Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine in People with Dementia

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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.

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Organisations Endorsing this Guideline

To be determined.

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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 can have important benefits to people with dementia and their carers.

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 itself 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 on 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. The cost implications of deprescribing may include reduced medication costs, reduced costs of

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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.

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Executive Summary

We followed the process of developing class-specific deprescribing guidelines [4], which are 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). 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: Summary of Findings and Evidence to Recommendations Tables).

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). We have rated the strength of the recommendations as 'Strong'. **A strong recommendation is provided when 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 and preferences and treatment goals is required before proceeding with the recommended course of action (such as the individual's preference on 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 scopes of practice of health care professionals.

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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.

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 even 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, i.e. depending on the health care 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 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 every four weeks to the lowest available dose, followed by discontinuation.

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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.

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

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

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.

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

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

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.

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Areas of Major Debate

There has been significant debate 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 the recommendation would not be appropriate. For example, the lines between 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 would make the recommended choice for or against an intervention.
>
> [a] weak recommendation [should be made] when … most informed people 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 TablesTable 11: Evidence to Recommendations—Cholinesterase Inhibitors and Table 13: Evidence to Recommendations—Memantine). The recommendations may also be complicated by the life-limiting nature of dementia and lack of alternative treatments, with significant hope being placed on 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. In the absence of external measures to determine if the medication is having a benefit, some clinicians view trial discontinuation as an appropriate measure to determine the need to continue the medication, while others prefer evidence of

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harm to trigger discontinuation, with avoidance of potential harm from deprescribing more highly valued.

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Introduction

People with dementia can be prescribed a cholinesterase inhibitor (donepezil, rivastigmine or galantamine) and/or memantine to treat the symptoms of dementia. This guideline discusses when it is suitable to consider deprescribing (withdrawal) of these medications for an individual. It also discusses how to conduct deprescribing (trial withdrawal with monitoring).

Dementia

Dementia describes a syndrome that is characterised by a progressive loss in cognition, function and behaviour [1]. The most common cause of dementia is AD, although there are numerous other aetiologies [1]. Dementia is a global public health priority [10]. Worldwide, the number of people living with dementia is increasing every year [2]. In 2017, approximately 413,106 Australians were living with dementia, with projections estimating that this figure will rise to 536,164 by 2025 [11]. The prevalence of dementia increases with increasing age [2]. There are substantial costs associated with caring for people with dementia, and the condition has major effects on the lives of people with dementia and their families and friends [2,3,10,12].

Two classes of medications are currently marketed and approved to treat the cognitive symptoms of dementia: cholinesterase inhibitors (ChEIs: donepezil, rivastigmine and galantamine) and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine [3]. ChEIs work by inhibiting the breakdown of acetylcholine—an important neurotransmitter that is reduced in people with dementia (the so-called 'cholinergic hypothesis') [13]. Memantine is thought to act through prevention of excitatory amino acid neurotoxicity, which is implicated in the pathogenesis of AD [14].

On average, people with dementia have four to six comorbidities and take five to 10 regular medications [12,15,16]. Thus, the use of medications among people with dementia needs to be considered in the context of the potential harms of polypharmacy with multimorbidity, particularly drug–drug and drug–disease interactions. People with dementia may have alterations in pharmacokinetics (how the body takes in and processes the drug) and pharmacodynamics (how the body responds to the drug) that make them more susceptible to medication-related harm [17]).

Deprescribing

The purpose of 'deprescribing' is to improve the overall risk–benefit profile of medication use in individuals through withdrawal of inappropriate medications (medications where the potential harms outweigh the potential benefits, such as high-risk and unnecessary medications) in a safe and effective manner [18,19]. While data are limited, deprescribing of inappropriate medications may have benefits, including a reduction in adverse drug events, improved

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adherence, reduced financial costs and reduced mortality. The potential harms of deprescribing (such as adverse drug withdrawal reactions and return of medical conditions) can be minimised with appropriate planning, individualised care practices and monitoring [20–23].

Guideline justification

There are currently no evidence-based guidelines internationally that focus on deprescribing ChEIs and memantine. Use of these medications is growing in Australia [24] and internationally [3,25], with greater use patterns than expected and evidence of potentially inappropriate use.

In Australia, approximately 20,000 people commence using a ChEI every year [24,26]. The initial randomised controlled trials of ChEIs and memantine only had a six- to 12-month duration, yet people with dementia typically remain on these medications for much longer periods [27]. The average duration of use in practice varies significantly across studies (likely due to differences in the requirements for subsidisation of the medication in different countries) from less than one year to over three years [24,28–36]. In Australia, a 2012 review found that these dementia medications are being used in a larger population and for a longer period than what has been considered in cost-effectiveness analyses [24].

It is estimated that up to one-third of cholinesterase use is from prescriptions that are initiated or continued inappropriately [37–41]. In particular, insufficient monitoring and lack of appropriate discontinuation seem to be the main contributors to inappropriate use of ChEIs [40]. For example, in a study of nursing home residents in the United States (US), 16% of all residents with advanced dementia continued to be prescribed a ChEI [42]. Three separate studies in Australia, Canada and the US found that, in approximately half of all observed deaths of ChEI users, therapy was continued into the last week before death [24,28,43]. Prescription in inappropriate indications, such as mild cognitive impairment (without dementia), is also common in the US [44].

Approximately one-third of memantine use is thought to be inappropriate [45] due either to use for an unsupported indication or failure to discontinue use where warranted. A study in the US found that 11% of people with mild cognitive impairment (without dementia) were inappropriately treated with memantine [44]. Approximately 10% of people with dementia in hospice or with advanced dementia are prescribed memantine [42,46]. Another study found that 20% of the use of ChEI, memantine or dual treatment is inappropriate [47]. It should be noted that there are limitations to the studies that describe the prevalence of inappropriate use of ChEIs and memantine. In particular, these studies rarely have the ability to assess appropriateness in the context of the individual. Concomitant use of medications that interact with ChEIs and/or memantine is common. Between 9 and 45% of users are also prescribed a medication that can possibly reduce its efficacy or increase the risk of harms to the person

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[28,36,48–51]. Potential drug–drug interactions do not necessitate deprescribing of ChEIs and/or memantine in all cases, but do highlight the complex nature of medication use among people with dementia.

A lack of evidence-based deprescribing guidelines has been identified by healthcare professionals as a significant barrier to optimisation of medication use among older people [52]. ChEIs have been identified as a medication class for which an evidence-based deprescribing guideline would be of significant benefit to clinicians [53]. Deprescribing of ChEIs and memantine **that are being used inappropriately** has the potential to improve quality of life for people with dementia and their family/carers through eliminating adverse drug reactions (ADRs) and reducing medication regimen complexity. However, there is also potential for harm from deprescribing (for example, if the individual was still receiving benefits from the medication). As such, it is necessary to implement appropriate consideration of who is suitable for deprescribing (in conjunction with the individual and/or their family/carer).

This guideline aims to provide guidance on who is suitable to continue and who is suitable to trial deprescribing (likely to benefit or not experience harm from withdrawal) of ChEIs and/or memantine. Deprescribing of these medications should proceed with careful monitoring and management if there is a return or worsening of symptoms.

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Scope

This guideline **does not** provide advice on when ChEIs and/or memantine should be initiated for people with dementia. Local treatment guidelines should be used to determine if it is appropriate to start one of these medications (see Appendix 3).

Target audience

The primary target audience for this guideline is healthcare professionals involved in the care of adults prescribed a ChEI and/or memantine. This includes general practitioners (also known as family physicians and primary care practitioners), specialist physicians (for example, but not limited to, geriatricians, internal medicine physicians, psychiatrists and neurologists), nurses (such as nurse practitioners, registered nurses and enrolled nurses with endorsement) and pharmacists. As with all clinical practice guidelines, this is a general guide to be followed subject to the clinician's judgement and the person's preference in each individual case. Clinicians with different specialisations or scopes of practice can use this guideline as is most appropriate for them.

The type of professional (based on training, qualifications and experience) who is suitable to conduct deprescribing (with appropriate consultation, such as with family members) is not dictated by this guideline. This should be considered in the local context in which this guideline is being implemented. See also 'When should a specialist/other healthcare professional be consulted?' in the Clinical Considerations section.

A consumer version of this guideline is also being developed.

Target population

The target population of this guideline is adults (aged ≥ 18 years old) prescribed one of the ChEIs (donepezil, rivastigmine or galantamine) and/or memantine. It is relevant to all care settings (community, residential care, inpatient and outpatient). Where applicable, indications (such as the type of dementia) and the severity of dementia (such as mild, moderate or severe) are specified.

Clinical research questions

- What are the outcomes (benefits and harms) of withdrawal (discontinuation) of ChEIs and/or memantine compared to continuation of these medications?
- For whom is it suitable to deprescribe ChEIs and/or memantine?

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Box 1: PICO framework of clinical research question

Population	People (aged > 18 years old) who are currently prescribed a ChEI (donepezil, galantamine or rivastigmine) and/or memantine
Intervention	Trial withdrawal of donepezil, galantamine, rivastigmine or memantine (attempted discontinuation with or without tapering/dose reduction)
Control	Continuation of donepezil, galantamine, rivastigmine or memantine [†]
Outcome	Primary outcomes: • Cognition • Behavioural symptoms • Global change/dementia stage (assessed via validated tool or via ability to remain off the medication/proportion of people who restart) • Quality of life (person with dementia and their carer)

[†] This was our ideal control population; however, as we found no studies that included this control population for memantine discontinuation in a preliminary scoping review, we also included studies without this control. See Technical Report for full details of systematic review method (http://sydney.edu.au/medicine/cdpc/news-events-participation/deprescribing-guideline.php).

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Methods

We followed the process of developing class-specific deprescribing guidelines described by the 'Deprescribing Guidelines in the Elderly' project [4]. The process is 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 Australian National Health and Medical Research Council (NHMRC) external guideline approval ('Procedures and Requirements for Meeting the 2011 NHMRC Standard for Clinical Practice Guidelines' [7]).

See Administrative Report and Technical Report for further details (http://sydney.edu.au/medicine/cdpc/news-events-participation/deprescribing-guideline.php).

Funding

The guideline development, publication, dissemination and implementation were funded through an NHMRC-ARC Dementia Research Development Fellowship awarded to Dr Emily Reeve (APP1105777).

Guideline Development Team composition

The Guideline Development Team (GDT) was composed of 9 clinicians (geriatrician/pharmacologist, geriatric psychiatrist, general practitioner, general practitioner with aged care accreditation, registered nurse and pharmacists) with experience in caring for people with dementia and research expertise in the field of deprescribing from both Australia and Canada. Three of these clinicians also had methodological expertise in the area of deprescribing guideline development, the GRADE approach and conducting systematic reviews. The GDT also included two consumer representatives (a person with mild dementia and a carer of a person with dementia). A research assistant, a research student, a data analyst and early career researchers conducted specific tasks within the guideline development process (for example, an academic librarian assisted with developing a search strategy for the systematic review). All people involved in guideline development are listed in Appendix 1. All GDT members and other people involved were required to declare any potential or perceived conflicts of interest (COIs). The process of declaration and dealing with COIs is outlined in the Administrative Report (http://sydney.edu.au/medicine/cdpc/news-events-participation/deprescribing-guideline.php).

Guideline development methods

The GDT lead conducted a scoping review to assess the available body of evidence. The results of the scoping review were presented at two meetings to GDT members (one held in an Australian location and time zone, and the other in a Canadian location and time zone).

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Through the meetings and follow-up electronic correspondence, the GDT determined the scope of the guideline and the clinical questions (see above).

To answer the clinical questions, we conducted a single systematic review of the outcomes of deprescribing of ChEIs and/or memantine. The systematic review protocol was registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016053544) and is detailed in the Technical Report (http://sydney.edu.au/medicine/cdpc/news-events-participation/deprescribing-guideline.php). We searched eight databases from date of inception through to July 2016, with no language restrictions. The search terms used related to deprescribing (such as withdrawal, cessation and discontinuation), dementia and related conditions, and ChEIs and memantine (including generic and brand names). We included multiple study types, including randomised controlled trials (RCTs) of continuation versus discontinuation, RCTs of discontinuation of treatment versus discontinuation of placebo, and non-randomised and before and after studies. To be included, the studies needed to measure an outcome at the time of discontinuation and more than one week after discontinuation. The primary outcomes of interest were cognition, global change/dementia stage, behavioural and psychological symptoms of dementia, quality of life, and ability to remain off the medication.

Evidence to recommendations

Following the GRADE method, the recommendations were drafted by reviewing the summary of the evidence (systematic review), assessing the quality of the evidence (systematic review) and converting the evidence to recommendations (based on the results of the systematic review, with consideration of the benefits and harms of these medications, consumer preferences and cost implications). This process was conducted separately for the ChEIs and memantine, and is outlined in Appendix 2: Summary of Findings and Evidence to Recommendations Tables. Recommendations were drafted by the GDT lead in consultation with supporting team members, and provided with an overall rating of the quality of the evidence and strength of the recommendation using the GRADE approach [8]. The recommendations that resulted from this process were then classified as Evidence-based Recommendations (EBR) or Consensus-based Recommendations (CBR). This is in accordance with the process and requirements of the Australian NHMRC guideline approval ('Procedures and Requirements for Meeting the 2011 NHMRC Standard for Clinical Practice Guidelines' [7]). EBR and CBR are recommendations that result from the systematic review of the evidence. EBR are assigned when the quality of the evidence is moderate or high quality, while CBR are assigned when the quality of the evidence is low or very low (Table 1). As both the ChEI and memantine quality of evidence was assessed as low or very low, none of the recommendations were classified as EBRs. While the recommendations are classified as 'consensus', they are still

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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).

While drafting and reviewing the CBRs, additional recommendations, labelled 'Practice Points' (PP) were also drafted. PP were not a direct result of the systematic review, and as such do not have an assessment of the quality of the evidence or strength of the recommendation. In this guideline, the PP essentially function to support users to apply and execute the CBRs.

After drafting the recommendations, all GDT members were provided with a summary of the systematic review findings and evidence to recommendation tables (Appendix 2: Summary of Findings and Evidence to Recommendations Tables). The recommendations were refined through discussion with GDT members via teleconference and email. Once deemed suitable by the GDT lead, a vote was conducted electronically to finalise the recommendations, with a consensus defined as greater than or equal to 80% agreement.

Table 1: System for classification of recommendations (as per the 'Procedures and Requirements for Meeting the 2011 NHMRC Standard for Clinical Practice Guidelines' [7]**)**

Classification	Description
EBR	Formulated based on the findings of the systematic review [±]
CBR	Formulated based on systematic review findings that are inconclusive or of low quality [±] (that is, insufficient to be classed as EBR)
PP	Provided to support the EBR and CBR; not based on the systematic review (content was outside the scope of the systematic review)

[±] As we used the GRADE method to assess the quality of the evidence, EBR were assigned when the quality of the evidence was rated as high or moderate, and CBR were assigned if the quality of the evidence was low or very low. We did not use any assessment of 'inconclusive' evidence.

External clinical review and public consultation

The draft guideline with recommendations agreed upon by the GDT was sent to two external stakeholders (clinicians) for external clinical review. Changes were made (where appropriate) in response to the reviewers comments.

Public consultation will occur from the 5th of June to the 6th of July 2017. The draft guideline, administrative report and technical report are publically available during this period via: http://sydney.edu.au/medicine/cdpc/news-events-participation/deprescribing-guideline.php

Clinical and consumer stakeholder groups will be specifically approached to provide comment on the guideline during this public consultation period. All comments and responses to the

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comments will be detailed in the final Administrative Report, with corresponding changes made to the guideline where necessary.

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Summary of Findings

Details of the systematic review can be found in the Technical Report (http://sydney.edu.au/medicine/cdpc/news-events-participation/deprescribing-guideline.php). Summary of the evidence can be found in Appendix 2: Summary of Findings and Evidence to Recommendations Tables.

Cholinesterase inhibitors (ChEIs)

Randomised controlled trials of discontinuation versus continuation of ChEIs

The systematic review identified seven RCTs that conducted blinded withdrawal versus continuation of a ChEI. Six included participants with AD, while the seventh included people with primary progressive aphasia (PPA) of predominantly aphasic symptoms at onset and/or predominantly frontotemporal dementia (FTD). The ChEIs included in these studies were donepezil (three studies), galantamine (three studies) or any ChEI (one study).

Three of the studies involved people with mild to moderate AD and had an initial treatment period of 12 months or less prior to withdrawal [54–56]. All three of these studies found worse cognitive and neuropsychiatric outcomes in the withdrawal group, compared with the continuation group (follow-up range six to 12 weeks). Johannsen et al. [56] specifically included participants who were judged to be non-responders (those who did not have an increased Mini-Mental State Examination [MMSE] [57] from baseline) to donepezil treatment after 12 to 24 weeks of treatment. These 'non-responders' who continued donepezil for a further 12 weeks performed better on average on the MMSE and Neuropsychiatric Inventory (NPI) than those who discontinued. However, they found no difference in their primary outcome (Alzheimer's Disease Assessment Scale—Cognitive [ADAS-Cog] [58]) or function (measured by Disability Assessment for Dementia) between groups. Gaudig and Richarz [54] also assessed blinded discontinuation of high-dose galantamine compared with continuation of a moderate dose of the drug. In a subgroup assessment of people who had significantly deteriorated prior to discontinuation, they found no difference in change in cognition (ADAS-Cog) between groups.

The three other RCTs among people with AD included participants with longer initial treatment duration. One included participants who had benefited from 12 months of treatment [59]. The study examined the number of participants in each group who experienced lack of efficacy (which led to study withdrawal), as well as study dropout for any reason. More participants in the drug withdrawal group dropped out than those in the continuation group. Of note, 47% of those in the continuation group completed the 24-month follow-up, versus 32% in the discontinuation group. In the 24 months following randomisation, approximately four of every 10 participants in the discontinuation group experienced a lack of efficacy (decrease of greater than or equal to four points on the ADAS-Cog scale), compared with three of every 10 in the

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continuation group. Howard and colleagues [60] randomised participants with moderate to severe dementia (standardised MMSE score of five to 13 inclusive) to four groups: continue donepezil, discontinue donepezil, continue donepezil and start memantine, and discontinue donepezil and start memantine. All participants' prescribing clinicians had been considering a change in therapy at the time of enrolment. The majority of participants had been on the study drug (donepezil) for longer than two years. The results indicated worsened cognition (as measured by the standardised MMSE) in the donepezil discontinuation groups (with or without memantine), but no difference between groups in their secondary outcomes of neuropsychiatric symptoms (NPI) or carer quality of life or health status. In a follow-up investigation, participants who had been randomised to discontinue donepezil (with or without memantine) were more likely to be admitted to a residential care facility in the first 12 months of the study (hazard ratio = 2.09, 95% confidence interval [CI] =1.29–3.39). The treatment group did not influence residential care facility admission over the following three years (hazard ratio = 0.89, 95% CI = 0.58–1.35) [61]. No difference in time to death was noted between groups [61]. The final study involved participants with moderate to severe AD in long-term care who had been taking a ChEI (donepezil, rivastigmine or galantamine) for at least two years [62]. There was no observed difference between the discontinuation and continuation groups in clinicians' global impression of change or other cognitive and neuropsychiatric outcomes, although participants with baseline hallucinations and possibly delusions were more likely to have deterioration, according to the clinicians' global impression of change. This study had the smallest sample size among the RCTs of people with AD.

In the last RCT, [63] participants with PPA or FTD were treated for 18 weeks with galantamine, and then randomised to blinded withdrawal (placebo versus continued galantamine) for a further 18 weeks. In the PPA subgroup, there was a greater change in clinicians' global assessment in the discontinuation versus continuation group; however, this was not significant when adjusted for multiple comparisons. There was no difference in cognitive outcomes between groups when assessed with the MMSE, Matis Dementia Rating Scale or Frontal Assessment Battery.

