Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine: Recommendations

Developing organisations:

The University of Sydney

NHMRC Partnership Centre: Dealing with Cognitive and Related Functional Decline in Older People (Cognitive Decline Partnership Centre)

Bruyère Research Institute, Deprescribing Guidelines in the Elderly Project

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The full guideline and supporting documents are available at:
http://sydney.edu.au/medicine/cdpc/resources/deprescribing-guidelines.php

Disclaimer

This document is a general guide to be followed subject to the clinician's judgement and the person's preference in each individual case. The guideline is designed to provide information to assist decision making and is based on the best evidence available at the time of developing this publication.

Publication approval

Australian Government
National Health and Medical Research Council

The guideline recommendations on pages 7-9 of this document were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 27 October 2017 under Section 14A of the *National Health and Medical Research Council Act 1992*. In approving the guideline recommendations, NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that the guideline recommendations are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals practising in an Australian healthcare setting.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

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Organisations endorsing this guideline

- Australian and New Zealand Society of Geriatric Medicine (ANZSGM)
- The Royal Australian and New Zealand College of Psychiatrists (RANZCP)
- Tasmanian Health Service: Royal Hobart Hospital
- Canadian Geriatrics Society (CGS)
- Canadian Society of Hospital Pharmacists (CSHP)

Plain English Summary

Dementia describes a syndrome that is characterised by a progressive loss in cognition, function and behaviour [1]. Worldwide, the number of people living with dementia is increasing every year [2]. There are currently two classes of medications available to treat the symptoms of dementia: cholinesterase inhibitors (ChEIs: donepezil, rivastigmine and galantamine) and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine [3]. These medications are not disease modifying, yet they can have important benefits to people with dementia and their carers (such as through improvement of cognitive function).

All medications come with the potential for benefits as well as risks, and these risks and benefits can change over time, such as 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 for individuals where the risks outweigh the benefits. However, deprescribing also has the potential for both benefit and harm to the individual. Thus, the purpose of this guideline is to assist healthcare professionals (particularly prescribers) to determine when it might be suitable to trial withdrawal of these medications for an individual. These recommendations only apply to individuals already taking one of the described medications (donepezil, rivastigmine, galantamine and/or memantine).

The main points of this guideline are as follows:

- A proportion of people who have used these medications for over 12 months or outside an approved indication may be able to stop the medication with minimal clinically relevant negative consequences. Discontinuation of ChEIs and/or memantine may lead to a worsening of cognitive function in certain populations of users. The limited data on person-important outcomes, such as quality of life and function, suggest that these outcomes may not be altered by discontinuation. However, there is considerable uncertainty in the benefits and harms of both prescribing and deprescribing in the individual.

- It is important to consider the values, preferences and experiences of the person with dementia and/or their carer/family when determining if trial deprescribing is appropriate. Carers have expressed fears associated with medication discontinuation, and individuals may feel that deprescribing is ‘giving up’ or a signal that they are no longer worth treating. Good communication between clinicians and people with dementia and/or carers/family about the benefits and harms of continuing versus discontinuing, in the context of their values and preferences, is necessary when discussing a potential trial of deprescribing.

- ChEIs and memantine have been found to be cost-effective in treating approved indications in some populations and settings, based on the data from short-term studies. While cost is not considered a motivation for deprescribing, the cost implications may include reduced medication costs, reduced costs of treating adverse drug effects, and an uncertain benefit or cost if there is a change in function that increases or decreases health service utilisation. Further research is required in this area.
- There are numerous clinical considerations when deprescribing ChEIs and/or memantine, including how to assess for ongoing benefit, how to conduct withdrawal and monitoring (plus actions to follow monitoring) and implementation of non-pharmacological management strategies.

