes in future research should be clinically meaningful and applicable to cost-effectiveness analyses. Evidence to inform the tapering and monitoring processes was also limited. Research into how health care professionals can best discuss deprescribing and enhance shared decision making with people with dementia and their family and carers will be imperative.

Accordingly, the guideline will be updated every 5 years, or sooner if a new study is released that may affect the recommendations.

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