In the meta-analysis of all seven studies, there was a significant difference in change in cognition between the continuation and discontinuation groups, with a standardised mean difference (SMD) of 0.40 (95% CI = 0.23–0.57) (when assessed with validated cognitive scales). Studies with a duration of use prior to discontinuation of greater than 12 months had similar, yet more varied, results (SMD = 0.44, 95% CI = 0.06–0.83). These studies assessed outcomes after different follow-up periods; thus, it can be difficult to interpret the clinical meaningfulness of this difference. A SMD of 0.2 has been described as small in magnitude, but (importantly) a clinically detectable difference [64]. By noting that our meta-analysis found a result of 0.40 (greater than 0.2), this supports the notion that the difference in cognition between

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continuation and discontinuation is clinically important [65]. In the studies with participants with AD, there is reasonable consistency in the outcomes and effect size of the difference between continuation and discontinuation groups. Indeed, our meta-analysis of these six studies found little heterogeneity (I^2 = 10%). There is some inconsistency across some of the studies, which found a difference in some, but not all, outcome measures used. For example, Johannsen et al. [56] found a difference in MMSE and NPI scores, but not ADAS-Cog or function (Disability Assessment for Dementia) scores. Overall, our analysis suggests that there is likely to be a clinically important worsening in cognition (on average) when ChEIs are discontinued (across the populations of users in the studies).

We also conducted a meta-analysis of neuropsychiatric symptoms as assessed by NPI from three studies (from which we were able to extract NPI results). When employing a random effects model, there was no significant difference in change in NPI between the continuation and discontinuation groups (SMD = 0.20, 95% CI = −0.24–0.65), although, the magnitude of the SMD did reach the threshold for a clinically detectable difference (0.20). There was some heterogeneity observed (I^2 = 67%), although this seemed to be due to the results of the study which included participants with a non-approved indication [63].

Of the three studies that used a global assessment of change tool (Clinical Global Impression or Clinician's Interview-based Impression of Change Plus Caregiver Input [CIBIC-Plus]), none found a significant difference between the ChEI continuation and discontinuation groups. The two studies that assessed quality of life outcomes [62,66] showed no difference between groups. Finally, one of the four studies [56,62,63,66] that measured a functional outcome (such as activities of daily living) found a significant difference in change between the continuation and discontinuation groups.

There are a number of limitations to these studies, mainly arising from a serious risk of bias and lack of generalisability (for details, see Appendix 2: Summary of Findings and Evidence to Recommendations Tables). Many of the RCTs were sponsored or funded by pharmaceutical companies (industry), had strict inclusion criteria (resulting in a younger average age of participants than the general population of people with dementia), had large dropout rates and had some reliance on observed case analysis. Additionally, the results represent the average difference across the population. The average change in MMSE likely represents a proportion of individuals who worsen on discontinuation of ChEIs, some who remain the same, and potentially some who improve.

Other study types of discontinuation of ChEIs

In addition to the RCTs of discontinuation versus continuation of ChEIs, we identified 31 studies that reported the outcomes of deprescribing ChEIs before and after discontinuation and/or in

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comparison to a control group (placebo discontinuation, no treatment at any time, initiation of treatment, non-randomised matched or unmatched continuers, or discontinuation of other cognitive-enhancing medications). These studies were of lower quality than the RCTs of discontinuation versus continuation; thus, we were primarily interested in the studies that had the greatest applicability to general practice and to guiding the development of the guideline recommendations. In particular, we were interested in the studies of participants with an approved indication, where prior duration of use of the ChEI was at least 12 months (long-term users) and follow-up was conducted after at least six weeks (to allow for complete washout of the medication and its effects). Six studies were identified that included this population.

Two studies compared ChEI discontinuation to continuation of an unmatched group (those unwilling to discontinue the ChEI [67] or those assessed to be unsuitable for discontinuation [68]). No significant difference in outcomes between those who continued and those who discontinued taking ChEIs was found in either study (cognition, activities of daily living, neuropsychiatric symptoms, carer burden or mortality). Additionally, one of the studies, found a reduction in other psychotropic medications in the group that discontinued ChEIs [67]. Both of these studies were limited by a small sample size (14/6 and 18/24 discontinuers/continuers). Suzuki et al. compared a group of participants with severe AD who discontinued donepezil to a group who had never received treatment with a ChEI [69]. There was no difference in the cognitive or neuropsychiatric outcomes between the two groups, although a reduction in use of psychotropics was again observed in the ChEI discontinuers, compared to the control group, who had an increase in use [69]. Rainer et al. compared discontinuation of ChEIs to discontinuation of other cognitive enhancers (nootropics) [70]. They found a significantly greater worsening in MMSE and ADAS-Cog scores in the ChEI versus nootropic discontinuers [70].

The final two studies had no control group, and discontinuation was conducted as considered appropriate by a review committee [37] or due to the stage of dementia [71]. Thirty-one per cent of participants in the study by Lee et al. were restarted on their ChEI [37], while, in the study by Simpson et al., 48% experienced global deterioration, 28% had no change and 4% improved [71].

Our systematic review identified nine studies conducted in populations with an indication that is not currently supported by guidelines: FTD with AD, late-stage dementia (MMSE < 3), mild cognitive impairment, high-level gait disorders or cognitive impairment from other causes (repaired ruptured aneurysm, stroke, brain irradiation and traumatic brain injury) [72–80]. The majority of outcomes measured and reported in these studies were not significantly altered by discontinuation (14/23). Three outcomes (from two studies) resulted in benefits (reduced neuropsychiatric symptoms [77], reduced carer burden [77], and improved computerised

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cognitive test result [72]). Negative outcomes included a reduction in verbal learning measures [73], a reduction in cognition (ADAS-Cog) [74], return of anxiety to pre-treatment levels [72], and an increase in apathy scores (although this population also had a decrease in the use of psychotropic drugs) [78]. Overall, these studies were limited by small sample sizes, lack of blinding, lack of an appropriate comparator group and no discussion of the clinical importance of the changes that occurred. Confirming the potential bias due to a lack of blinding, a drop in cognitive scores during an open washout phase has been observed in those previously on blinded placebo [81–83].

In summary, discontinuation of ChEIs among people with dementia can lead to worsened cognitive function (of likely clinical meaningfulness magnitude) and possible increased neuropsychiatric symptoms, compared to those who continue ChEIs. Conversely, the RCTs that used global change outcome measures found no differences between ChEI continuation and discontinuation. While none of the studies discussed found an effect on person-centred outcomes, such as function and quality of life, there are limited data on this issue; thus, no firm conclusions can be made. The findings of this systematic review need to be interpreted cautiously, since most studies introduced serious bias and the findings could not be generalised (see Appendix 2: Summary of Findings and Evidence to Recommendations Tables). A review of non-randomised trials indicated that, among people who have been on long-term ChEI therapy and people taking a ChEI for a non-approved indication, there may be minimal effects on cognition, activities of daily living, neuropsychiatric symptoms, carer burden, quality of life and mortality following discontinuation of ChEIs (although these studies have significant risk of bias due to their methodology). Further studies with a low risk of bias that can produce generalisable results are required to determine which people are suitable for deprescribing of ChEIs.

Memantine

We could identify no blinded RCTs of discontinuation versus continuation of memantine. Eight studies that reported outcomes after discontinuation of memantine were included in the review.

Four studies compared withdrawal of memantine to withdrawal of placebo (after a RCT of treatment versus placebo). The studies included participants with different indications for memantine (mild cognitive impairment, acquired immune deficiency syndrome [AIDS] dementia complex, Parkinson's disease dementia [PDD] and PDD/Lewy body dementia [LBD]) and the duration of use prior to discontinuation ranged from 16 to 52 weeks, with follow-up after discontinuation between two and six weeks [74,84–86]. Regarding cognitive outcomes, there was no significant difference observed between groups in the three studies that included this as an outcome [74,84,86]. Three studies found no difference between groups regarding

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global change scores and the dementia rating scale [74,84,85], although two of these found that significantly more participants in the memantine discontinuation group deteriorated or had a recurrence of symptoms, versus those who had previously been on placebo [84,85].

Two studies reported outcomes before and after discontinuation (no control) [78,87]. In participants with late-stage dementia, discontinuation of memantine (or ChEI) did not result in a change in neuropsychiatric symptoms (measured with NPI), although there was a significant worsening in the sub-score for apathy. However, this was accompanied by a significant reduction in the total number of psychotropic medications [78]. In premenopausal women at risk of dementia, treatment with memantine was associated with some worsening in verbal learning and memory, which improved following discontinuation of the medication [87].

The final two studies identified were conducted with people living in nursing homes who had been previously prescribed memantine. The first was a prospective observational study that found a greater increase in AD symptoms among people who discontinued versus people who continued usage. This remained even when only considering participants who discontinued for a non-medical reason, according to case notes (although about 40% of these cases were for an unknown reason) [88]. In the final study, people with advanced dementia who volunteered to stop either memantine or ChEI use had no difference in the stage of dementia, activities of daily living, neuropsychiatric symptoms or mortality, compared to those who continued [67].

None of these studies were appropriately designed to determine the outcome of discontinuation versus continuation of memantine (that is, a blinded, placebo-controlled RCT of discontinuation versus continuation). None of the studies reported blinding of either the study participants or the assessors to discontinuation. Most were limited by a small sample size and/or the use of medication for indications where there was no clear evidence of benefit.

Evidence to recommendations summary

The process by which the evidence discussed above was used to create the recommendations is outlined in Table 11: Evidence to Recommendations—Cholinesterase Inhibitors and Table 13: Evidence to Recommendations—Memantine. It is clear from the evidence review that there is the potential for worsened outcomes (especially cognition) after discontinuation of ChEIs and/or memantine in individuals. However, in certain users, the risk–benefit ratio for discontinuation may be more favourable than the risk–benefit ratio of continuation.

The recommendations in this guideline (Recommendations) provide guidance about which individuals are suitable for trial deprescribing of ChEIs and/or memantine, while noting the need to consider the recommendations within the context of the individual and their values and preferences. Due to the potential for risk, deprescribing should proceed with careful monitoring and re-initiation of the medication if appropriate. Please consult the Clinical

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Considerations section for more details on this (including: *Assessing benefit/continued need*, *Recommended tapering schedule*, *Monitoring* and *When should a specialist/other healthcare professional be consulted?*).

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Benefits of Cholinesterase Inhibitors and Memantine

NB: This is not a treatment guideline. For guidance of appropriate initiation of ChEIs and memantine, please refer to your national/local treatment guideline (Appendix 3). Where it is noted below that use of ChEI and/or memantine are recommended/supported by guidelines, this means that the guidelines state that a trial of these medications can be considered in the individual (that is, the suitability for the individual should still be reviewed by the prescribing clinician).

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. Improvement, stabilisation and even reduced rate of decline in cognition can all be considered benefits of treatment, as this can have an important impact on the person with dementia and their family. The pharmacological management of people with dementia is very complex and requires balancing the potential for benefit against the potential for harm. The benefits to treatment that an individual can experience may vary greatly (from important lasting response to no response at all). In this section, we discuss guideline recommendations and the evidence to support the beneficial effects of these medications. While the limitations of these studies are discussed (such as the relatively short duration of the studies and lack of generalisability of participants), this does not invalidate the potential benefits that they may have.

Cholinesterase inhibitors (donepezil, rivastigmine and galantamine)

Mild to severe Alzheimer's disease

The use of ChEIs for mild to moderate AD is recommended by national guidelines [89–95]. All three ChEIs (donepezil, rivastigmine and galantamine) are considered to have equivalent efficacy, as per these guidelines and systematic reviews/meta-analyses. Their use is supported for people with severe AD in several guidelines, although there are generally fewer trials to guide these recommendations, and participants with advanced/end-stage dementia were often not included [89,91,94–96]. The guidelines and systematic reviews emphasise that the effect of ChEIs in AD is modest, and that these medications treat symptoms, yet do not alter the course of dementia [13,97]. The 'modest' effect is an average across participants, which does not fully represent the proportion of people with dementia prescribed this medication who experience a pronounced improvement in cognitive symptoms, achieve stabilisation or gain a reduced rate of decline. Therefore, the potential benefit that these medications may have for an individual should not be discounted.

ChEIs have been shown to have an effect on improving, stabilising and/or slowing cognitive decline, as well as benefits on global change assessment measures and activities of daily living

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(functional outcomes). There also may be an effect on the behavioural and psychological symptoms of dementia (neuropsychiatric symptoms); however, there are some inconsistencies across studies and the magnitude of the clinical importance is unclear [13,96,98–104].

The benefits for cognition, activities of daily living and neuropsychiatric symptoms are likely to have important positive effects on other person-relevant outcomes, such as quality of life, carer burden and institutionalisation. However, there are a lack of studies that directly measure these benefits [105–108]. The use of ChEIs has been associated with delayed nursing home admission in observational studies [109–113], although this was not seen in a large non-industry-funded, two-year randomised placebo-controlled trial (although there are a number of limitations of this study, including important recruitment and attrition bias) [108].

It is currently unclear whether ChEI treatment in people with AD improves survival. A two-year RCT of galantamine found a significantly lower rate of mortality in the treatment group versus the placebo group [114], although other long-term RCTs have not found this effect [108].

There are limitations to the evidence used to inform treatment guidelines. Participants of RCTs are often not representative of the real-world population of people with dementia, as they generally include a higher proportion of younger and healthier individuals [115–117]. People with dementia with multimorbidity may have a reduced response to treatment, compared to people without [118]. The majority of RCTs that inform the treatment guidelines had a limited duration of six to 12 months and RCT data on the long-term benefits are lacking [94,119,120]. RCTs that have lasted over 12 months indicate a possible reduction in effect over time [121]. However, the limited long-term RCT data do not mean that there is no long-term benefit. Indeed, long-term, placebo-controlled studies in which a short-term benefit has been established may be considered unethical in this population. However, these data do make it unclear when it might be appropriate to consider deprescribing. Open-label and observational studies indicate a sustained benefit (such as delayed symptom progression compared to historical cohorts) for up to five years [120]; however, there are limitations to these types of studies, including high dropout rates, handling of missing data, survivor bias and use of historical controls [122].

A high rate of placebo response has been found in RCTs—it has been estimated that only approximately 10 to 20% more people with AD prescribed a ChEI achieve a benefit over those in the placebo groups [119,120].

Non-AD dementia

National guidelines also recommend the use of ChEIs for PDD [89,91,93–95] and LBD [89,93–95]. The results of systematic reviews and meta-analyses indicate that there is a positive effect on cognitive function, global assessment, activities of daily living and behavioural disturbances

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in Parkinson's disease–related dementia; however, they noted that there were limitations in the data available [123,124]. Again, the overall benefit may be modest. A 2012 Cochrane review reported that treatment with a ChEI led to a clinically meaningful improvement in 19.8% of people in the intervention groups, versus 14.5% in the placebo group [123]. A benefit in cognition, global change, activities of daily living, behavioural disturbances and neuropsychiatric symptoms have been reported for ChEIs in LBD; however, there are limited high-quality data in this population [106,123,125]. There are insufficient long-term data to conclude whether ChEIs have an effect on mortality for people with PDD and LBD [106,124].

The use of ChEIs for vascular dementia is supported by some guidelines [89,90], yet not others, which report that there are a lack of data and inconsistent results to make an overall recommendation for all people with vascular dementia [91–95,126–130]. The use of ChEIs may be considered in mixed dementia, especially where there is an element of AD [89,93].

Studies conducted to date do not support the use of ChEIs for mild cognitive impairment, the prevention of cognitive impairment or FTD [89,92,93,95,131,132].

While different causes of dementia have distinct symptom patterns and subsequently specific diagnostic criteria, long-term observational and autopsy studies have indicated that many people with dementia have brain abnormalities that would indicate more than one cause of dementia (mixed dementia) [133].

Memantine and dual therapy

The use of memantine is supported in moderate to severe AD in many national guidelines [90,93–95], although some guidelines stipulate that this medication should only be used if the person is intolerant or has a contraindication to ChEIs [89,92]. Data support that memantine produces a benefit to cognition, behaviour, function and global measures of change. As with ChEIs, its efficacy is considered modest [14,96,100,134], and the long-term benefit and sustained efficacy of memantine are unclear [94]. There are inconsistent and unclear data on the potential benefits of memantine for both mild AD and vascular dementia [129,135]. Moreover, concerns have been expressed that the results of the clinical drug trials may not be generalisable to the real-world population of memantine users, who are older and have less severe cognitive impairment than the participants in the initial trials [45].

The benefit of dual therapy with a ChEI and memantine is unclear [94,97]. Recent reviews have reported a possible benefit for moderate to severe AD in terms of activities of daily living, global assessment of change, behavioural measures and cognitive scores [90,136,137]. However a meta-analysis published in 2016 did not find a significant effect on cognition, function or neuropsychiatric or behavioural outcomes, compared to monotherapy [138].

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Summary of benefits

Overall, there is sufficient evidence to support a wide range of benefits (cognition, function, neuropsychiatric symptoms and so forth) for the use of ChEIs and memantine among people with dementia. Limited unbiased information is available on the long-term efficacy of these medications [3] and there are limitations to their efficacy (not all people with dementia will achieve a benefit). However, given the progressive and disabling nature of dementia, small improvements, stabilisation or reduced rate of decline may have an important impact on the person and their carers/family.

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Harms of Cholinesterase Inhibitors and Memantine

Method of review of harms

To conduct this review of harms, we searched PubMed with terms related to ChEIs and memantine, ADRs and systematic reviews to identify relevant reviews on the potential harms of these medications (search strategy available upon request). Additionally, we used reference lists of national guidelines (Appendix 3: Other Relevant Guidelines) and searched the Cochrane library for any meta-analyses that presented the harms of donepezil, rivastigmine, galantamine and/or memantine. There is not currently compelling evidence to conclude that any of the three ChEIs reviewed differ in relation to potential for harm; thus, they are discussed here as a group.

Introduction to harms

As with every medication, the use of ChEIs or/and memantine can lead to adverse events and increase the risk of harms. ADRs can arise after short-term or long-term use or when other circumstances change (such as a new medical condition, worsening of a medical condition comorbid with dementia, or introduction of a new medication). **When any new symptoms arise in people with dementia, it is very important to consider whether one of their medications is the cause or may be contributing to this new symptom.**

Based on RCT data of use up to six months, ChEIs and memantine are generally well tolerated. However, it is important to remember that RCT participants are generally younger and healthier than the real-world population of people with dementia seen in clinical practice. Exclusion criteria for many of the RCTs include upper and lower age limits, comorbidities (such as psychiatric disorders, cardiovascular disease, insulin-dependent diabetes and asthma/chronic obstructive pulmonary disease), medications (psychotropics, anticholinergics, warfarin or antidepressants), hearing and/or visual impairments, and requiring the regular presence of a carer. Moreover, participants are required to be non-specifically otherwise healthy [117,139]. Increasing age and cognitive impairment are associated with an increased risk of ADRs, highlighting the possibility that the prevalence of ADRs reported in RCTs is lower than what is experienced in people with dementia seen in typical clinical practice [140–142].

Additionally, the medications are often taken for longer in clinical practice than in the original clinical trials [24,28–36]. This means that these RCTs may not capture side effects associated with comorbidities or concomitant medications, rare side effects, or side effects associated with long-term use [122,143]. There are also concerns about how adverse events are recorded and reported during clinical drug trials [107,130]. For example, a systematic review of ChEIs and memantine in the treatment of vascular dementia found that reporting of cardiovascular, renal

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and other adverse effects was too inconsistent to allow for meaningful comparisons [130]. These limitations in knowledge do not mean that these medications are unsafe for all people who have dementia with comorbidities/polypharmacy; however, monitoring and consideration of possible ADRs should be conducted throughout treatment.

Potential harms of ChEIs

ChEIs can cause a variety of adverse effects due to an extension of their mechanism of action—that is, through increased cholinergic stimulation, both centrally and peripherally [121]. In meta-analyses of RCTs (the majority of which had a duration of use ≤ 6 months), significantly more participants dropped out in the ChEI group compared to the placebo group (ranges 25 to 29% versus 16 to 18%). Dropouts specifically due to adverse events were also more common in the treatment group (ranges 13 to 18% versus 8 to 9%). There was an increased risk of experiencing any adverse effect in all meta-analyses identified in this review, with prevalence ranging from 61 to 80% in the ChEI group versus 42 to 70% in the placebo group [13,101,103,119,123–125,130,144]. Table 2 presents the types of ADRs reported.