Executive Summary

We followed the process of developing class-specific deprescribing guidelines [4] based on a comprehensive checklist for successful guideline development (Guideline 2.0) [5] and the AGREE II criteria [6]. We also incorporated the requirements for the Australian National Health and Medical Research Council (NHMRC) external guideline approval [7]. This process involves a systematic review and uses the GRADE process to assess the quality of the evidence and convert the evidence into recommendations (see Methods in full Guideline). Developing the recommendations involved considering the quality of the evidence, the risks and benefits of deprescribing, the risks and benefits of continuation, consumer values and preferences, and economic considerations (see individual sections, plus Appendix 2 in full Guideline).

The recommendations below are classed as one of three possible types of recommendations: Evidence-based Recommendations (EBR), Consensus-based Recommendations (CBR) or Practice Points (PP). In this guideline, we employ CBR, which are recommendations based on a systematic review where there is limited or low-quality evidence, as well as PP, which are recommendations outside the scope of the systematic review based on expert opinion and non-systematically reviewed evidence.

Each recommendation contains a rating of the quality of the evidence and strength of the recommendations. **The recommendations below are rated as based on low- or very low-quality evidence.** The major limitations to the quality of the evidence were a high risk of bias and a lack of generalisability (for details, see Appendix 2: Summary of Findings and Evidence to Recommendations Tables in full Guideline). We have rated the strength of the recommendations as 'strong'. **A strong recommendation is provided when, based on the available evidence, all or most individuals would be best served with that course of action, and the outcomes align with their values and preferences.** A weak recommendation reflects that consideration of the individual's values, preferences and treatment goals is required before proceeding with the recommended course of action (such as the individual's preference or competing interests). There is considerable heterogeneity in the population of people with dementia in terms of both their condition and their values and preferences. The rating of strong is primarily based on the evidence presented (despite its low quality) and a reasonable judgement of the limited potential for harm in a carefully monitored **trial of discontinuation**.

This document is a general guide. Implementation of recommendations should only be conducted by qualified/trained personnel in consultation with appropriate parties (such as the prescriber, family, nurses and care staff). The people involved in these parties for consultation will vary by setting and should be considered in the local context, considering the scopes of practice of healthcare professionals.

Recommendations

NB: This is not a treatment guideline—the recommendations below should not be applied to assist in the decision to initiate medication. They should not be used to dissuade against prescribing these medications or as reason to prescribe them.

The recommendations below apply to adults who have already been prescribed and have been regularly taking a ChEI and/or memantine for a sufficient amount of time at the maximum tolerated dose. These recommendations are to 'trial deprescribing'.

> **Trial deprescribing** refers to slowly reducing the medication dose (tapering) prior to complete cessation, with monitoring throughout the process. If the person has a noticeable decline after dose reduction/cessation (after exclusion of other causes), then the medication should be restarted at the previous minimum effective dose. If the person does not have a noticeable decline, then the medication should remain ceased.

These recommendations should be considered in the context of the individual. People with dementia vary in their condition (such as progress, age of onset, symptom profile and aetiology), overall health state (such as comorbidities, polypharmacy, frailty and life expectancy), values, preferences and treatment goals. It is also important to consider their previous response to the medication. Improvement, stabilisation and reduced rate of decline in cognition can all be considered benefits of treatment, and this can have an important impact on the person with dementia and their family. However, it is very difficult to quantify the ongoing benefit of long-term use in the individual. Trial withdrawal may help identify individuals who are still benefiting from the medication. Decisions surrounding deprescribing should be conducted as shared decision making with the person with dementia and/or their family/carer, ensuring that they are informed of the likely potential benefits and harms of both continuing and discontinuing these medications. Other healthcare professionals may need to be consulted to determine the appropriateness to trial withdrawal, or to ensure monitoring is conducted throughout the process. Application of these recommendations may need to be adapted depending on the context in which they are used—that is, depending on the healthcare organisation and professionals involved.

We present these recommendations for clinicians to consider within the context of each individual:

PP: Deprescribing of cholinesterase inhibitors and/or memantine should be a **trial discontinuation**, with close periodic monitoring (such as every four weeks) and re-initiation of the medication if the individual evidences clear worsening of condition after withdrawal.

PP: The dose of the cholinesterase inhibitors and/or memantine should be tapered prior to discontinuation by halving the dose (or by stepping down through available dose formulations) every four weeks to the lowest available dose, followed by discontinuation.