Commonly reported side effects (especially gastrointestinal adverse events) generally occur upon initiation of therapy or dose escalation, and can be dose related. They can also be transient and do not always require cessation of therapy [89,90,107,118,121,122,145–147].

A systematic review of 'real-world' studies of people taking ChEIs found similar common adverse events at a similar rate to that found in RCTs, although with less gastrointestinal adverse events (perhaps due to less strict dose escalation schedules) and more weight loss (perhaps due to different population settings) [148]. Studies of national pharmacovigilance databases (post-marketing monitoring of spontaneously reported ADRs) have found that the most common adverse reactions reported include neuropsychiatric symptoms and gastrointestinal, cardiovascular and administration site reactions (for the patch formulation) [149–151]. These databases are not able to determine the prevalence of the symptoms or attribute causality.

Meta-analyses of studies that have reported 'serious adverse events' have found no statistically significant difference between ChEI and placebo groups [89,107,123,131,132,144,152]. However, a large number of serious ADRs to ChEIs have been reported through national pharmacovigilance databases [149–151].

Tremor and Parkinsonian symptoms have been reported to increase with the use of ChEIs, both in people with and without Parkinson's disease. Tremor has been reported to increase sevenfold among people with AD and two- to threefold among people with PDD and LBD [121,123–125,144].

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Table 2: Adverse drug reactions reported in meta-analyses of randomised controlled trials of ChEIs *

Type of side effect	Side effects	References
Gastrointestinal side effects (two to five times more likely among people taking ChEIs versus placebo [121])	Abdominal pain (11%) Nausea and/or vomiting (4 to 40%) Diarrhoea (4 to 17%) Weight loss or anorexia (3 to 12%)	[13,89,100,101,125,145,153]
Non-gastrointestinal commonly reported side effects (occurred more frequently in ChEI than placebo participants)	Headache and dizziness (3 to 19%) Agitation (up to 13%) Syncope (3%) Insomnia (6 to 9%)	[13,89,100,101,103,119,121,125,145,154]
Rare and less commonly reported side effects	Abnormal dreams, asthenia, fatigue, somnolence, sweating, anxiety, muscle cramps, peripheral oedema, tremor, vertigo, pain, hallucinations, aggression, urinary incontinence, urinary tract infections, rash and pruritus, accident and injury, common cold, rhinitis, confusion, dyspepsia, gastric and duodenal ulcers, fever, hypertension and Pisa syndrome	[13,103,121,122,131,143,145,146]
Immediately life-threatening rare side effects	Bradycardia, gastrointestinal haemorrhage and seizures	[13,103,121,122,131,143,145,146,154]

* Consult individual drug monographs/product information for full list of all possible ADRs.

Several of the rarer yet more serious potential side effects are discussed in more detail below. There is pharmacological rationale about the potential for ChEIs to cause urinary, cardiovascular and pulmonary complications [146].

Urinary incontinence can be caused by increased peripheral acetylcholinesterase (due to acetylcholinesterase inhibition). Two pharmacovigilance studies have found that new prescription of anticholinergic medications used to treat urinary incontinence may be increased after the first prescription of a ChEI (a so-called 'prescribing cascade', where one medication is prescribed to treat the side effect of another) [155,156], although another study did not substantiate this result [154]. Prospective cohort studies have identified a 7% chance of precipitation of urinary incontinence with prescription of a ChEI; however, for those who responded favourably to the ChEI (in cognition and behaviour), this risk was reduced [157,158].

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A systematic review and meta-analysis of RCTs and extension studies of ChEIs examined the risk of falls, syncope, fracture and accidents. They identified an increased risk of syncope, yet not falls, fractures or accidental injury among people taking ChEIs. The risk of syncope with ChEIs was greater among people with AD and mild cognitive impairment. Notably, very few studies included in this meta-analysis had a follow-up duration of greater than 12 months. The authors of this review reported that their conclusions were limited by the small number of studies, possible underreporting of events, and inclusion of healthier (younger and mostly community-dwelling) participants in the original RCTs [159]. Several large observational studies have identified an increased risk of symptomatic bradycardia, syncope, pacemaker insertion, falls, hip fractures and hospitalisations for these symptoms among people prescribed with ChEIs. However, other studies have not found this association [121,160,161]. A dose response relationship has been reported with a greater incidence of bradycardia among people on high-dose ChEI [162]. Additionally, there have been case reports of QT prolongation and torsades de pointes ventricular tachycardia in people taking ChEIs [122,160].

While there is plausibility due to the mechanism of action of ChEIs, there is currently insufficient evidence to support whether or not ChEIs increase the risk of pulmonary complications and/or gastrointestinal bleeding [122,145,146,163–166].

Weight loss and anorexia are side effects that commonly occur soon after initiation of ChEIs; however, the potential effects of long-term use are unclear. There are a number of other factors that can cause weight loss in people with dementia (especially for people with late-stage dementia who might have difficulties with swallowing and digestion, apathy and other forms of functional deterioration) [94,122]. A recent systematic review and meta-analysis of 25 RCT, open-label and longitudinal studies found an approximately doubled risk of weight loss in people prescribed ChEIs. The results indicated that the risk remained with long-term use; however, the data past six months use were limited [167].

Post-marketing warnings of potentially life-threatening adverse reactions caused by ChEIs have appeared over the past few years (more than 10 years after they were placed on the market). These include Stevens-Johnson syndrome (and other serious dermatological reactions), rhabdomyolysis and neuroleptic malignant syndrome [168,169].

Potential harms of memantine

Memantine appears to be very well tolerated, with an adverse event profile similar to placebo [143]. Meta-analyses of memantine use have found no statistical difference in total number of dropouts (ranges 18 to 19% versus 18 to 21%), dropouts due to ADRs (10 to 13% versus 8 to 10%), or total number of adverse events in the treatment versus placebo group (70 to 73% versus 70 to 73%) [100,103,106,121,125,130,134,135,143]. Memantine has not been associated

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with an increased risk of serious adverse events in RCTs [100,106,134,170]. These data should be interpreted in consideration of the fact that these trials were conducted with people with moderate to severe dementia, who may have difficulty reporting adverse events.

The most commonly reported ADRs in the clinical drug trials of memantine are constipation, diarrhoea, dizziness, headache, insomnia, hypertension, somnolence, falls, agitation, weight loss, confusion, anxiety, depression, peripheral oedema, urinary tract infection, upper respiratory tract infection and accidental injury. However, in most of the meta-analyses of RCTs, there was no difference in the prevalence of these reported adverse events between the memantine and placebo groups [89,121,134,143,145,170,171]. The exceptions to this were a meta-analysis of the use of memantine and amantadine in schizophrenia that found an increased risk of weight loss [171], and increased somnolence in a meta-analysis of treatment for AD [170].

A meta-analysis of the effect of memantine on falls and related events found no difference in falls, syncope or accidental injury, and a reduced risk of fractures [159]. It has been suggested that memantine might lead to clinically important bradycardia and other cardiovascular outcomes based on pharmacovigilance data and observational studies [160,172,173].

The tolerability of dual treatment with memantine and a ChEI appears to be similar to that of single therapy with a ChEI [136,138,174].

Drug–drug interactions with ChEIs and memantine

Both ChEIs and memantine can be involved in drug–drug interactions through pharmacokinetic and pharmacodynamic mechanisms. The clinical significance of many of these drug–drug interactions is unknown; however, it appears likely to be minimal [146]. Formal pharmacokinetic interaction studies are often completed with healthy volunteers with acute administration. As such, the potential for interactions in people with polypharmacy with long-term use is mostly unknown [146]. Drug–drug interactions may be responsible for approximately one-third of ChEI ADR reports [175].

Donepezil and galantamine are metabolised by the enzymes CYP3A4 and 2D6. Theoretically, co-administration with other medications that are inducers, inhibitors or substrates can alter the rate of metabolism of ChEIs, which may lead to higher or lower plasma concentrations, subsequently leading to toxicity or sub-therapeutic treatment. Rivastigmine is not metabolised by CYP enzymes and subsequently has reduced potential for pharmacokinetic drug–drug interactions [143,146,176]. Memantine is eliminated renally; thus, medications that alter the pH of the urine or compete with memantine for renal excretion (such as trimethoprim) may affect the clearance of memantine [176,177].

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Pharmacodynamically, concomitant administration of medications with similar mechanisms of action and/or ADRs may increase the risk of harm. Medications that can cause bradycardia, lower the QTc interval and reduce the seizure threshold, as well as succinylcholine-type medications, should be used with caution for people taking ChEIs [176]. Co-administration of ChEIs and anticholinergics can theoretically reduce the efficacy of both medications. Co-prescribing of anticholinergics with ChEIs has been found to be a predictor of early discontinuation of ChEIs, potentially due to reduced efficacy of these medications [36,49]. The clinical significance of this is mostly unknown; however, anticholinergics are generally not recommended for people with dementia, as they have the potential to worsen cognition [143,176]. Table 3 lists the potential drug–drug interactions with ChEIs and memantine.

Table 3: Potential drug–drug interactions with ChEIs and memantine interactions [143,146,176–181]

Drug	**Metabolism/ excretion**	**Potential drug–drug interactions**	**Outcome of interaction**
ChEIs	See individual drugs below	Other drugs with cholinergic activities (such as succinylcholine-type medications used as muscle relaxants during anaesthesia, and bethanechol)	May potentially prolong the action of the cholinergic effect (such as prolonged muscle relaxation following anaesthesia)
		Anticholinergics	Opposite mechanisms of action; may reduce efficacy of both drugs
		Drugs that can cause bradycardia, such as beta-blockers, antiarrhythmics, and calcium channel blockers	Additive risk of bradycardia
		Drugs that can prolong the QT interval, such as antiarrhythmics, calcium channel blockers, and antihistamines	Additive risk of QT prolongation and torsades de pointes
Donepezil and galantamine	CYP2D6, CYP3A4 and glucuronidation	Can theoretically interact with drugs that are metabolised via the same pathways	May reduce metabolism of other drugs metabolised by the same pathway; however, is unlikely to have a clinically significant effect

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		Drugs that can induce or inhibit CYP2D6 (such as paroxetine, quinidine and fluoxetine) or CYP3A4 (such as ketoconazole and erythromycin)	May reduce concentrations (reducing efficacy) or increase concentrations (increasing risk of cholinergic side effects); clinical importance of these interactions is unclear
Rivastigmine	Hydrolysis via plasma cholinesterase	Metoclopramide	Additive risk of extrapyramidal effects; concomitant use is not recommended
		Nicotine may increase the clearance of rivastigmine	May reduce concentrations (reducing efficacy); clinical importance is unclear
Memantine	60 to 80% excreted unchanged in the urine	Other NMDA antagonists amantadine, ketamine and/or dextromethorphan	Increased risk of central nervous system (CNS)–related adverse reactions, including pharmacotoxic psychosis; combination should be avoided
		Drugs affecting the CNS (L-dopa and dominergic agonists, anticholinergics, barbiturates, neuroleptics, anticonvulsants, dantrolene and baclofen)	Theoretically, memantine may potentiate the effect of CNS active drugs
		Warfarin	Possible increase in international normalised ratio (INR); additional INR monitoring recommended
		Drugs using the same renal cationic transport system (trimethoprim, cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine)	May lead to increased levels of other drugs that use the same cationic transport system; clinical significance unknown
		Drugs that can affect the pH of the urine (urinary alkalisers)	May reduce the clearance of memantine

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		Diuretics (hydrochlorothiazide and triamterence)	Memantine may reduce the bioavailability of hydrochlorothiazide and/or triamterence, but is unlikely to be clinically significant
		Atropine	Serious interaction observed in rats (occurred with high-dose memantine); unclear relevance for humans treated with a therapeutic dose
		Selective serotonin reuptake inhibitors	May increase the risk of visual hallucinations

Summary of harms

There is considerable uncertainty about the risk of serious ADRs associated with long-term use of ChEI and/or memantine. This is due to a lack of data in a representative population (older, with comorbidities and polypharmacy), scarce unbiased information and conflicting results. The prevalence of dementia is associated with increasing chronological age and frailty. Therefore, people with dementia may be at a greater risk of ADRs due to altered physiology, which can lead to decreased clearance and increased sensitivity to some medications [17,182,183]. Multiple comorbidities and polypharmacy are also common in people with dementia, yet conditions and medications that can increase the risk of ADRs are often exclusion criteria in RCTs. Increasing age has been found to be a factor associated with serious ADRs due to ChEIs in a French pharmacovigilance database [151]. In a study examining the most common ADRs among people with dementia, the anti-dementia medications were the most common causative agents (followed by cardiovascular medications and psychotropic drugs) [184].

The potential adverse effects of ChEIs and memantine—such as falls, weight loss and urinary incontinence—can all have significant adverse sequelae in older people (such as hip fracture after a fall), which will have important implications for their quality of life [120,121,143,146]. Due to these potential consequences and the limitations of current evidence, frequent monitoring for ADRs is required. Healthcare professionals should consider the potential benefits and risks of ChEIs and memantine when discussing whether or not to continue their use.

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Consumer Values and Preferences

In general, the vast majority of older adults would hypothetically like to take fewer medications and are willing to have a medication ceased if their doctor says it is possible [185,186].

Any discussion about values and preferences with regard to ChEI and/or memantine therapy must consider the expectations of people with dementia and their carer/family in regard to therapy benefit. Discrepancies have been cited between the evidence for beneficial outcomes of such therapy and the expectations expressed by the lay public and healthcare professionals [187–189]. People with dementia, carers and nurses tend to have high expectations of benefit, including that these medications will improve memory, enhance quality of life, delay progression of dementia, ease carer distress and delay long-term care admission [187,190,191], although other studies have found more conservative consumer expectations [192]. While physicians and pharmacists express desire for such effectiveness, they recognise the limitations of existing evidence [187]. Some studies have found that carers initiate drug therapy in the hopes of a response, but may become less positive over time [193,194]. The quality of life of the person with dementia is regularly discussed as central to treatment decisions (starting, continuing and discontinuing) [194].

High expectations coupled with limited observed benefit may prompt thoughts about stopping therapy among some carers [194,195]. Factors in making a decision to discontinue therapy include the progression of dementia, eventual lack of benefits, considerations of cost and a rapid decline in physical health [192,196,197]. The majority of carers interviewed about such decisions felt that a lack of effect was a good reason to stop therapy, though the authors of this study recommended discussing plans for deprescribing early on in the prescribing process in order to avoid feelings of 'giving up' [198]. Other studies have found that carers would consider stopping therapy only when the person was totally dependent on others, while people with dementia were reluctant to think that there would be a time that they would stop this medication [191]. There has been major fear reported in relation to withdrawal of therapy, with carers worrying that stopping therapy may worsen dementia, trigger a rapid decline or even precipitate death [191,194,195]. They are also concerned that stopping ChEIs and/or memantine means 'giving up', and may experience guilt over making such a decision [191,198,199]. Studies have emphasised the importance of counselling the carers who are making such decisions in order to ameliorate a sense of hopelessness [200].

Thus, importantly, any deprescribing discussion must consider the viewpoints of the person with dementia and their carers, and include education about the potential benefits versus harms of both continuing and discontinuing the medications. It is important to acknowledge that initiating medication in the hopes of response is reasonable; however, when benefit is

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unclear after a suitable trial period, it is also reasonable to consider stopping therapy. This is consistent with what many carers expect in terms of eventual decision making for drug use [201]. Carers value the diverse benefits of therapy for the person, such as the ability to socially interact, recognise family and perform activities of daily living, and can place less emphasis on the improvement of objective measures of cognition [196,197,202]. Potential outcomes of deprescribing should be placed in the context of what is important for the person with dementia and their family.

Our literature review found less discussion about how carers view the potential side effects of treatment. One study found that carers viewed side effects differently than researchers—for example, carers rated severe vomiting as 'major', while researchers ranked this as 'minor' [203]. In a follow-up survey, most carers (> 59%) were willing to continue therapy in the face of weight loss or diarrhoea, but not in the face of headache, dizziness, nausea, vomiting, blood pressure drops, insomnia, muscle cramps or stomach bleeding. Although, if currently using a ChEI, carers tended to be more willing to accept greater numbers of adverse effects [204]. This study illustrates that carers make a risk–benefit assessment when deciding to continue or stop therapy, and that such decisions would be facilitated by education about risks (including what side effects to monitor for) and benefits (including what to monitor for, as well as the limitations of such benefits) [205].

The burden of medication management on the carer cannot be underestimated [206–209]. In addition to stress, worry and the restriction of carer activities associated with the administrative tasks of medication management and managing negative side effects, there is an emotional burden to the responsibility of making decisions about medications [190,206,208,210]. Medication administration for people with dementia can be burdensome to carers and nurses/care staff, and may be distressing for people with dementia, especially those with swallowing difficulties [211]. Carers can experience guilt and self-remonstration when they feel a decision has led to ill-health for the person with dementia [208]. This supports the need for carer access to expert knowledge and information about medication benefits and side effects to make informed decisions [188].

The need to address the information needs of people with dementia and their carers is a common theme throughout the qualitative work on understanding perspectives on dementia diagnosis and treatment [212].

Finally, surrogate decision making by carers, as well as ethnic and cultural differences in risk taking, must be taken into account [197]. There have been shown to be differences in the preferences for care between carers and people with dementia [213–216]; thus, it is reasonable to suggest that discussions about dementia medication prescribing and eventual decisions

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about deprescribing should occur early in therapy, when the person with dementia is still able to participate in decision making, and should continue throughout therapy in order to reflect the varying balance of involvement between the person with dementia and the carer as time passes [217,218].

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Resource Implications and Cost-effectiveness

The global costs of dementia were estimated to be US$818 billion in 2015, including direct medical care (19.5%), social sector care (40.1%) and informal care (40.4%). This amount represents 1.09% of global gross domestic product, and these costs are increasing [2]. Even after adjusting for age, gender and comorbidities, providing care for people with dementia is more expensive than for those without dementia [219]. Nevertheless, there are relatively few published cost-effectiveness studies in the field of providing quality care for this population. More research is required to determine the most cost-effective ways of providing high-quality care to people with dementia [2,89,220].

Among older Canadians, ChEIs are commonly prescribed for people with dementia, representing the seventh most costly medication to Canada's publicly funded drug benefit programs. The cost of ChEIs for this population in 2012 was CAD$129.4 million [221]. In Australia in 2008, the cost of ChEIs to the government was AUD$55.2 million—an almost 20% increase from 2004 [24]. However, these tangible costs are only a small fraction of the total costs required to care for people with dementia. The major contribution to costs are the support services required (formal and informal) for people with dementia, owing to these people's significantly increased need for cognitive and functional support [113].

Cost-effectiveness studies of ChEIs and memantine have prompted the Australian and Canadian Governments to subsidise these mediations for targeted individuals through the Australian Pharmaceutical Benefits Scheme (PBS) and Canadian Provincial Drug Benefit Programs (Table 4). The majority of studies indicate that ChEIs are cost-effective for mild to moderate AD from both a health and societal perspective [113,220,222]. Memantine may be cost-effective as a second-line treatment or for moderate to severe AD [113,220,222]. There are too few cost-effectiveness studies on dual treatment to draw conclusions [113]. The 2012 National Institute for Health Research—Health Technology Assessment (NIHR-HTA) programme in the United Kingdom (UK) found a greater than 99% probability that ChEIs are cost-effective for mild to moderate AD at a willingness-to-pay threshold of £30,000 per quality-adjusted life year (QALY). The probability of memantine being cost-effective for moderate to severe AD is only 38% at the same level of willingness to pay [97].

There are a number of significant limitations of the cost-effectiveness analyses of the use of ChEI and memantine for dementia. In particular, the data used to evaluate cost benefit are derived almost exclusively from studies of a short duration (six months or less) and studies sponsored by pharmaceutical companies. Additional limitations include complexity in the progression of dementia, variability in service use, and a relatively small quantity of data on costs and other important outcome measures (such as time to institutionalisation, mortality

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and effect on carer time). The cost of medications and services are also country specific; consequently, conclusions cannot be generalised [97,113,220,222]. Indeed, as reported by the NIHR-HTA, there are a number of limitations with cost modelling studies. The data used for time to institutionalisation and other cost parameters rely on a relatively small sample of 92 people with AD over the period 1988 to 1999. In addition, studies assume that the treatment effect is sustained after therapy is ceased [97]. Another important consideration is that the main data used in these analyses from ChEI/memantine RCTs consider cognitive outcomes only [222–224]. The QALYs gained are not from direct data of improvement of quality of life observed with drug treatment [222,224,225].

There is evidence internationally that ChEIs and memantine are being used for longer periods and outside of indications that were assessed in the cost-effectiveness studies [24,28,31,38,42,43,45,47,226,227]. Up to 30% of ChEI and memantine prescribing may not comply with national guidelines or government reimbursement criteria [37,38,40,45,47]. Additionally, in studies that conducted an economic evaluation, there was a tendency to assume that ChEIs are discontinued on institutionalisation [222], which is not always the case (up to 50% of people with dementia in nursing homes are prescribed a ChEI and/or memantine) [35,37,43,226,228].

The availability of generic medications in several countries has greatly reduced the costs of ChEIs and memantine to the government/consumer; thus, their cost-effectiveness may have improved in recent times [113,222].

The cost-effectiveness of continuation versus discontinuation of the ChEI donepezil was reported in a single study conducted in the UK [229]. The DOMINO-AD study was a 52-week double-blind placebo-controlled trial that investigated the effect of continuing donepezil versus discontinuing donepezil, switching to memantine, and adding memantine to continued donepezil. The participants (n = 295) were community-dwelling people with moderate to severe AD, who had been prescribed donepezil for longer than three months. Seventy-three and 62% of participants had complete data for health and social care and societal perspective analyses, respectively. Participants who continued on donepezil had slightly lower health and social care and societal costs than those who discontinued; however, the difference was not statistically significant. QALY was calculated based on the results of the generic health-related quality of life tool (EQ-5D-3L) and societal weights. The QALY gain for continuation versus discontinuation of donepezil was 0.11 (95% CI = 0.02 to 0.20) and their cost-effectiveness analysis found continuation of donepezil to be dominant to discontinuation (lower cost and higher benefit). There were several important limitations of this study (small select participant group, difficulties calculating societal costs and benefits, and medication costs based on the generic price) that limit its generalisability [229]. Additionally, the generic quality of life score—the EQ-

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5D-3L (proxy rated by carers)—may not be appropriate to use for people with dementia because it has been reported to have problems with validity in this population, with a substantial ceiling effect, poor associations between individual and proxy ratings, and poor reliability of the visual analogue scale [230]. A dementia-specific quality of life tool (DEMQOL-Proxy) was also used in the study, but was not used in the cost-effectiveness calculations (no difference between groups was found in DEMQOL-Proxy scores [60]).

Cros et al. [78] conducted a study of discontinuation of ChEIs and memantine among 24 people with advanced dementia living in a residential care facility. They estimated that this resulted in a saving of €20,000 over one year, based on the cost of the medications. This amount corresponds to the cost of a half-time care staff, thereby highlighting the potential to use the money spent of prescription medications for non-pharmacological care. However, this study had a very small sample size (n = 24) and did not conduct any formal cost-effectiveness analyses; therefore, no widespread conclusions can be made from these results.

Although the research findings on the cost-effectiveness of ChEIs and memantine use in dementia care are limited, both the Australian and Canadian treatment guidelines recommend trialling these medications in non-subsidised government-sponsored indications (such as non-AD dementia). The 2016 Australian Clinical Practice Guidelines and Principles of Care for people with dementia acknowledge that this creates a position where people with non-AD dementia who are prescribed ChEI and/or memantine and their families may incur large out-of-pocket costs, thereby increasing health inequity for this population group [89]. While the majority of economic considerations are conducted at a committee/governmental level (e.g. to determine subsidisation), individual clinicians should be aware of cost implications for the individual based on local subsidisation criteria (Table 4). In a study of the perspectives of healthcare professionals from the UK, the US and Canada, the majority of participants felt that the bulk of public investments for the treatment of dementia should be spent on non-pharmaceutical interventions, including carer education and support, respite care and home care [231].

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Table 4: Subsidisation of ChEIs and memantine in Australia and Canada

Medication	Approved indication
Australia—National PBS *Specific requirements must be met for prescription and ongoing treatment with one of these medications. Dual therapy is not approved for subsidisation. Prescribers must obtain authority from PBS to initiate and continue treatment. Individuals must demonstrate a clinically meaningful response to treatment after six months to qualify for ongoing subsidisation. Individuals are required to make a co-payment for medications (level of co-payment depends on concession status and annual medication costs).* http://www.pbs.gov.au/pbs/home	
Donepezil	Mild to moderately severe AD
Galantamine	Mild to moderately severe AD
Rivastigmine oral	Mild to moderately severe AD
Rivastigmine patch	Mild to moderately severe AD
Memantine	Moderately severe AD
Canada—Provincial Drug Benefit Programs *In all provinces and territories, specific conditions must be fulfilled for initial and ongoing supply.* *Each provincial and territorial government has a drug benefit plan for eligible individuals—see http://www.hc-sc.gc.ca/hcs-sss/pharma/acces/ptprog-eng.php. Eligibility requirements differ; some are based on income, while others are based on categories of individuals who have high drug costs (such as older adults). The Non-Insured Health Benefits Program may also apply to eligible First Nations and Inuit populations—see http://www.healthycanadians.gc.ca/publications/health-system-systeme-sante/nihb-drug-list-2016-liste-medicaments-ssna/index-eng.php.* *In most provinces and territories, individuals are required to make a co-payment for medications.*	
Donepezil	Mild to moderate AD [1]
Galantamine	Mild to moderate AD [1]
Rivastigmine oral	Mild to moderate AD [1]
Rivastigmine patch	Mild to moderate AD [1,2]
Memantine	Moderate to severe AD (living at home) [1,2]
[1] Specific criteria vary by province/territory—some include LBD and AD with vascular component. [2] Not reimbursed by all provinces.	

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Clinical Considerations

This guideline and its recommendations are designed as a tool for healthcare professionals to aid in assessment of whether it is suitable to deprescribe ChEIs and/or memantine. Of course, there are many additional individual-specific factors that must be considered by the clinician when making this decision. This section on 'Clinical Considerations' provides extra discussion on making the decision to trial deprescribing and guidance on how to conduct deprescribing. Such discussion is informed by the findings of the systematic review we conducted and is supplemented with targeted search strategies to identify relevant evidence. While several review articles have informed this discussion, a comprehensive review of each of these topics is beyond the scope of the guideline.

Assessing benefit/continued need

The decision to continue or discontinue ChEIs and/or memantine needs to consider the potential for ongoing benefit (considering indication, effectiveness, duration of use and life expectancy) and the potential for harm (ADRs, drug–drug and drug–disease interactions, pill/administration burden and cost) (Figure 1). This needs to be undertaken within the context of the individual's care goals, values and preferences, ideally through shared decision making with the person with dementia and/or their carer/family members.

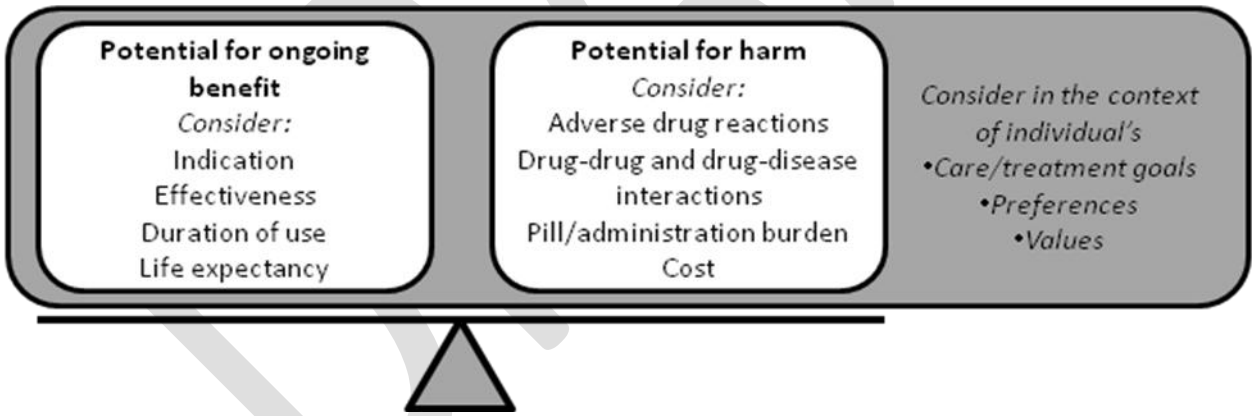

Figure 1: Weighing up the potential benefits and harms of ongoing use of ChEIs and memantine

Due to the progressive and fluctuating nature of dementia [232,233], it can be very difficult for healthcare providers and people with dementia and their families/carers to assess whether there is an ongoing benefit from the medication. The rates of decline of cognition and function in dementia are not constant [234]. Dementia tends to progress faster in the moderate stage than in the mild and severe stages [235]. Additionally, there is a large amount of heterogeneity in how individuals progress [233–235]. In a progressive condition, predicting response to treatment, and therefore lack of response to treatment, is very difficult [93,236]. It may be

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nearly impossible to reliably predict whether an individual will decline when the drug is discontinued.

Tools that measure cognition, such as the MMSE [57] and ADAS-Cog [58], are regularly used in research and practice. Changes of two to three points on the MMSE and four points on the ADAS-Cog over six months are used in clinical drug trials to indicate a clinically important change in cognition [121,233,236,237]. However, there are significant limitations to these tools, including a poor test–retest reliability, high measurement error, floor effect (meaning they are less suitable in the severe stages of the condition), reliance on ability to communicate in English, and cut-offs that are based on expert opinion with little inherent meaning [120,233,236]. As such, use of these tools in isolation to monitor progression is not recommended. If there has been no change in these measures, this does not guarantee that there is an ongoing benefit from the medication, and vice versa. They only measure limited categories of cognitive function and not the many other symptoms that are important in people with dementia, such as independence with activities of daily living, executive function and mood [93]. Tools that measure global change (such as the CIBIC-Plus or Goal Attainment Scaling [GAS] [238,239]) may be more suitable in assessing clinically important changes because they are based on clinician and carer assessment and detection of noticeable change, although these too have some limitations [65,120,237].

The Dementia Outcomes Measurement Suite (http://dementiakt.com.au/doms/) is a list of tools that are recommended for use among people with dementia, along with manuals and scoring guides.

In general, a sustained decline (in cognition, function and/or behaviour), noticeable by both clinician and family members/carers, at a greater rate than previous may indicate that the person with dementia is no longer obtaining a benefit from the ChEIs and/or memantine. However, simply looking at benefit does not provide a complete assessment of the suitability for deprescribing. Benefit must be balanced against the potential for harm (see 'Harms' section). There is limited evidence on risk of harm with long-term use and the risk of harm among the oldest-old, frail and/or multi-morbid population. The harms of polypharmacy (multiple medication use) are well established, and include increased ADRs, falls, hospitalisation and mortality [240–244]. Pill burden and burden of medication administration to both the person with dementia and their carer must also be considered. People with severe dementia may have difficulty swallowing or may be resistive to medication use [211].

The final step after considering benefits and harms is to place these in the context of the care goals of the individual. Reassessment of care goals (and therefore appropriateness of medication use) should be conducted at regular intervals and may be triggered by new medical

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conditions, change in residence and/or level of external care required, and shortened life expectancy.

How to conduct deprescribing

There is very little evidence to guide the process of discontinuation of ChEIs and memantine. In our systematic review, two of the seven RCT ChEI discontinuation studies [62,66] and two of the memantine discontinuation studies [74,78] employed tapering prior to discontinuation. Where the tapering regimen was described, the majority were stepped down through available doses (such as donepezil 10 mg changed to 5 mg, and then ceased). Those taking the lowest available dose (such as donepezil 5 mg) had the medication ceased abruptly. Periods between steps were two to four weeks for ChEIs and two weeks for memantine. Tapering did not appear to influence whether there were worsened clinical outcomes (such as cognition and function) in these studies; however, due to the large variations in study types and populations, it is not possible to make a definitive conclusion about this.

Many of the discontinuation studies identified in our systematic review reported that abrupt discontinuation of ChEIs and/or memantine is safe (from recommended doses). In reviewing the need for tapering versus abrupt discontinuation, we attempted to differentiate between re-emergence of the condition after discontinuation (worsening of symptoms that the dementia medications treat) versus a physiological adverse drug withdrawal event (ADWE). Five of the RCT discontinuation versus continuation of ChEIs studies employed abrupt discontinuation. There was no difference in prevalence of adverse drug/withdrawal reactions between the two groups. However, it is possible that the adverse effects of discontinuation may have been balanced against the side effects of continuation of the drug. It was not possible to compare the rate or type of adverse effects across studies due to differences in recording and reporting. The timing of adverse effects was also not reported (proximity to discontinuation).

While there may not have been a detectable rate of adverse drug withdrawal reactions in the above mentioned studies, there have been case reports of discontinuation syndromes on abrupt discontinuation of both ChEIs and memantine. It is possible that the RCTs were not sufficiently powered or monitored to detect on a small sub-population who may experience an adverse drug withdrawal reaction.

There have been five case reports (four publications) of an ADWE on abrupt cessation of ChEIs [245–248] and two case reports of a memantine ADWE [249]. In three cases of abrupt discontinuation of donepezil 10 mg and 5 mg daily doses (prescribed for LBD, AD with vascular dementia and AD), a discontinuation syndrome occurred within three to seven days. The timing of the discontinuation syndrome is in concordance with the clearance of donepezil, which has a half-life of approximately 70 hours. The symptoms included fluctuating level of consciousness,

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hallucinations, insomnia, increased anxiety and agitation, and altered mood. In two of these cases, donepezil was restarted, leading to resolution of the syndrome, while in the third case, the syndrome resolved without restarting the medication [245,246]. There have also been case reports of paralytic ileus [247] and angle-closure glaucoma [248] on abrupt discontinuation of donepezil. The pathophysiological mechanism of this discontinuation syndrome is not fully understood, but has been proposed to be related to adaptive changes within the CNS due to prolonged acetylcholinesterase inhibition [245]. Specifically, long-term administration of rapid-reversible ChEIs (donepezil, galantamine and tacrine) has been shown to increase acetylcholinesterase protein expression and activity [250]. Therefore, abrupt discontinuation may lead to exaggerated reduction in acetylcholine, which could lead to the symptoms described in the case reports.

Two people with AD and cerebrovascular infarction who were prescribed memantine, and then discontinued use of the medication because of insurance limitations, experienced a withdrawal syndrome consisting of insomnia, aggression, delusions and disinhibited behaviour. Both individuals had memantine restarted after approximately two weeks, which resulted in a reduction of the symptoms over the following four months [249].

Regardless of the physiological need to conduct tapering in medication withdrawal, there are additional rationales that encourage this as good practice. The other main reasons are to reduce the effect of return of symptoms (if they occur), identify the lowest effective dose (if the medication is not able to be completely withdrawn) and increase individual and family/carer comfort with deprescribing [20].

Recommended tapering schedule

Based on all of the above considerations, we have recommended a tapering schedule that is in accordance with the dose forms available in Australia and Canada (Table 5). We have recommended timing between dose reductions of four weeks. This timing is based on allowing time for the reappearance of dementia-related symptoms (re-emergence of the condition and need for ongoing medication use), while also considering the rate of clearance of the medication. Studies indicate that, after short-term use, the cognitive symptomatic effect of ChEIs reduced to the level of placebo-treated participants after approximately four to six weeks [251,252]. Also considered was a time period that would allow for appropriate monitoring of fluctuating symptoms and the quantity of tablets that usually come in a package (one month's supply). However, duration between dose reduction/monitoring can be altered to suit the person with dementia/family/carer.

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Table 5: Recommended tapering schedule for ChEIs and memantine

Drug	**Dose-reduction schedule** *(start at individual's current dose)*	**Time until next dose reduction**	**Five half-lives of the medication** [1] *(duration of inhibition of acetylcholinesterase)* [178–181,250]
Donepezil (available in 5 and 10 mg tablets)	10 mg once daily → 5 mg once daily → cease	Four weeks	15 days (reversible inhibitor)
Galantamine (available in 8, 16 and 24 mg extended release capsule)	24 mg once daily → 16 mg once daily → 8 mg once daily → cease	Four weeks	Two days [2,3] (reversible inhibitor)
Rivastigmine capsule (available in 1.5, 3, 4.5 and 6 mg capsules)	6 mg twice daily → 4.5 mg twice daily → 3 mg twice daily → 1.5 mg twice daily → 1.5 mg once daily → cease	Four weeks	One day [2,3] (six to nine hours)
Rivastigmine patch (available in 4.6, 9.5, 13.3 mg/24 hours)	13.3 mg/24 hours → 9.5 mg/24 hours → 4.6 mg/24 hours → cease	Four weeks	17 days [2,3] (six to nine hours)
Memantine (available in 10 and 20 mg tablets)	20 mg once daily (or 10 mg twice daily) → 10 mg once daily → cease	Four weeks	21 days [2]

[1] Time after which over 96% of the medication is expected to be cleared from the system, rounded up to the nearest whole day.

[2] Product information reports that clearance of drug or metabolites may be reduced in people with renal impairment.

[3] Product information reports that clearance of drug or metabolites may be reduced in people with hepatic impairment.

This recommended tapering schedule needs to be tailored to the individual. If abrupt cessation is considered, it is recommended that the person with dementia/family/carer is aware of the potential for an adverse drug withdrawal reaction. The deprescribing plan should be developed in partnership with the person family/carer and any other healthcare professionals who are involved in the care of the person (such as pharmacists, nurses and care staff). Consider the supply of tablets that the person with dementia has to minimise wastage, although it is

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advisable for the person to have a small supply of the previous dose available if there is a withdrawal reaction or a need to restart the medication.

Monitoring

The person with dementia and/or their family/carers, nurses and care staff should be provided with information on what types of symptoms to monitor for and what to do if symptoms return (Table 6). At each dose-reduction step, the person's symptoms should be monitored (by clinician, family/carer, nurses or care staff) to determine suitability to continue tapering. Monitoring should focus on both cognitive and functional abilities and neuropsychiatric symptoms, and consider how these have changed over the four-week period. It may be beneficial for medical practitioners to conduct standardised cognitive and functional tests (such as MMSE, ADAS-Cog, CIBIC-Plus or GAS) to compare to previous progress. A discussion with a plan about how monitoring is going to occur should be conducted and documented (for example, whether the person and/or family/carer prefer face-to-face follow-up or telephone calls). It is important that the individual/carer/family has access to a clinician that they can contact if necessary [185]. If the recommendation to withdraw the medication is being made due to progression of dementia, it is important to remind family members/carers that the person with dementia may continue to decline after withdrawal of the medication, and explain the reasons for this. Other causes of change in condition at the time of deprescribing should also be considered, such as infection or dehydration leading to delirium.

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Table 6: 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
Less than one week	Severe symptoms, including agitation, aggression, hallucinations or reduced consciousness	Restart previous dose immediately and contact responsible healthcare professional as soon as possible	ADWE
Two to six weeks	Worsening of cognition, behavioural or psychological symptoms or function	Restart previous dose and make an appointment to see responsible healthcare professional at the next available time	Re-emergence of symptoms that were being treated by ChEI/memantine
Six weeks to three months	Worsening of cognition, behavioural or psychological symptoms or function	Contact responsible healthcare professional at the next available time to make an appointment	Progression of condition or possible re-emergence of symptoms that were being treated by ChEI/memantine
> 3 months	Any	As per usual care	Progression of condition

Will temporary dose reduction/cessation cause irreversible harm?