CBR: For individuals taking a cholinesterase inhibitor (donepezil, rivastigmine or galantamine) for Alzheimer's disease, dementia of Parkinson's disease, Lewy body dementia or vascular dementia for greater than 12 months, we recommend trial discontinuation if:

- cognition and/or function has significantly worsened over the past six 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 (some characteristics of this stage include dependence in most activities of daily living, inability to respond to their environment and/or limited life expectancy).

(Strength of recommendation: Strong; Level of evidence: Low)

CBR: For individuals taking a cholinesterase inhibitor (donepezil, rivastigmine or galantamine) for an indication other than Alzheimer's disease, dementia of Parkinson's disease, Lewy body dementia or vascular dementia, we recommend trial discontinuation (Strength of recommendation: Strong; Level of evidence: Low).

CBR: For individuals taking memantine for Alzheimer's disease, dementia of Parkinson's disease or Lewy body dementia for greater than 12 months, we recommend trial discontinuation if:

- cognition and/or function has significantly worsened over the past six 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 (some characteristics of this stage include dependence in most activities of daily living, inability to respond to their environment and/or limited life expectancy).

(Strength of recommendation: Strong; Level of evidence: Very Low)

CBR: For individuals taking memantine for indications other than Alzheimer's disease, dementia of Parkinson's disease or Lewy body dementia, we recommend trial discontinuation (Strength of recommendation: Strong; Level of evidence: Very Low).

PP: Other situations in which trial deprescribing of cholinesterase inhibitors and/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.

Box 1: Additional guidance on monitoring and follow-up

What to do after discontinuation

See section How to conduct deprescribing, Table 5 and Table 6 for further details, discussion and references (in full Guideline).

- Close monitoring during and after withdrawal of ChEIs and memantine is very important.
- Establish a plan for when and how follow-up is going to occur. This guideline recommends a face-to-face follow-up after four weeks; however, this should be tailored to the individual. This period is based on allowing time for the reappearance of dementia-related symptoms (re-emergence of the condition), the rate of clearance of the medications, and the ability to assess overall change in a condition that can have fluctuating symptoms. A shorter follow-up (one to two weeks) may be appropriate if there is high concern about return of symptoms.
- Monitoring should focus on both cognitive and functional abilities and behavioural and psychological symptoms, and should consider how these have changed, on average, over the follow-up period.
- The individual and/or carer/family should be aware of what to look out for and what to do if a change in condition occurs—consider verbal and written communication. A decline in condition can reflect an adverse drug withdrawal event, reversal of drug effect or progression of condition. The likely cause of change in condition may differ depending on the time since discontinuation (for further details, see Table 6).
- Other causes of change in condition at the time of deprescribing should be considered, such as infection or dehydration leading to delirium.
- It is important that the individual/carer/family has access to a clinician who they can contact if necessary.

Tapering

- Recommend slowly reducing the dose by halving the previous dose or stepping down through available dose formulations to the lowest available dose (Table 5).
- Abrupt cessation may be appropriate in some individuals, such as if the individual is experiencing an adverse drug reaction. Instructions should be provided to the individual and/or carer/family on what to look out for and what to do if symptoms occur (particularly the possible risk of an adverse drug withdrawal event).

Table 1: Summary of the potential benefits and harms of continuing and discontinuing ChEIs and memantine

See relevant sections (outlined in footnotes) for further details and supporting evidence. The potential benefits and harms may vary depending on the indication for and duration of use; however, outcomes in an individual may be highly variable and difficult to predict. The recommendations in this guideline aim to identify individuals who have the greatest potential for benefit and the least risk of harm from deprescribing.