It has been reported in the literature that discontinuation of ChEIs for six weeks has a detrimental effect on cognition that is not fully recovered upon re-initiation of the medication. This is based on the results of a study conducted by Doody and colleagues that involved a 24-week double-blind RCT (placebo versus donepezil 5 and 10 mg), followed by a six-week washout and then open-label treatment with donepezil for all participants [251]. The study reported that, during the six-week washout, participants who had been on donepezil had their ADAS-Cog scores drop below baseline levels and, while an increase in scores was observed on re-initiation, the mean ADAS-Cog score did not reach their original baseline level. However, there are limitations to this conclusion. The main consideration is that the end of washout was 30 weeks after baseline, and, while ChEIs can lead to improvement/stabilisation of cognitive scores on initiation, dementia is still progressive and a general decline is observed even with long-term treatment. There was no continuation group; thus, it is impossible to know whether

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scores obtained following re-initiation after the six-week washout would be comparable to continuation. Cognition scores peaked at approximately 36 weeks (six weeks after re-initiation) and were reported not to reach baseline levels; however, variability in the change (such as standard error, standard deviation or 95% CIs) was not reported. Other studies of continuous treatment with donepezil show that participants' cognitive scores returned to around baseline levels at 36 weeks [108,118,253].

Doody and colleagues [251] also described the outcomes of withdrawal in a three-week washout (after 12 weeks of treatment), followed by open-label treatment. They concluded that the effect had not been completely reversed in this period (three weeks) because the average of participants' scores remained above baseline. Noting, however, that the time from baseline was only 15 weeks (not 30 weeks, as with the six-week washout) [251].

Similarly, Homma and colleagues [252] employed a washout period of between two and eight weeks (not by study design, but due to times when appointments could be made) after 24 weeks treatment, followed by 52 weeks open treatment with donepezil. Those with a four- to eight-week washout dropped to levels similar to the previously placebo-treated groups, with cognition improving on re-initiation to a level similar to baseline. However, the mean change did not exceed original baseline values. In this study, the peak occurred approximately 16 to 24 weeks after re-initiation (longer than observed by Doody and colleagues [251]). In the studies by Doody et al. [251] and Homma et al. [252]), participants had been on short-term treatment (24 weeks); thus, it is unknown how their findings apply to those on long-term ChEI.

Other studies report that there is no negative long-term effect of temporary discontinuation. In the RCT of discontinuation versus continuation by Johannsen and colleagues [56], donepezil was re-initiated after the 12-week discontinuation phase for a further 12 weeks. There was no difference at the end of the study between the group who had the 12-week break in therapy and those who continued throughout. However, the numbers of participants were quite low by the end of the study. Pariente and colleagues conducted a real-world analysis of ChEI users and found no negative effect on institutionalisation or mortality for those who had received treatment gaps of greater than six weeks in the first year, compared to those who had continuous use [254]. Another study of real practice reported that people with dementia who were restarted on ChEI therapy due to worsened condition after discontinuation improved to previous levels after the medication was restarted [255]. Again, this study was very small (n = 8 who restarted) and objective outcomes for these participants were not reported.

In a study of memantine discontinuation followed by re-initiation, there was an improvement in cognitive scores after re-initiation to a level similar to prior to discontinuation. However, the number of participants was too small by the end of the study to find statistical significance in

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the final improvement [85]. We did not identify any other evidence to guide whether there are long-term concerns with interrupted treatment of memantine.

In summary, there is inconsistency in the evidence regarding whether there is a detrimental long-term, irreversible effect of trial discontinuation, and the available evidence is limited to breaks of treatment early in the course (first 12 months). Review of the evidence does not provide a clear case for concern and we do not believe that this should prevent trial deprescribing in situations outlined in the recommendations. If there is clear deterioration upon discontinuation, the medication should be assessed for re-initiation as quickly as possible (Table 6), while acknowledging that the symptoms and signs of such deterioration are likely to be non-specific and multifactorial.

Alternatives to cessation: Switching agents or dose reduction

Current evidence suggests that lack of an initial response (benefit) to one ChEI does not preclude response to another. In addition, if a person cannot tolerate one ChEI due to side effects, they may be able to tolerate another. Approximately half of people who did not respond to initial treatment with one ChEI have been shown to respond when switched to another (although evidence on switching agents comes almost exclusively from pharmaceutical industry–sponsored trials) [93,146,256,257]. If there was insufficient response to initial treatment or a loss of benefit early in the treatment course (such as less than one year), it may be suitable to consider switching to another ChEI (after ensuring an adequate trial of at least six months at the maximum tolerated dose) [120,256–259]. It should be noted that there is the possibility of deterioration when switching ChEIs (if indeed the first medication was giving a benefit), of which the individual and carers/families should be advised [259]. The addition of memantine to existing ChEI therapy for people who have progressed to severe dementia is another treatment option; however, as discussed in the benefits section, there is limited evidence to support a clinically important improvement across multiple outcomes with dual therapy [138]. It is recommended to consult national treatment guidelines (Appendix 3: Other Relevant Guidelines) and reimbursement/insurance criteria (Table 4: Subsidisation of ChEIs and memantine in Australia and Canada) if initiating an alternative ChEI, changing to memantine or trialling dual therapy. Recommendations regarding monitoring, documentation and follow-up should be followed as per initiation of a new therapy. If the decision is made to switch to a different ChEI, switch from a ChEI to memantine, or change to dual therapy, this is a good opportunity to discuss with the person with dementia and carer/family when these alternative strategies might be deprescribed in the future.

Several (but not all) studies have found an association with higher doses of ChEIs and better outcomes for the person, including cognition, function, delay to institutionalisation and increased lifespan [13,110,260–265]. However, higher doses have been found to result in a

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higher rate of side effects, especially cholinergic effects [259,260,262]. People who are very old and have multimorbidities and polypharmacy are regularly excluded from randomised clinical drug trials, even drug trials for the treatment of dementia, where these conditions are common. As such, the populations in these studies are generally not representative of the real-world population of people with dementia [115–117,139,266]. Donepezil, galantamine, rivastigmine metabolites and memantine all undergo clearance through the liver and/or the kidneys. Dementia is associated with ageing, frailty and multiple comorbidities, all of which can increase the likelihood of reduced drug metabolism and clearance, placing such people at an increased risk of ADRs [17,182,183]. The optimal dose of ChEIs and memantine among people who are frail with multimorbidity and polypharmacy has not been fully investigated.

If, during the course of tapering, a person does not experience a worsening of their condition with the first dose reduction, but does after cessation of the medication, returning them to the lowest dose on which they had been stable may be indicated on clinical grounds. A dose reduction may also be suitable where the person and/or family/carer is concerned about complete discontinuation of the medication (with reassessment after a suitable period). In our systematic review, we identified a single study that collected outcome data on dose reduction of the rivastigmine patch, although the study was not designed for this purpose; it employed a short-term dose reduction to maintain blinding of a previous RCT of high versus low dose. Participants with severe AD were treated with either 4.6 mg/24 hours or 13.3 mg/24 hours for 24 weeks, after which all were treated with 9.5 mg/24 hours for four weeks, followed by open-label treatment with 13.3 mg/24 hours for an additional 20 weeks. Over the four weeks, the dose-reduction group experienced a non-significant drop in Severe Impairment Battery scores, with essentially unaltered activities of daily living [267]. Further research is required to guide who is suitable for dose reduction and when, while maintaining efficacy and minimising harm.

When should a specialist/other healthcare professional be consulted?

Geriatricians, pharmacologists, psychiatrists, neurologists, geriatric psychiatrists, psychologists, pharmacists, clinical nurse consultants and many other healthcare professionals can all play a role in the process of deprescribing of ChEIs and memantine. It is important that the general practitioner (primary care physician or family physician) be aware of the resources available in their local area to support people with dementia and their carers, and to make appropriate referrals for unmet needs to support the deprescribing process [259]. For example, if a carer is reluctant to trial medication withdrawal because they are experiencing a high level of burden and are fearful that their burden might worsen, they should be referred to carer support groups and other support services (whether or not the medication is deprescribed). Local Alzheimer's/dementia associations and carer/caregiver websites are good resources to identify available support.

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Other situations where referral to another healthcare professional may be required include the following:

- Consult a pharmacist if there are concerns about reversal of drug–drug interactions, suspicion of a prescribing cascade, non-adherence, complex medication regimen or polypharmacy requiring a medication review.
- Refer to a specialist, clinical nurse consultant/educator, occupational therapist or other relevant professional if the person with dementia is experiencing severe and/or ongoing behavioural and psychological symptoms of dementia, depression or other problems with their overall condition [89].
- Refer to appropriate specialist if unclear/uncertain dementia diagnosis [89].
- If the medication was started by a specialist, and the person/family member expresses concern about stopping a medication started by this specialist, then consulting the original prescriber or gaining a referral for a second opinion could be recommended.

Engaging people with dementia and their family/carers

The concept of withdrawal of medications is often less familiar to people than prescription of medications. In regard to treatment for dementia, which is a life-limiting illness, there is potential that recommendation of deprescribing dementia medications might be misinterpreted that the person is no longer 'worth' treating, or that their situation is hopeless [198]. As such, care needs to be taken by the healthcare provider to ensure there is an open dialogue in which the person/family can express and discuss any concerns they may have. As discussed in our 'Consumer Values and Preferences' section, there is significant hope placed on anti-dementia medications, which may not align with the evidence of potential for benefit [188,193]. Discussing future deprescribing early in the treatment course will help the individual/family/carer understand that the medication is not lifelong treatment. This may prevent feelings of guilt of 'giving up' that can be experienced by carers making a proxy decision to deprescribe [190,198].

It is extremely important to engage the person with dementia and/or their family/carers in the conversation about deprescribing, as this conversation is required to determine if it is suitable to deprescribe (or not). This conversation can include the stability of the person's condition and their goals of care [268,269]. It is vital to explain why the medication is (or might be) suitable for trial deprescribing, including potential lack of ongoing benefit, and potential risks and burden associated with ongoing use (if this is true for the individual). Additionally, any fears should be addressed. This may be achieved through slowly reducing the dose (with monitoring of condition) and reassurance that dose reduction and discontinuation is a trial (the medication will be restarted if necessary) [199,211,269,270]. Additionally, it is important for people with dementia and their family/carers to understand that there is a level of uncertainty

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about the benefits and harms of continuing and discontinuing medications, as well as having an appreciation for the continually changing nature of science and evidence [271,272] (Table 7).

This conversation may not occur in a single appointment; instead, it can be viewed as beginning a dialogue to be continued over future appointments. Where possible, the person with dementia should be included in the conversation, as well as all carers/family members. Healthcare professionals need to present the information in a way that is understandable to the person with dementia and their family (where possible) [89].

Table 7: Points to discuss with individuals/family/carers regarding deprescribing of ChEIs and/or memantine

To aid in determining suitability for deprescribing • What are their treatment goals—that is, what do they value the most (cognition, quality of life, remaining independent)? • What has been their experience of the symptoms of dementia with treatment and over the past six months? • Are they experiencing any potential side effects of treatment?
To educate the consumer to make an informed decision • Deprescribing is a trial—the individual will be monitored and the medication will be restarted if determined appropriate. • There are potential benefits and harms of continuing the medication, as well as potential benefits and harms of discontinuing the medication—discuss why they are being considered for deprescribing (tailored to their situation). • There is uncertainty surrounding the benefits and harms of both continuing and discontinuing. • What fears/concerns do they have about discontinuation of the ChEI and/or memantine? • Costs of the medication and local reimbursement/subsidisation criteria.

Once the decision to trial deprescribing is agreed upon by the person with dementia and/or family/carers and healthcare provider, a plan must be made for tapering and monitoring (as discussed above). Verbal and written information should be provided to all family/carers. Additionally, liaison with other healthcare professionals may be required to achieve the plan. For example, the community pharmacist may need to be consulted to make alterations to dosage administration aids, or residential care medication administration charts may need to be altered and nurses/care staff informed about monitoring [273].

Ethical and legal considerations

Two recent articles have discussed the potential ethical issues of deprescribing for older adults and nursing home residents with a limited life expectancy [274,275]. When framed within the

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four principles of medical ethics, this involves considering the potential for benefit and harm, ensuring informed consent and shared decision making, and considering the financial costs within the context of limited resource environments. Prescribers should be encouraged to consider the potential outcomes of the decision to deprescribe ChEIs and/or memantine equally against the potential outcomes of the decision to continue ChEIs and/or memantine.

Barnett and Kelly outlined that the potential legal ramifications surrounding deprescribing are the same as those surrounding initiation and continuation of medications [276]. This again highlights that continuation should not be considered the 'null action'.

Australian Aboriginal and Torres Strait Islander peoples, Indigenous Canadians, and culturally and linguistically diverse populations

There is a higher prevalence of dementia in indigenous populations than in the global population, although there are limited quality data internationally [277]. A high-quality study that used a culturally appropriate assessment tool with Indigenous Australians found that the prevalence was approximately five times higher than the wider Australian population [278]. The rate is especially high among those living in rural and remote areas. Dementia occurs at a younger age in this population and may disproportionately affect males [279]. This appears to be true in the Canadian First Nations population as well [280].

People of ethnic minorities were under-represented in the pivotal drug trials for the anti-dementia medications, and have a longer average duration of symptoms before seeing a healthcare provider [281]. Minority people with dementia have also been found to be undertreated with ChEIs (versus a non-minority population), and being non-Caucasian, having a low socioeconomic status and living in a rural setting can negatively affect adherence and persistence to anti-dementia treatment [282,283].

There are significant barriers to the delivery of pharmacy services to rural Aboriginal Australian populations, and greater coordination across care services is required [284,285]. Based on what has been discussed above, it is important to focus on optimising care of dementia for indigenous and minority populations. When considering deprescribing of anti-dementia medications in indigenous populations and people with different cultural or linguistic backgrounds, it is especially important to discuss the recommendation in a culturally suitable manner, with a trained interpreter if necessary [259]. When reviewing consumer attitudes towards discontinuation of these medications, we did not identify any studies that focused specifically on an indigenous or minority group. However, the impression and interpretation of dementia can be different in these populations, and one factor to consider is that remaining in the community may be a particularly strong goal for Indigenous populations [285]. As with the wider population, care needs to be taken to ensure that the person/family/carer knows that

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the recommendation is not being made because they are not 'worth' treating, particularly in order to ensure that the patient–doctor relationship is preserved. Further research is required in the area of optimal prescribing and deprescribing of ChEIs and memantine for Indigenous and minority people with dementia.

Please also consult the Clinical Practice Guidelines and Principles of Care for People with Dementia: 'Considerations for Aboriginal and Torres Strait Islander People' and 'Considerations for Culturally and Linguistically Diverse Populations' [89].

Medications outside the scope of the guideline

Several other prescription and non-prescription medications have been reported to have a benefit in either the prevention or treatment of dementia. Some of the non-prescription medications that have been reported to improve cognition include antioxidants; Vitamins E, C, B12, B1 and B6; carotenes; fatty acids and folic acid. There is limited and inconclusive evidence to support any of these in the prevention or treatment of dementia, with the majority of studies and reviews on these concluding that they are unlikely to be significantly beneficial. Ginkgo biloba, a herbal medication, has some evidence to suggest that it may have a (small) benefit; however, there are major methodological concerns with many of the studies and there is clear potential for harm from this medication (including bleeding risk) [3,259].

Studies of nonsteroidal anti-inflammatory drugs, statins and hormone replacement therapy have either failed to show a benefit or have only shown a small (questionable) benefit for the prevention or management of dementia. At this stage, there is insufficient evidence to recommend these or any other medications as alternative treatment to ChEIs or memantine [3,259]. If an individual is taking one of these or other medications for the sole indication of dementia (treatment or prevention), then it may be suitable for deprescribing (although an individualised review of appropriateness is required to determine this).

While not included in the search strategy of our systematic review, we did identify an article in which the discontinuation of ChEIs was compared to the discontinuation of other cognitive-enhancing medications (nootropics). Rainer and colleagues [70] conducted an open discontinuation study in 47 participants with AD taking either a ChEI or other nootropics (ginkgo extract, ergot alkaloids, piracetam, neurotrophic peptides or calcium channel blockers). There was no significant worsening in cognitive outcomes in the nootropics group over an average of six to seven weeks after discontinuation.

Anticholinergic and sedative medications

People with dementia are more likely to be prescribed an anticholinergic medication than those without dementia [286–289]. As discussed in the 'Harms' section, this is concerning because

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there is a pharmacodynamic interaction between these and ChEIs, and the use of anticholinergics has been associated with reduced cognitive function and increased risk of dementia [143,176,290]. Yet concomitant use of anticholinergics and ChEIs is common [28,36,50,51]. There is limited evidence that chronic use of this combination of medications results in worse cognitive outcomes than for people with dementia taking a ChEI without concomitant anticholinergic use [291]. There is also some (although inconsistent) evidence that discontinuation of anticholinergic drugs leads to improved cognitive performance [290].

Sedative medications (such as benzodiazepines) have also been associated with cognitive impairment, with some studies reporting a relationship between the use of sedative medications and diagnosis of AD [292,293]. An inconsistent relationship between cumulative anti-cholinergic and sedative exposure and cognitive function has also been observed [294]. Therefore, all medications with anticholinergic and/or sedative properties should be reviewed for people with dementia and considered for deprescribing if appropriate (noting, however, the need for individualised review of appropriateness).

Non-pharmacological management and ongoing care after deprescribing

With or without deprescribing of ChEIs and memantine, there are many non-pharmacological techniques that have been shown to be beneficial for people with dementia.

One of the concerns about withdrawal of anti-dementia medications, as found in several of the discontinuation studies, is worsening of the behavioural and psychological symptoms of dementia. In the deprescribing study by Herrmann and colleagues, they found no difference in outcomes for the group who discontinued versus those who continued for the participants as a whole; however, those with greater hallucinations or delusions prior to discontinuation tended to be more likely to have worsening symptoms after withdrawal [62]. Therefore, it is important that non-pharmacological measures are used to manage the behavioural and psychological symptoms of dementia throughout the deprescribing process. Non-pharmacological interventions (such as training and education for carers, activity planning, music therapy, reminiscence and environmental design) can have a significant benefit on reducing the frequency of the behavioural and psychological symptoms of dementia, as well as reducing the effect that these symptoms have on carers [3,89,295,296]. The magnitude of the effect of non-pharmacological interventions is similar to that achieved with the use of antipsychotics [295]. Antipsychotics are not recommended for long term use (> 3 months) for the behavioural and psychological symptoms of dementia due to their limited efficacy for most symptoms and high risk of harm [89,297,298].

Cognitive stimulation or training may have a beneficial effect on cognitive and functional outcomes; however, the magnitude of the effect appears to be smaller than what is considered

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clinically important [3,259,299]. Environmental modification and exercise interventions may also have a beneficial effect on cognition, activities of daily living and function [259,300,301]. Consult relevant guidelines and resources for further information on non-pharmacological management of dementia.

Management of other medical conditions may aid in the deprescribing process. People with dementia may be less likely to be offered recommended therapy for their other medical conditions, compared to people without dementia [302]. For example, it is known that people with dementia are undertreated for pain conditions (compared to people without dementia) and that untreated pain can result in psychological or behavioural symptoms [42,89,303]. Pain relief should be offered in a stepped approach, with a specified period of trial, and plan for discontinuation if no benefit is observed [89]. Depression is common among people with dementia. The evidence to support the use of antidepressants for people with dementia is unclear, but a trial may be appropriate for some individuals [89,304]. Ensure that there is a plan for monitoring with a review date that is discussed with the person with dementia and/or family/carers upon initiation of any new medication. This can manage expectations in relation to how long the medication is going to be used, and can encourage a culture of regular deprescribing of medications that are no longer required.

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Implementation and Follow-up

Dissemination

This guideline will be made publicly available to aid in dissemination. The final guideline will be promoted through a peer-reviewed publication and presentations at local and international conferences and professional development workshops. We will also encourage relevant professional and consumer organisations (those contacted during the public consultation period) to promote the guideline to their members through their regular mechanisms (such as electronic newsletters).

Implementation

We have secured funding for the period 2019 to 2020 to conduct implementation of the guideline in Australia (NHMRC-ARC Dementia Research Development Fellowship awarded to Dr Emily Reeve [APP1105777]). All recommendations and PP are believed to be central to improving health outcomes, and will subsequently be included in the implementation strategy. Implementation strategies will be informed by the ongoing work of the Deprescribing Guidelines in the Elderly project group [4,305–307] and the field of implementation science for guidelines [308–311].

To aid in implementation, we will develop a one-page (double-sided) algorithm for healthcare professionals and a consumer-directed information leaflet.

Guidance on staging dementia is available, and there are several prognostic tools which have been developed to aid in identification of those with end-stage dementia [312–316]. The Dementia Outcomes Measurement Suite (http://dementiakt.com.au/doms/) may also be useful to healthcare professionals; it is a list of tools that are recommended for use among people with dementia, along with manuals and scoring guides.

Recommendations for wider implementation

Implementation of the recommendations may need to be adapted depending on the context in which they are used, i.e. depending on the health care organisation, and professionals involved. Consideration should be given to the scopes of practice of professionals and available resources.

Various resources are available to assist individuals/organisations with implementing guideline recommendations. A companion document (workbook) was developed for the Clinical Practice Guidelines and Principles of Care for People with Dementia [317] which outlines a 6-step implementation process:

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1. Identify guideline recommendation that you wish to implement and the people that would be involved in the implementation work
2. Measure current practice
3. Identify potential barriers (and enablers) to implementing the recommendation
4. Determine interventions to mitigate the identified barriers (using the Theoretical Domains Framework (TDF))
5. Implement the strategies to improve adherence to the selected recommendation (using Behaviour Change Technique mapped to the identified TDF [318])
6. Measure and evaluate change

This guideline may be also used within other evidence-based practice frameworks such as the care pathway [319] and the Knowledge to Action (KTA) framework [320].

Future updates

We did not identify any trials currently in progress that could lead to changes in the recommendations. However, there are significant gaps in the literature, and future studies may lead to changes in the recommendations. We recommend that this guideline be updated no longer than five years from the date of the NHMRC approval of recommendations (August 2022).

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Other Guidelines

No other evidence-based guidelines were identified that focused solely on the deprescribing of ChEIs and/or memantine.

We sought to identify treatment guidelines from Australia, Canada, the US and the UK to determine if they provided information on when or how to deprescribe ChEIs and/or memantine (see Appendix 3). The recommendations provided in this guideline support the content of the guidelines that we identified. Many of the guidelines recommend regular monitoring after initiation of ChEI and memantine, and that the medication only be continued if there are ongoing benefits and no obvious harm. They highlight the complexity of the decision based on a lack of good information about optimal duration of use and the need to consider individuals' treatment goals and preferences.

The recently developed and NHMRC-approved Australian Clinical Practice Guidelines and Principles of Care for People with Dementia include the following PP recommendation: 'Review and consideration of de-prescribing is recommended at regular intervals including at the time of admission to residential care' [89]. Of all the guidelines we reviewed, the 4th Canadian Consensus Conference on Dementia Care provided the most comprehensive recommendations regarding deprescribing [91]. It reports that worsening of cognitive function and functional impairment may occur on discontinuation of therapy, and outlines situations where deprescribing could be considered (such as intolerable side effects or advanced dementia stage). It also recommends tapering and monitoring, with re-initiation of the medication if appropriate (see Appendix 3). Additionally, one of the Choosing Wisely recommendations of the American Geriatrics Society calls for regular reassessment of ChEIs with consideration for discontinuation if treatment goals have not been realised [321].

The recommendations and supporting information provided in this guideline contribute to the existing literature and available guidelines by providing evidence-based, explicit recommendations as a result of a multidisciplinary systematic development process.

This guideline does not make any recommendations for interventions or treatments that are not available or are restricted in Australia.

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Gaps in Knowledge

As discussed throughout the guideline, there is a lack of generalisable, high-quality studies to guide when it is suitable to deprescribe ChEIs and/or memantine. Specifically, more information is required to better identify who is suitable for deprescribing and when (and subsequently who is not). Uncertainty is acknowledged as part of our evidence-base; however, greater exploration of this uncertainty and how to use this to make treatment decisions and shared decision making would be beneficial.

Few studies have included person-centred outcomes, such as quality of life, function or goal achievement. Along this line, we need to continue to work on meaningful outcome measures, and incorporate these into cost-effectiveness analyses. Pharmacoeconomic analyses of deprescribing in general are needed to further work in this field. Better pharmacovigilance data would aid in the identification of rare ADRs and ADWEs.

There is limited information to guide how to conduct deprescribing (the process of tapering), and what issues to monitor for and how often to monitor during the deprescribing process.

Research about how to discuss deprescribing of ChEIs and/or memantine with people with dementia and their family would be beneficial (such as development of a conversation guide).

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References

1. Alzheimer Association. 2016 Alzheimer's Disease Facts and Figures. Alzheimer's Dement. 2016. 2016;12:1–80.

2. Prince M, Wimo A, Guerchet M, Gemma-Claire A, Wu Y-T, Prina M. World Alzheimer Report 2015: The Global Impact of Dementia - An analysis of prevalence, incidence, cost and trends. Alzheimer's Dis. Int. 2015.

3. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol. 2016;15:455–532.

4. Farrell B, Pottie K, Rojas-Fernandez C, Bjerre L. Methodology for Developing Deprescribing Guidelines: Using Evidence and GRADE to Guide Recommendations for Deprescribing. PLoS One. 2016;11:e0161248.

5. Schünemann HJ, Wiercioch W, Etxeandia I, Falavigna M, Santesso N, Mustafa R, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ. Canadian Medical Association; 2014;186:E123–42.

6. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. Canadian Medical Association; 2010;182:E839–42.

7. National Health and Medical Research Council. Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines. Melbourne; 2011.

8. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336.

9. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J. Clin. Epidemiol. 2013;66:719–25.

10. WHO and Alzheimer's Disease International. Dementia: a public health priority. Geneva: World Health Organization; 2012.

11. Alzheimer's Australia. Key Facts and Statistics for Media [Internet]. 2017 [cited 2017 Mar 6]. Available from: https://www.fightdementia.org.au/media/key-facts-and-statistics

12. Australian Institute of Health and Welfare. Dementia in Australia. Cat. no. AGE 70. Canberra: AIHW; 2012.

13. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Birks JS, editor. Cochrane database Syst. Rev. Chichester, UK: John Wiley & Sons, Ltd; 2006;CD005593.

14. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. In: McShane R, editor. Cochrane Database Syst. Rev. Chichester, UK: John Wiley & Sons, Ltd; 2006.

15. Parsons C. Polypharmacy and inappropriate medication use in patients with dementia: an under-researched problem. Ther. Adv. Drug Saf. SAGE Publications; 2016;2042098616670798.

16. Hoffmann F, van den Bussche H, Wiese B, Schön G, Koller D, Eisele M, et al. Impact of

Do not cite or copy without permission, contact emily.reeve@sydney.edu.au for information.

geriatric comorbidity and polypharmacy on cholinesterase inhibitors prescribing in dementia. BMC Psychiatry. BioMed Central; 2011;11:190.

17. Reeve E, Trenaman SC, Rockwood K, Hilmer SN. Pharmacokinetic and pharmacodynamic alterations in older people with dementia. Expert Opin. Drug Metab. Toxicol. Taylor & Francis; 2017;13:651–68.

18. Scott IA, Hilmer SN, Reeve E, Potter K, Couteur D Le, Rigby D, et al. Reducing inappropriate polypharmacy: The process of deprescribing. JAMA Intern Med. 2015;175:827–34.

19. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging definition of "deprescribing" with network analysis: implications for future research and clinical practice. Br. J. Clin. Pharmacol. 2015;80:1254–68.

20. Reeve E, Thompson W, Farrell B. Deprescribing: A narrative review of the evidence and practical recommendations for recognizing opportunities and taking action. Eur. J. Intern. Med. 2017;

21. Page AT, Clifford RM, Potter K, Schwartz D, EthertonBeer CD. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. Br. J. Clin. Pharmacol. 2016;82:583–623.

22. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older: a systematic review. Drugs and Aging. 2008;25:1021–31.

23. Gnjidic D, Le Couteur DG, Kouladjian L, Hilmer SN. Deprescribing trials: methods to reduce polypharmacy and the impact on prescribing and clinical outcomes. Clin. Geriatr. Med. 21 Feb 201. 2012;28:237–53.

24. Le Couteur DG, Robinson M, Leverton A, Creasey H, Waite L, Atkins K, et al. Adherence, persistence and continuation with cholinesterase inhibitors in Alzheimer's disease. Australas. J. Ageing. Blackwell Publishing Ltd; 2012;31:164–9.

25. Pitkala KH, Juola A-L, Hosia H, Teramura-Gronblad M, Soini H, Savikko N, et al. Eight-Year Trends in the Use of Opioids, Other Analgesics, and Psychotropic Medications Among Institutionalized Older People in Finland. J. Am. Med. Dir. Assoc. 2015;16:973–8.

26. Hollingworth SA, Byrne GJ. Prescribing trends in cognition enhancing drugs in Australia. Int. Psychogeriatrics. 2010;23:1–8.

27. O'Regan J, Lanctôt KL, Mazereeuw G, Herrmann N. Cholinesterase Inhibitor Discontinuation in Patients With Alzheimer's Disease: A Meta-Analysis of Randomized Controlled Trials. J. Clin. Psychiatry. 2015;76:e1424–31.

28. Herrmann N, SS G, CM B, GM A, SE B, KI S, et al. A population-based study of cholinesterase inhibitor use for dementia. J. Am. Geriatr. Soc. 2007;55:1517–23 7p.

29. Taipale H, Tanskanen A, Koponen M, Tolppanen A-M, Tiihonen J, Hartikainen S. Antidementia drug use among community-dwelling individuals with Alzheimer's disease in Finland. Int. Clin. Psychopharmacol. 2014;29:216–23.

30. Gadzhanova S, Roughead L, Mackson J. Anticholinesterase Duration in the Australian Veteran Population. Aust. New Zeal. J. Psychiatry. 2010;44:469–74.

31. Kröger E, Van Marum R, Souverein P, Egberts T. Discontinuation of cholinesterase inhibitor

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treatment and determinants thereof in the netherlands: A retrospective cohort study. Drugs and Aging. 2010;27:663–75.

32. Amuah JE, Hogan DB, Eliasziw M, Supina A, Beck P, Downey W, et al. Persistence with cholinesterase inhibitor therapy in a population-based cohort of patients with Alzheimer's disease. Pharmacoepidemiol. Drug Saf. 2010;19:670–9.

33. Sun Y, Lai MS, Lu CJ, Chen RC. How long can patients with mild or moderate Alzheimer's dementia maintain both the cognition and the therapy of cholinesterase inhibitors: A national population-based study. Eur. J. Neurol. 2008;15:278–83.

34. Suh D-C, Thomas SK, Valiyeva E, Arcona S, Vo L. Drug Persistency of Two Cholinesterase Inhibitors. Drugs Aging. Springer International Publishing; 2005;22:695–707.

35. Rojas-Fernandez C, Mikhail M. Psychotropic and cognitive-enhancing medication use and its documentation in contemporary long-term care practice. Ann. Pharmacother. 2014;48:438–46.

36. Bloomfield K, John N, McGrogan A, Jones R, De C. Co-prescribing of medications with anticholinergic properties to those using cholinesterase inhibitors for dementia. Pharmacoepidemiol. Drug Saf. 2010;19.

37. Lee J, Monette J, Sourial N, Monette M, Bergman H. The use of a cholinesterase inhibitor review committee in long-term care. J. Am. Med. Dir. Assoc. 2007;8:243–7.

38. Vantelon C, Gilbert S, Kerneis S, Wolmark Y, Legrain S, Kergoat M-J. [Cholinesterase inhibitor therapy in long term care settings]. La Rev. Med. interne. 2006;27:588–94.

39. Purandare N, Swarbrick C, Fischer A, Burns A. Cholinesterase inhibitors for Alzheimer's disease: Variations in clinical practice in the north-west of England. Int. J. Geriatr. Psychiatry. 2006. p. 961–4.

40. Dartigues J, Douet C, Rey M, Sencey M, Pigeon M, Sardin F, et al. Prescription of cholinesterase inhibitors in Alzheimer's disease in France in 2000-2001: An assessment of compliance with national guidelines for diagnosis and follow-up. Rev. Geriatr. 2005. p. 957–62.

41. Cameron I, Curran S, Newton P, Petty D, Wattis J. Use of Donepezil for the Treatment of Mild - Moderate Alzheimer'S Disease: an Audit of the Assessment and Treatment. Int. J. Geriatr. Psychiatry. 2000;15:776–80.

42. Tjia J, Rothman MR, Kiely DK, Shaffer ML, Holmes HM, Sachs GA, et al. Daily medication use in nursing home residents with advanced dementia. J Am Geriatr Soc. 2010;58:880–8.

43. Mansour D, Wong R, Kuskowski M, Dysken M. Discontinuation of acetylcholinesterase inhibitor treatment in the nursing home. Am. J. Geriatr. Pharmacother. 2011;9:345–50.

44. Weinstein AM, Barton C, Ross L, Kramer JH, Yaffe K. Treatment practices of mild cognitive impairment in California Alzheimer's Disease Centers. J. Am. Geriatr. Soc. 2009;57:686–90.

45. Vidal J-S, Lacombe J-M, Dartigues J-F, Pasquier F, Robert P, Tzourio C, et al. Memantine therapy for Alzheimer disease in real-world practice: an observational study in a large representative sample of French patients. Alzheimer Dis. Assoc. Disord. 2008;22:125–30.

46. Hunnicutt JN, Tjia J, Lapane KL. Abstracts: Questionable care: use of memantine hydrochloride and cholinesterase inhibitors in patients with advanced dementia at the end of life who were enrolled in a hospice. Pharmacoepidemiol. Drug Saf. 2015;24:1–587.

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47. Tifratene K, Duff F Le, Pradier C, Quetel J, Lafay P, Schück S, et al. Use of drug treatments for Alzheimer's disease in France: a study on a national level based on the National Alzheimer's Data Bank (Banque Nationale Alzheimer). Pharmacoepidemiol. Drug Saf. 2012;21:1005–12.

48. Rungsanpanya T, Muangpaisan W, Praditsuwan R. Clinical practice with antidementia drugs in a Geriatric clinic. J. Med. Assoc. Thail. 2012;95:1081–9.

49. Gardette V, Andrieu S, Lapeyre-Mestre M, Coley N, Cantet C, Ousset PJ, et al. Predictive factors of discontinuation and switch of cholinesterase inhibitors in community-dwelling patients with alzheimers disease: A 2-year prospective, multicentre, cohort study. CNS Drugs. Springer International Publishing; 2010;24:431–42.

50. Cross A, George J, Woodward M, Ames D. Potentially inappropriate medications and anticholinergic burden in older people attending memory clinics in Australia. Drugs Aging. 2016;33:37–44.

51. Robinson M, Rowett D, Leverton A, Mabbott V. Changes in utilisation of anticholinergic drugs after initiation of cholinesterase inhibitors. Pharmacoepidemiol. Drug Saf. 2009;18:659–64.

52. Anderson K, Freeman C, Stowasser D, Scott I. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: A systematic review and thematic synthesis. BMJ Open. 2014;4:e006544.

53. Farrell B, Tsang C, Raman-Wilms L, Irving H, Conklin J, Pottie K, et al. What Are Priorities for Deprescribing for Elderly Patients? Capturing the Voice of Practitioners: A Modified Delphi Process. Dalal K, editor. PLoS One. Public Library of Science; 2015;10:e0122246.

54. Gaudig M, Richarz U, Han J, Van Baelen B, Schauble B. Effects of galantamine in Alzheimer's disease: Double-blind withdrawal studies evaluating sustained versus interrupted treatment. Curr. Alzheimer Res. 2011;8:789–97.

55. Holmes C, Wilkinson D, Dean C, Vethanayagam S, Olivieri S, Langley a, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. Neurology. 2004;63:214–9.

56. Johannsen P, Salmon E, Hampel H, Xu Y, Richardson S, Qvitzau S, et al. Assessing Therapeutic Efficacy in a Progressive Disease. CNS Drugs. 2006;20:311–25.

57. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 1975;12:189–98.

58. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am. J. Psychiatry. American Psychiatric Assn; 1984. p. 1356–64,.

59. Scarpini E, Bruno G, Zappalà G, Adami M, Richarz U, Gaudig M, et al. Cessation versus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial. J. Alzheimers. Dis. 2011;26:211–20.

60. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med. 2012;366:893–903.

61. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, et al. Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease

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(DOMINO-AD) trial: secondary and post-hoc analyses. Lancet Neurol. 2015;14:1171–81.

62. Herrmann N, O'Regan J, Ruthirakuhan M, Kiss A, Eryavec G, Williams E, et al. A Randomized Placebo-Controlled Discontinuation Study of Cholinesterase Inhibitors in Institutionalized Patients With Moderate to Severe Alzheimer Disease. J. Am. Med. Dir. Assoc. 2015;142–7.

63. Kertesz A, Morlog D, Light M, Blair M, Davidson W, Jesso S, et al. Galantamine in frontotemporal dementia and primary progressive aphasia. Dement. Geriatr. Cogn. Disord. 2008;25:178–85.

64. Cohen J. Statistical Power Analysis for the Behavioural Sciences. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.

65. Rockwood K, Macknight C. Assessing the clinical importance of statistically significant improvement in anti-dementia drug trials. Neuroepidemiology. 2001. p. 51–6.

66. Howard R, McShane R, RLindesay J, Ritchie C, Dening T, Findlay D, et al. Donepezil and Memantine for moderate-to-severe Alzheimer's disease. N. Engl. J. Med. 2012;366:893–903.

67. Burns E, Kane R, Akbar ST, Weiss BA, Fleming R. Stopping pharmacological treatment for advanced dementia: No change in status. J. Am. Geriatr. Soc. 2010. p. S104.

68. Peyro Saint-Paul L, Martin J, Gaillard C, Garnier A, Mosquet B, Guillamo J-S, et al. [Sudden Discontinuation of Anti-dementia Drugs in Moderate and Severe Alzheimer's Disease in a Residency for Dependent Elderly People: a Longitudinal Descriptive Pilot Study]. Thérapie. 2015;70:313–9.

69. Suzuki H, Inoue Y, Mikami K, Gen K. The influence and changes in the dosages of concomitantly used psychotropic drugs associated with the discontinuation of donepezil in severe Alzheimer's disease with behavioral and psychological symptoms on dementia: A preliminary open-label trial. Ther. Adv. Psychopharmacol. 2014. p. 37–42.

70. Rainer M, Mucke HAM, Krüger-Rainer C, Kraxberger E, Haushofer M, Jellinger KA. Cognitive relapse after discontinuation of drug therapy in Alzheimer's disease: Cholinesterase inhibitors versus nootropics. J. Neural Transm. 2001;108:1327–33.

71. Simpson S, Beavis D, Leddy A, Ball S, Johnson I. Naturalistic audit of NICE criteria for the use of cholinesterase inhibitors. Psychiatr Bull. 2005;29:410–2.

72. Gurevich T, Balash Y, Merims D, Peretz C, Herman T, Hausdorff JM, et al. Effect of rivastigmine on mobility of patients with higher-level gait disorder: A pilot exploratory study. Drugs R D. 2014;14:57–62.

73. Benke T, Koylu B, Delazer M, Trinka E, Kemmler G. Cholinergic treatment of amnesia following basal forebrain lesion due to aneurysm rupture - an open-label pilot study. Eur. J. Neurol. Blackwell Science Ltd; 2005;12:791–6.