	Potential benefits	Potential harms
Continuation of ChEI or memantine	Potential continued benefit through improvement, stabilisation or reduced rate of decline in cognition, behaviour and function. There may also be a benefit on quality of life, carer burden and institutionalisation. However, there are limited long-term robust data on the benefit of continued long-term use.[1]	Potential risk of future adverse drug reactions.[2] Risk of harm (reduced efficacy or increased adverse reactions) through drug–drug and drug–disease interactions.[3] Cost of continued medication supply to the individual/family.[4] Cost of continued medication supply to government/other funding organisations that could be spent on other healthcare interventions.[4]
Discontinuation of ChEI or memantine	Reduced pill burden for the individual and potential reduced medication management burden for carers.[5] Potential reduced risk of adverse drug reactions and drug–drug and drug–disease interactions.[6] Reduced cost of medication supply to the individual.[4] Reduced cost of medication supply to government/other funding organisations that could be spent on other healthcare interventions.[4] Reduced time/cost of medication administration in residential care facilities.[4] Potential improved adherence to other medications and cessation of other inappropriate medications.[5, 6]	Possible worsening in cognition and/or behaviour.[6] Potential damage to the doctor–patient relationship.[7] Possible (although unlikely/rare) adverse drug withdrawal reactions.[8] (These harms are likely to be minimised through a deprescribing process involving discussion with the individual and carers/family, planning, tapering, monitoring and re-initiation of medication where appropriate.)[8,9]

Relevant sections for further details, discussion and references (in full Guideline):

[1] Benefits of Cholinesterase Inhibitors and Memantine, page 36. [2] Harms of Cholinesterase Inhibitors and Memantine, page 40. [3] Drug–drug interactions with ChEIs and memantine, page 44. [4] Resource Implications and Cost-effectiveness, page 52. [5] Table 11: Evidence to Recommendations—Cholinesterase Inhibitors, and Table 13: Evidence to Recommendations—Memantine, pages 114 and 123. [6] Summary of Findings, page 29. [7] Consumer Values and Preferences, page 49. [8] How to conduct deprescribing, page 58. [9] Clinical Considerations, page 56. See also Appendix 2—Table 11: Evidence to Recommendations—Cholinesterase Inhibitors, and Table 13: Evidence to Recommendations—Memantine.

Areas of Major Debate

There has been significant discussion between our Guideline Development Team (GDT) members about the need to tailor the recommendations to the individual. Some stakeholder GDT members could recall previous individuals who had been treated and for whom a recommendation would not be appropriate. For example, the lines between the underlying causes of dementia (such as Alzheimer's disease [AD] versus non-AD dementia) are not always clear. There was tension between wishing to add qualifiers and keeping the recommendations clear and straightforward for end-users. To resolve this debate, we have included a preamble to the recommendations to ensure that users of the guideline are focused on the individual and aware of the significant variability among people with dementia. This debate, in turn, led to a discussion about the rating of the strength of the recommendations of 'Strong' versus 'Weak'. According to the GRADE process [8,9]:

> [a] strong recommendation [should be made] when … all or almost all informed people [based on the evidence available] would make the recommended choice for or against an intervention.
> [a] weak recommendation [should be made] when … most informed people [based on the evidence available] would choose the recommended course of action, but a substantial number would not.

Much debate can be held over what constitutes a 'substantial number', as we agree that some people with dementia and/or their family/carer may not wish to discontinue the ChEI and/or memantine. However, we feel that the majority of people in the situations outlined by the recommendations who are **informed** would agree to a **trial** discontinuation. This is based on assumptions with value based on adopting a 'less is more' approach (as outlined in Appendix 2: Summary of Findings and Evidence to Recommendations Tables in full Guideline). The recommendations may also be complicated by the life-limiting nature of dementia and lack of alternative treatments, with significant hope being placed in these medications by people with dementia and their family. It is also important to remember that the strength of the recommendation is based not only on the systematic review evidence, but also on the review of benefits and harms, consumer values and preferences, and economic considerations.

The GDT also encountered tension between wishing to trial discontinuation to determine if the medication is still having a benefit, versus not wishing to 'rock the boat' for people with dementia who are otherwise stable. Some clinicians view trial discontinuation as an appropriate measure to determine the need to continue the medication, while others prefer evidence of harm to trigger discontinuation, with avoidance of potential harm from deprescribing more highly valued.

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