74. Peters O, Lorenz D, Fesche A, Schmidtke K, Hüll M, Perneczky R, et al. A combination of galantamine and memantine modifies cognitive function in subjects with amnestic MCI. J. Nutr. Heal. Aging. 2012;16:544–8.

75. Shaw EG, Rosdhal R, D'Agostino RB, Lovato J, Naughton MJ, Robbins ME, et al. Phase II study of donepezil in irradiated brain tumor patients: effect on cognitive function, mood, and quality of life. J. Clin. Oncol. American Society of Clinical Oncology; 2006;24:1415–20.

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76. Zhang L, Plotkin RC, Wang G, Sandel ME, Lee S. Cholinergic augmentation with donepezil enhances recovery in short-term memory and sustained attention after traumatic brain injury. Arch. Phys. Med. Rehabil. 2004;85:1050–5.

77. Kimura T, Takamatsu J. Pilot study of pharmacological treatment for frontotemporal dementia: Risk of donepezil treatment for behavioral and psychological symptoms. Geriatr. Gerontol. Int. 2013. p. 506–7.

78. Cros JM, Richard H, Geronimi L, Strubel D. Suivi de l'arrêt des traitements antidémentiels au stade très sévère de la maladie d'Alzheimer (MA) chez 24 patients en institution. Rev. Geriatr. Gériamed; 2013;38:331–9.

79. Chang WH, Park YH, Ohn SH, Park C, Lee PKW, Kim Y-H. Neural correlates of donepezil-induced cognitive improvement in patients with right hemisphere stroke: A pilot study. Neuropsychol. Rehabil. 2011;21:502–14.

80. J. T, J. S, Y. M. Efficacyand safety of an herbal therapy in patients with early stage of Alzheimer's disease: A 24-week randomized phase III trial. Alzheimer's Dement. 2011. p. S790.

81. Burns A, Rossor M, Hecker J, Gauthier S. The Effects of Donepezil in Alzheimer's Disease–Results from a Multinational Trial1. Dement. Geriatr. 1999;

82. Ravina B. Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. J. Neurol. Neurosurg. Psychiatry. 2005;76:934–9.

83. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, Group* DS. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology. Lippincott Williams & Wilkins; 1998;50:136–45.

84. Leroi I, Overshott R, Byrne EJ, Daniel E, Burns A. Randomized controlled trial of memantine in dementia associated with Parkinson's disease. Mov. Disord. 2009;24:1217–21.

85. Johansson C, Ballard C, Hansson O, Palmqvist S, Minthon L, Aarsland D, et al. Efficacy of memantine in PDD and DLB: An extension study including washout and open-label treatment. Int. J. Geriatr. Psychiatry. 2011;26:206–13.

86. Schifitto G, Navia BA, Yiannoutsos CT, Marra CM, Chang L, Ernst T, et al. Memantine and HIV-associated cognitive impairment: a neuropsychological and proton magnetic resonance spectroscopy study. AIDS. 2007;21:1877–86.

87. Wroolie TE, Kenna HA, Williams KE, Powers BN, Holcomb M, Lazzeroni L, et al. Cognitive effects of memantine in postmenopausal women at risk of dementia: A pilot study. Acta Neurol. Scand. 2009;119:172–9.

88. Fillit H, Hofbauer RK, Setyawan J, Tourkodimitris S, Fridman M, Pejovi?? V, et al. Memantine discontinuation and the health status of nursing home residents with alzheimer's disease. J. Am. Med. Dir. Assoc. 2010;11.

89. Guideline Adaptation Committee. Clinical Practice Guidelines and Principles of Care for People with Dementia. Sydney: Guideline Adaption Committee; 2016.

90. Ihl R, Frölich L, Winblad B, Schneider L, Burns A, Möller H-J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Alzheimer's disease and other dementias. World J. Biol. Psychiatry. Taylor & Francis; 2011;12:2–32.

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91. Gauthier S, Patterson C, Chertkow H. Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4). Can. Geriatr. 2012;

92. National Collaborating Centre for Mental Health. Dementia: supporting people with dementia and their carers in health and social care. NICE: National Institute for Health and Care Excellence; 2006. p. Last update May 2016.

93. O'Brien JT, Burns A, BAP Dementia Consensus Group on behalf of the BDC. Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. J. Psychopharmacol. SAGE Publications; 2011;25:997–1019.

94. Rabins P V, Barry Rovner MW, Rummans T, Schneider LS, Tariot PN, and S. GUIDELINE WATCH (OCTOBER 2014): PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH ALZHEIMER'S DISEASE AND OTHER DEMENTIAS. 2012;

95. Ngo J, Holroyd-Leduc JM. Systematic review of recent dementia practice guidelines. Age Ageing. Oxford University Press; 2015. p. 25–33.

96. Di Santo SG, Prinelli F, Adorni F, Caltagirone C, Musicco M. A meta-analysis of the efficacy of donepezil, rivastigmine, galantamine, and memantine in relation to severity of Alzheimer's disease. J. Alzheimer's Dis. 2013;35:349–61.

97. Bond M, Rogers G, Peters J, Anderson R, Hoyle M, Miners A, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of technology appraisal no. 111): A systematic review and Economic model. Health Technol. Assess. (Rockv). 2012;16:1–469.

98. Birks J, Chong L, Evans JG. Rivastigmine for Alzheimer ' s Disease. Birks JS, editor. Cochrane Database Syst. Rev. Chichester, UK: John Wiley & Sons, Ltd; 2015;

99. Laver K, Dyer S, Whitehead C, Clemson L, Crotty M. Interventions to delay functional decline in people with dementia: a systematic review of systematic reviews. BMJ Open. British Medical Journal Publishing Group; 2016;6:e010767.

100. Tan C-C, Yu J-T, Wang H-F, Tan M-S, Meng X-F, Wang C, et al. Efficacy and Safety of Donepezil, Galantamine, Rivastigmine, and Memantine for the Treatment of Alzheimer's Disease: A Systematic Review and Meta-Analysis. J. Alzheimers. Dis. 2014;41:615–31.

101. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin. Interv. Aging. NIH Public Access; 2008;3:211–25.

102. Campbell N, Ayub A, Boustani MA, Fox C, Farlow M, Maidment I, et al. Impact of cholinesterase inhibitors on behavioral and psychological symptoms of Alzheimer's disease: a meta-analysis. Clin. Interv. Aging. Dove Press; 2008;3:719–28.

103. Wang J, Yu J-T, Wang H-F, Meng X-F, Wang C, Tan C-C, et al. Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatry. 2015;86:101–9.

104. Rodda J, Morgan S, Walker Z, Black SE, Doody R, Li H, et al. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. Int. Psychogeriatrics. Cambridge University Press; 2009;21:813.

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105. Cooper C, Mukadam N, Katona C, Lyketsos CG, Blazer D, Ames D, et al. Systematic Review of the Effectiveness of Pharmacologic Interventions to Improve Quality of Life and Well-being in People With Dementia. Am. J. Geriatr. Psychiatry. 2013;21:173–83.

106. Wang H-F, Yu J-T, Tang S-W, Jiang T, Tan C-C, Meng X-F, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. J. Neurol. Neurosurg. Psychiatry. BMJ Publishing Group Ltd; 2015;86:135–43.

107. Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M, et al. Effectiveness of Cholinesterase Inhibitors and Memantine for Treating Dementia: Evidence Review for a Clinical Practice Guideline. Ann. Intern. Med. American College of Physicians; 2008;148:379.

108. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet (London, England). Elsevier; 2004;363:2105–15.

109. Rongve A, Vossius C, Nore S, Testad I, Aarsland D. Time until nursing home admission in people with mild dementia: comparison of dementia with Lewy bodies and Alzheimer's dementia. Int. J. Geriatr. Psychiatry. 2014;29:392–8.

110. Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil Is Associated with Delayed Nursing Home Placement in Patients with Alzheimer's Disease. J. Am. Geriatr. Soc. Blackwell Science Inc; 2003;51:937–44.

111. Lopez OL, Becker JT, Wisniewski S, Saxton J, Kaufer DI, DeKosky ST. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry. BMJ Publishing Group Ltd; 2002;72:310–4.

112. Gaugler JE, Yu F, Krichbaum K, Wyman JF. Predictors of Nursing Home Admission for Persons with Dementia. Med. Care. 2009;47:191–8.

113. Versijpt J. Effectiveness and cost-effectiveness of the pharmacological treatment of Alzheimer's disease and vascular dementia. J Alzheimers Dis. 2014;42.

114. Hager K, Baseman AS, Nye JS, Brashear HR, Han J, Sano M, et al. Effects of galantamine in a 2 ‐ year , randomized , placebo-controlled study in Alzheimer ' s disease. Neuropsychiatr. Dis. Treat. 2014;10:391–401.

115. Banzi R, Camaioni P, Tettamanti M, Bertele' V, Lucca U. Older patients are still under-represented in clinical trials of Alzheimer's disease. Alzheimers. Res. Ther. BioMed Central; 2016;8:32.

116. Jongsma KR, van Bruchem-Visser RL, van de Vathorst S, Mattace Raso FUS. Has dementia research lost its sense of reality? A descriptive analysis of eligibility criteria of Dutch dementia research protocols. Neth. J. Med. 2016;74:201–9.

117. Leinonen A, Koponen M, Hartikainen S, Cerreta F, Eichler H, Rasi G, et al. Systematic Review: Representativeness of Participants in RCTs of Acetylcholinesterase Inhibitors. Scuteri A, editor. PLoS One. Public Library of Science; 2015;10:e0124500.

118. R. R, M. M, G.C. S, N. M, B. C, N. V. A cohort study of effectiveness of acetylcholinesterase inhibitors in Alzheimer's disease. Eur. J. Clin. Pharmacol. 2005;61:361–8.

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119. Lanctôt KL, Herrmann N, Yau KK, Khan LR, Liu BA, LouLou MM, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ. Canadian Medical Association; 2003;169:557–64.

120. Deardorff WJ, Feen E, Grossberg GT. The Use of Cholinesterase Inhibitors Across All Stages of Alzheimer's Disease. Drugs Aging. Springer International Publishing; 2015;32:537–47.

121. Buckley J, Salpeter S. A risk-benefit assessment of dementia medications: systematic review of the evidence. Drugs Aging. 2015;

122. Hogan DB. Long-term efficacy and toxicity of cholinesterase inhibitors in the treatment of Alzheimer disease. Can. J. Psychiatry. 2014;59:618–23.

123. Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. In: Rolinski M, editor. Cochrane Database Syst. Rev. Chichester, UK: John Wiley & Sons, Ltd; 2012.

124. Pagano G, Rengo G, Pasqualetti G, Femminella GD, Monzani F, Ferrara N, et al. Cholinesterase inhibitors for Parkinson's disease: a systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatry. BMJ Publishing Group Ltd; 2015;86:767–73.

125. Stinton C, McKeith IG, Taylor J-P, Lafortune L, Mioshi E, Mak E, et al. Pharmacological Management of Lewy Body Dementia: A Systematic Review and Meta-Analysis. Am. J. Psychiatry. 2015;172:731–42.

126. Birks J, McGuinness B, Craig D. Rivastigmine for vascular cognitive impairment. In: Birks J, editor. Cochrane Database Syst. Rev. Chichester, UK: John Wiley & Sons, Ltd; 2013.

127. Malouf R, Birks J. Donepezil for vascular cognitive impairment. In: Malouf R, editor. Cochrane Database Syst. Rev. Chichester, UK: John Wiley & Sons, Ltd; 2004.

128. Birks J, Craig D. Galantamine for vascular cognitive impairment. Cochrane Libr. 2013;4:CD004746.

129. Eskes GA, Lanctôt KL, Herrmann N, Lindsay P, Bayley M, Bouvier L, et al. Canadian Stroke Best Practice Recommendations: Mood, Cognition and Fatigue Following Stroke practice guidelines, update 2015. Int. J. Stroke. 2015;10:1130–40.

130. Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet Neurol. 2007;6:782–92.

131. Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment. In: Russ TC, editor. Cochrane Database Syst. Rev. Chichester, UK: John Wiley & Sons, Ltd; 2012.

132. Fitzpatrick-Lewis D, Warren R, Ali MU, Sherifali D, Raina P. Treatment for mild cognitive impairment: a systematic review and meta-analysis. C. Open. 2015;3:E419–27.

133. Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers. Dement. 2015;11:332–84.

134. Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis. PLoS One. 2015;10:e0123289.

135. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst. Rev. 2006;CD003154.

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DRAFT

136. Matsunaga S, Kishi T, Iwata N. Combination Therapy with Cholinesterase Inhibitors and Memantine for Alzheimer's disease: A Systematic Review and Meta-analysis. Int. J. Neuropsychopharmacol. 2014;

137. Schmidt R, Hofer E, Bouwman FH, Buerger K, Cordonnier C, Fladby T, et al. EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. Eur. J. Neurol. 2015;22:889–98.

138. Tsoi KKF, Chan JYC, Leung NWY, Hirai HW, Wong SYS, Kwok TCY. Combination Therapy Showed Limited Superiority Over Monotherapy for Alzheimer Disease: A Meta-analysis of 14 Randomized Trials. J. Am. Med. Dir. Assoc. 2016;17:863.e1–863.e8.

139. Gill SS, Bronskill SE, Mamdani M, Sykora K, Li P, Shulman KI, et al. Representation of patients with dementia in clinical trials of donepezil. Can. J. Clin. Pharmacol. 2004;11:e274–85.

140. Ganjavi H, Herrmann N, Rochon PA, Sharma P, Lee M, Cassel D, et al. Adverse drug events in cognitively impaired elderly patients. Dement. Geriatr. Cogn. Disord. 2007;23:395–400.

141. Corsonello A, Pedone C, Incalzi RA. Age-Related Pharmacokinetic and Pharmacodynamic Changes and Related Risk of Adverse Drug Reactions. Curr. Med. Chem. 2010;17:571–84.

142. Hajjar ER, Hanlon JT, Artz MB, Lindblad CI, Pieper CF, Sloane RJ, et al. Adverse drug reaction risk factors in older outpatients. Am J Geriatr Pharmacother. 2003;1:82–9.

143. Jones RW. A review comparing the safety and tolerability of memantine with the acetylcholinesterase inhibitors. Int. J. Geriatr. Psychiatry. 2009;n/a – n/a.

144. Matsunaga S, Kishi T, Yasue I, Iwata N. Cholinesterase Inhibitors for Lewy Body Disorders: A Meta-Analysis. Int. J. Neuropsychopharmacol. 2016;19:pyv086.

145. Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, et al. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. CMAJ. Canadian Medical Association; 2008;179:1019–26.

146. Thompson S, Lanctôt KL, Herrmann N. The benefits and risks associated with cholinesterase inhibitor therapy in Alzheimer's disease. Expert Opin. Drug Saf. 2004;3:425–40.

147. Takeda A, Loveman E, Clegg A, Kirby J, Picot J, Payne E, et al. A systematic review of the clinical effectiveness of donepezil, rivastigmine and galantamine on cognition, quality of life and adverse events in Alzheimer's disease. Int. J. Geriatr. Psychiatry. 2006;21:17–28.

148. Lockhart IA, Mitchell SA, Kelly S. Safety and tolerability of donepezil, rivastigmine and galantamine for patients with alzheimer's disease: Systematic review of the "real-world" evidence. Dement. Geriatr. Cogn. Disord. 2009. p. 389–403.

149. Kroger E, Mouls M, Wilchesky M, Berkers M, Carmichael PH, van Marum R, et al. Adverse Drug Reactions Reported With Cholinesterase Inhibitors: An Analysis of 16 Years of Individual Case Safety Reports From VigiBase. Ann. Pharmacother. 2015;49:1197–206.

150. Ali TB, Schleret TR, Reilly BM, Chen WY, Abagyan R, Qiu C, et al. Adverse Effects of Cholinesterase Inhibitors in Dementia, According to the Pharmacovigilance Databases of the United-States and Canada. Cavalli A, editor. PLoS One. Public Library of Science; 2015;10:e0144337.

151. Pariente A, Sanctussy DJ, Miremont-salame G, Moore N. Factors Associated with Serious

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Adverse Reactions to Cholinesterase Inhibitors. CNS Drugs. 2010;24:55–63.

152. Diniz BS, Pinto JA, Gonzaga MLC, Guimarães FM, Gattaz WF, Forlenza OV. To treat or not to treat? A meta-analysis of the use of cholinesterase inhibitors in mild cognitive impairment for delaying progression to Alzheimer's disease. Eur. Arch. Psychiatry Clin. Neurosci. 2009;259:248–56.

153. Li Y, Hai S, Zhou Y, Dong BR. Cholinesterase inhibitors for rarer dementias associated with neurological conditions. In: Dong BR, editor. Cochrane Database Syst. Rev. Chichester, UK: John Wiley & Sons, Ltd; 2015.

154. Venäläinen O, Bell J, Kirkpatrick C. Adverse Drug Reactions Associated With Cholinesterase Inhibitors—Sequence Symmetry Analyses Using Prescription Claims Data. J. Am. Med. Dir. Assoc. 2016;

155. Gill SS, Mamdani M, Naglie G, Streiner DL, Bronskill SE, Kopp A, et al. A Prescribing Cascade Involving Cholinesterase Inhibitors and Anticholinergic Drugs. Arch. Intern. Med. American Medical Association; 2005;165:808.

156. Kröger E, Van Marum R, Souverein P, Carmichael P-H, Egberts T. Treatment with rivastigmine or galantamine and risk of urinary incontinence: results from a Dutch database study. Pharmacoepidemiol. Drug Saf. 2015;24:276–85.

157. Starr JM, J.M. S. Cholinesterase inhibitor treatment and urinary incontinence in Alzheimer's disease. J. Am. Geriatr. Soc. 2007;55:800–1.

158. Hashimoto M, Imamura T, Tanimukai S, Kazui H, Mori E. Urinary incontinence: an unrecognised adverse effect with donepezil. Lancet. 2000;356:568.

159. Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD. Dementia Medications and Risk of Falls, Syncope, and Related Adverse Events: Meta-Analysis of Randomized Controlled Trials. J. Am. Geriatr. Soc. 2011;59:1019–31.

160. Howes LG. Cardiovascular Effects of Drugs Used to Treat Alzheimer's Disease. Drug Saf. 2014;37:391–5.

161. Gill SS, Anderson GM, Fischer HD, Bell CM, Li P, Normand S-LT, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. Arch. Intern. Med. 2009;169:867–73.

162. Farlow M, Veloso F, Moline M, Yardley J, Brand-Schieber E, Bibbiani F, et al. Safety and tolerability of donepezil 23 mg in moderate to severe Alzheimer's disease. BMC Neurol. 2011;11:57.

163. Thavorn K, Gomes T, Camacho X, Yao Z, Juurlink D, Mamdani M. Upper Gastrointestinal Bleeding in Elderly Adults with Dementia Receiving Cholinesterase Inhibitors: A Population-Based Cohort Study. J. Am. Geriatr. Soc. 2014;62:382–4.

164. Mahan RJ, Blaszczyk AT. COPD Exacerbation and Cholinesterase Therapy in Dementia Patients. Consult. Pharm. 2016;31:221–5.

165. Stephenson A, Seitz DP, Fischer HD, Gruneir A, Bell CM, Gershon AS, et al. Cholinesterase Inhibitors and Adverse Pulmonary Events in Older People with Chronic Obstructive Pulmonary Disease and Concomitant Dementia. Drugs Aging. 2012;29:213–23.

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166. Thacker M, Schneeweiss S. Initiation of acetylcholinesterase inhibitors and complications of chronic airways disorders in elderly patients. Drug Saf. 2006;

167. Soysal P, Isik AT, Stubbs B, Solmi M, Volpe M, Luchini C, et al. Acetylcholinesterase inhibitors are associated with weight loss in older people with dementia: a systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatry. BMJ Publishing Group Ltd; 2016;jnnp – 2016–313660.

168. Health Canada. REMINYL ER (galantamine hydrobromide) - New Safety Information Regarding the Risk of Serious Skin Reactions - For the Public - Recalls and safety alerts [Internet]. 2014 [cited 2017 Mar 8]. Available from: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/42237a-eng.php?_ga=1.55363051.1360896303.1489007191

169. Health Canada. Summary Safety Review - ARICEPT (donepezil) - Risk of Rhabdomyolysis and Neuroleptic Malignant Syndrome [Internet]. Drug Heal. Prod. 2015 [cited 2016 Apr 22]. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/aricept-eng.php#fnb1

170. Jiang J, Jiang H. Efficacy and adverse effects of memantine treatment for Alzheimer's disease from randomized controlled trials. Neurol. Sci. 2015;36:1633–41.

171. Kishi T, Iwata N. NMDA receptor antagonists interventions in schizophrenia: Meta-analysis of randomized, placebo-controlled trials. J. Psychiatr. Res. 2013;47:1143–9.

172. Gallini A. Does memantine induce bradycardia? A study in the French PharmacoVigilance Database. … drug Saf. 2008;

173. Babai S, Auriche P, Le-Louët H, Le-Louët H. Comparison of Adverse Drug Reactions with Donepezil *versus* Memantine: Analysis of the French Pharmacovigilance Database. Therapie. EDP Sciences; 2010;65:255–9.

174. Muayqil T, Camicioli R. Systematic Review and Meta-Analysis of Combination Therapy with Cholinesterase Inhibitors and Memantine in Alzheimer's Disease and Other Dementias. Dement. Geriatr. Cogn. Dis. Extra. 2012;2:546–72.

175. Lima C de M. S48-02 Drug interactions with antidementia drugs: Clinical consequences. Eur. Psychiatry. 2009;24:S243.

176. Pasqualetti G, Tognini S, Calsolaro V, Polini A, Monzani F. Potential drug???drug interactions in alzheimer patients with behavioral symptoms. Clin. Interv. Aging. 2015. p. 1457–66.

177. Herrmann N, Li A, Lanctôt K. Memantine in dementia: a review of the current evidence. Expert Opin. Pharmacother. 2011;12:787–800.

178. Anticholinesterases in Alzheimer's disease - Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2017.

179. Aricept (donepezil hydrochloride). Full Product Information [cited Dec 2016; last update Nov 2011]. Database MIMs Online. MIMs Australia. Available from https://www.mimsonline.com.au/Login/Login.aspx?ReturnUrl=%2fdefault.aspx;

180. Reminyl (galantamine). Full Product Information [cited Dec 2016; last update Jan 2015]. Database MIMs Online. MIMs Australia. Available from https://www.mimsonline.com.au/Login/Login.aspx?ReturnUrl=%2fdefault.aspx;

Do not cite or copy without permission, contact emily.reeve@sydney.edu.au for information.

181. Exelon (rivastigmine hydrogen tartrate). Full Product Information [cited Dec 2016; last update Jun 2016]. Database MIMs Online. MIMs Australia. Available from https://www.mimsonline.com.au/Login/Login.aspx?ReturnUrl=%2fdefault.aspx;

182. Mehta DC, Short JL, Hilmer SN, Nicolazzo JA. Drug access to the central nervous system in Alzheimer's disease: Preclinical and clinical insights. Pharm. Res. 2015. p. 819–39.

183. McLean AJ, Le Couteur DG. Aging biology and geriatric clinical pharmacology. Pharmacol. Rev. 2004;56:163–84.

184. Laroche M-L, Perault-Pochat M-C, Ingrand I, Merle L, Kreft-Jais C, Castot-Villepelet A, et al. Adverse drug reactions in patients with Alzheimer's disease and related dementia in France: a national multicentre cross-sectional study. Pharmacoepidemiol. Drug Saf. 2013;22:n/a – n/a.

185. Reeve E, Wiese MD, Hendrix I, Roberts M, Shakib S. People's attitudes, beliefs, and experiences regarding polypharmacy and willingness to deprescribe. J. Am. Geriatr. Soc. 2013;61:1508–14.

186. Sirois C, Ouellet N, Reeve E. Community-dwelling older people's attitudes towards deprescribing in Canada. Res. Soc. Adm. Pharm. 2016;Published .

187. Andersen E, Silvius J, Slaughter S, Dalziel W, Drummond N. Lay and professional expectations of cholinesterase inhibitor treatment in the early stage of Alzheimer's disease. Dement. Int. J. Soc. Res. Pract. SAGE Publications; 2008;7:18.

188. Post SG, Stuckey JC, Whitehouse PJ, Ollerton S, Durkin C, Robbins D, et al. A focus group on cognition-enhancing medications in Alzheimer disease: Disparities between professionals and consumers. Alzheimer Diseas Assoc Disord. 2001;15:80–8.

189. Shega JW, Ellner L, Lau DT, Maxwell TL. Cholinesterase inhibitor and N-methyl-D-aspartic acid receptor antagonist use in older adults with end-stage dementia: a survey of hospice medical directors. J Palliat Med. 2009;12:779–83.

190. Hutchings D, Vanoli A, Mckeith I, Brotherton S, Mcnamee P, Bond J. Good days and bad days: The lived experience and perceived impact of treatment with cholinesterase inhibitors for Alzheimer's disease in the United Kingdom. Dementia. SAGE Publications; 2010;9:409–25.

191. Lindstrom HA, Smyth KA, Sami SA, Dawson N V., Patterson MB, Bohinc JH, et al. Medication use to treat memory loss in dementia: Perspectives of persons with dementia and their caregivers. Dementia. SAGE Publications; 2006;5:27–50.

192. Leung K, Karen. Towards the Development of an Expectations Assessment Instrument for Caregivers of People with Alzheimer's Disease and Related Dementias: A Pilot Study. University of Calgary; 2012.

193. Bunn F, Goodman C, Sworn K, Rait G, Brayne C, Robinson L, et al. Psychosocial Factors That Shape Patient and Carer Experiences of Dementia Diagnosis and Treatment: A Systematic Review of Qualitative Studies. de Craen AJM, editor. PLoS Med. Public Library of Science; 2012;9:e1001331.

194. Smith A, Kobayashi K, Chappell N, Hoxsey D. The controversial promises of cholinesterase inhibitors for Alzheimer's disease and related dementias: A qualitative study of caregivers' experiences. J. Aging Stud. 2011;25:397–406.

195. Franchi C, Arosio F, Djade C, Porro G. Caregivers' perceptions of the therapeutic benefits of

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drug treatments for dementia. Aging Clin. 2013;

196. Hutchings D, Vanoli A, Mckeith I, Brotherton S, Mcnamee P, Bond J. Cholinesterase inhibitors and Alzheimer's disease: Patient, carer and professional factors influencing the use of drugs for Alzheimer's disease in the United Kingdom. Dementia. SAGE PublicationsSage UK: London, England; 2010;9:427–43.

197. Karlawish JHT, Casarett DJ, James BD, Tenhave T, Clark CM, Asch DA. Why would caregivers not want to treat their relative's Alzheimer's disease? J Am Geriatr Soc. 2003;51:1391–7.

198. Huizing AR, Berghmans RLP, Widdershoven GAM, Verhey FRJ. Do caregivers' experiences correspond with the concerns raised in the literature? Ethical issues relating to anti-dementia drugs. Int. J. Geriatr. Psychiatry. John Wiley & Sons, Ltd.; 2006;21:869–75.

199. Reeve E, Low L-F, Hilmer SN. Beliefs and attitudes of older adults and carers about deprescribing of medications. Br. J. Gen. Pract. 2016;66:e552–60.

200. Smith B, Chur-Hansen A, Neale A, Symon J. Quality of life and cholinesterase inhibitors: a qualitative study of patients with Alzheimer's disease and their carers. Australas. Psychiatry. SAGE Publications; 2008;16:433–7.

201. Manthorpe J, Samsi K, Campbell S, Abley C, Keady J. The transition from cognitive impairment to dementia: older people's experiences. Final report. NIHR Service Delivery and Organisation programme. 2010.

202. Karlawish JHT, Klocinski JL, Merz J, Clark CM, Asch DA. Caregivers' preferences for the treatment of patients with Alzheimer's disease. Neurology. 2000;55:1008–14.

203. Oremus M, Cosby JL, Wolfson C. A hybrid qualitative method for pretesting questionnaires: The example of a questionnaire to caregivers of Alzheimer disease patients. Res. Nurs. Heal. Wiley Subscription Services, Inc., A Wiley Company; 2005;28:419–30.

204. Oremus M, Wolfson C, Vandal AC, Bergman H, Xie Q. Caregiver Acceptance of Adverse Effects and Use of Cholinesterase Inhibitors in Alzheimer's Disease. Can. J. Aging / La Rev. Can. du Vieil. John Wiley & 2007;26:205.

205. Smith F, Grijseels MS, Ryan P, Tobiansky R. Assisting people with dementia with their medicines: experiences of family carers. Int. J. Pharm. Pract. 2015;23:44–51.

206. Alsaeed D, Jamieson E, Gul M, Smith F. Challenges to optimal medicines use in people living with dementia and their caregivers: A literature review. Int. J. 2015;

207. Francis S, Smith F, Gray N, Denham M. Partnerships between older people and their carers in the management of medication. Int J Older People Nurs. 2006;1:201–7.

208. Poland F, Mapes S, Pinnock H, Katona C, Sorensen S, Fox C, et al. Perspectives of carers on medication management in dementia: lessons from collaboratively developing a research proposal. BMC Res. Notes. 2014;7:463.

209. Gillespie R, Mullan J, Harrison L. Managing medications: the role of informal caregivers of older adults and people living with dementia. A review of the literature. J. Clin. Nurs. 2014;23:3296–308.

210. While C, Duane F, Beanland C, Koch S. Medication management: The perspectives of

Do not cite or copy without permission, contact emily.reeve@sydney.edu.au for information.

people with dementia and family carers. Dementia. 2012;12:734–50.

211. Reeve E, Bell S, Hilmer SN. Barriers to optimising prescribing and deprescribing in older adults with dementia: a narrative review . Curr Clin Pharmacol. 2014;10:168–77.

212. Prorok JC, Horgan S, Seitz DP. Health care experiences of people with dementia and their caregivers: A meta-ethnographic analysis of qualitative studies. C. Can. Med. Assoc. J. Canadian Medical Association; 2013;185:E669–80.

213. Fetherstonhaugh D, Tarzia L, Nay R. Being central to decision making means I am still here!: The essence of decision making for people with dementia. J. Aging Stud. 2013;

214. Ayalon L, Bachner YG, Dwolatzky T, Heinik J. Preferences for end-of-life treatment: concordance between older adults with dementia or mild cognitive impairment and their spouses. Int. Psychogeriatrics. 2012;24:1798–804.

215. Dening KH, Jones L, Sampson EL. Preferences for end-of-life care: a nominal group study of people with dementia and their family carers. Palliat. Med. SAGE Publications; 2013;27:409–17.

216. Livingston G, Leavey G, Manela M, Livingston D, Rait G, Sampson E, et al. Making decisions for people with dementia who lack capacity: qualitative study of family carers in UK. BMJ. 2010;341:c4184.

217. Hirschman KB, Xie SX, Feudtner C, Karlawish JHT. How Does an Alzheimer's Disease Patient's Role in Medical Decision Making Change Over Time? J. Geriatr. Psychiatry Neurol. 2004;17:55–60.

218. Karlawish JHT, Casarett D, Propert KJ, James BD, Clark CM. Relationship between Alzheimer's disease severity and patient participation in decisions about their medical care. J. Geriatr. Psychiatry Neurol. 2002;15:68–72.

219. Fillit H, Hill JW, Futterman R. Health care utilization and costs of Alzheimer's disease: the role of co-morbid conditions, disease stage, and pharmacotherapy. Fam Med. 2002;34:528–35.

220. Knapp M, Iemmi V, Romeo R. Dementia care costs and outcomes: a systematic review. Int. J. Geriatr. Psychiatry. 2013;28:551–61.

221. Canadian Institute for Health Information. Drug Use Among Seniors on Public Drug Programs in Canada, 2012: Revised October 2014. Ottawa, ON; 2012.

222. Hyde C, Peters J, Bond M, Rogers G, Hoyle M, Anderson R, et al. Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease: systematic review and economic model. Age Ageing. Oxford University Press; 2013;42:14–20.

223. Green C, Picot J, Loveman E, Takeda A, Kirby J, Clegg A. Modelling the cost effectiveness of cholinesterase inhibitors in the management of mild to moderately severe Alzheimer's disease. Pharmacoeconomics. 2005;23:1271–82.

224. Ward A, Caro J, Getsios D, Ishak K, O'Brien J, Bullock R, et al. Assessment of health economics in Alzheimer's disease(AHEAD): treatment with galantamine in the UK. Int. J. Geriatr. Psychiatry. 2003;18:740–7.

225. Green C, Picot J, Loveman E, Takeda A, Kirby J, Clegg A. Modelling the cost effectiveness of cholinesterase inhibitors in the management of mild to moderately severe Alzheimer's disease.

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Pharmacoeconomics. 2005;23:1271–82.

226. Parsons C, Briesacher BA, Givens JL, Chen Y, Tjia J. Cholinesterase inhibitor and memantine use in newly admitted nursing home residents with dementia. J. Am. Geriatr. Soc. 2011;59:1253–9.

227. Purandare N, Swarbrick C, Fischer A, Burns A. Cholinesterase inhibitors for Alzheimer's disease: Variations in clinical practice in the north-west of England. Int. J. Geriatr. Psychiatry. 2006. p. 961–4.

228. Weschules DJ, Maxwell TL, Shega JW. Acetylcholinesterase inhibitor and N-methyl-D-aspartic acid receptor antagonist use among hospice enrollees with a primary diagnosis of dementia. J Palliat Med. 2008;11:738–45.

229. Knapp M, King D, Romeo R, Adams J, Baldwin A, Ballard C, et al. Cost-effectiveness of donepezil and memantine in moderate to severe Alzheimer's disease (the DOMINO-AD trial). Int. J. Geriatr. Psychiatry. 2016;

230. Hounsome N, Orrell M, Edwards RT. EQ-5D as a Quality of Life Measure in People with Dementia and Their Carers: Evidence and Key Issues. Value Heal. 2011;14:390–9.

231. Dormuth C, Maclure CKM, Chair BCA. Alzheimer's Drug Therapy Initiative (ADTI): Research Report UNIVERSITY OF VICTORIA. 2015;

232. Rockwood K, Fay S, Hamilton L, Ross E, Moorhouse P. Good days and bad days in dementia: a qualitative chart review of variable symptom expression. Int. Psychogeriatr. 2014;26:1–8.

233. Clark CM, Sheppard L, Fillenbaum GG, Galasko D, Morris JC, Koss E, et al. Variability in annual Mini-Mental State Examination score in patients with probable Alzheimer disease: a clinical perspective of data from the Consortium to Establish a Registry for Alzheimer's Disease. Arch. Neurol. American Medical Association; 1999;56:857–62.

234. Mendiondo MS, Ashford JW, Kryscio RJ, Schmitt FA. Modelling mini mental state examination changes in Alzheimer's disease. Stat. Med. 2000;19:1607–16.

235. Wattmo C. Prediction Models for Assessing Long-Term Outcome in Alzheimer's Disease. Am. J. Alzheimer's Dis. Other Dementias®. SAGE PublicationsSage CA: Los Angeles, CA; 2013;28:440–9.

236. Shabbir SH, Sanders AE. Clinical significance in dementia research: a review of the literature. Am. J. Alzheimers. Dis. Other Demen. SAGE Publications; 2014;29:492–7.

237. Molnar FJ, Man-Son-Hing M, Fergusson D. Systematic review of measures of clinical significance employed in randomized controlled trials of drugs for dementia. J. Am. Geriatr. Soc. 2009;57:536–46.

238. Kiresuk TJ, Sherman RE. Goal attainment scaling: A general method for evaluating comprehensive community mental health programs. Community Ment. Health J. 1968;4:443–53.

239. Rockwood K, Graham JE, Fay S. Goal setting and attainment in Alzheimer's disease patients treated with donepezil. J. Neurol. Neurosurg. Psychiatry. 2002;73:500–7.

240. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am. J. Geriatr.

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Pharmacother. 2007;5:345–51.

241. Jyrkkä J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. Drugs and Aging. 2009;26:1039–48.

242. Olsson IN, Runnamo R, Engfeldt P. Medication quality and quality of life in the elderly, a cohort study. Heal. Qual Life Outcomes. 2011/11/08 ed. 2011;9:95.

243. Wallace E, McDowell R, Bennett K, Fahey T, Smith SM. Impact of Potentially Inappropriate Prescribing on Adverse Drug Events, Health Related Quality of Life and Emergency Hospital Attendance in Older People Attending General Practice: A Prospective Cohort Study. Journals Gerontol. Ser. A Biol. Sci. Med. Sci. Oxford University Press; 2016;Published .

244. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin. Drug Saf. 2014;13:57–65.

245. Singh S, Dudley C. Discontinuation syndrome following donepezil cessation. Int. J. Geriatr. Psychiatry. John Wiley & Sons, Ltd.; 2003;18:282–4.

246. Bidzan L, Bidzan M. Withdrawal syndrome after donepezil cessation in a patient with dementia. Neurol. Sci. Springer Milan; 2012;33:1459–61.

247. Okazaki T, Furukawa K, Kubo H, Tsutsui M, Furukawa E, Asada M, et al. Paralytic ileus after discontinuation of cholinesterase inhibitor. J. Am. Geriatr. Soc. 2006. p. 1620–1.

248. Enzenauer R, Bowers P. Angle-closure glaucoma after discontinuing donepezil hydrochloride (Aricept). Journals Gerontol. Ser. A Biol. Sci. Med. Sci. 2005;60:1083.

249. Kwak YT, Han I-W, Suk S-H, Koo M-S. Two cases of discontinuation syndrome following cessation of memantine. Geriatr. Gerontol. Int. Blackwell Publishing Asia; 2009;9:203–5.

250. Darreh-Shori T, Soininen H. Effects of cholinesterase inhibitors on the activities and protein levels of cholinesterases in the cerebrospinal fluid of patients with Alzheimer's disease: a review of recent clinical studies. Curr. Alzheimer Res. Bentham Science Publishers; 2010;7:67–73.

251. Doody RS, Geldmacher DS, Gordon B, Perdomo C a, Pratt RD. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. Arch. Neurol. 2001;58:427–33.

252. Homma A, Imai Y, Tago H, Asada T, Shigeta M, Iwamoto T, et al. Long-term safety and efficacy of donepezil in patients with severe Alzheimer's disease: results from a 52-week, open-label, multicenter, extension study in Japan. Dement. Geriatr. Cogn. Disord. Karger Publishers; 2009;27:232–9.

253. Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology. Lippincott Williams & Wilkins; 2001;57:489–95.

254. Pariente A, Fourrier-Réglat A, Bazin F, Ducruet T, Dartigues JF, Dragomir A, et al. Effect of treatment gaps in elderly patients with dementia treated with cholinesterase inhibitors. Neurology. 2012;78:957–63.

255. Matthews H, Korbey J, Wilkinson D. Donepezil in Alzheimer's disease: eighteen month results from Southampton Memory Clinic. J. Geriatr. …. 2000;

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256. Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg GT, Potkin SG. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. Curr. Med. Res. Opin. Taylor & Francis; 2003;19:707–14.

257. Wong CW. Pharmacotherapy for Dementia: A Practical Approach to the Use of Cholinesterase Inhibitors and Memantine. Drugs and Aging. 2016;33:451–60.

258. Cummings JL, Isaacson RS, Schmitt FA, Velting DM. A practical algorithm for managing Alzheimer's disease: what, when, and why? Ann. Clin. Transl. Neurol. Wiley-Blackwell; 2015;2:307–23.

259. Hogan DB, Bailey P, Carswell A, Clarke B, Cohen C, Forbes D, et al. Management of mild to moderate Alzheimer's disease and dementia. Alzheimer's Dement. 2007;3:355–84.

260. Zemek F, Drtinova L, Nepovimova E, Sepsova V, Korabecny J, Klimes J, et al. Outcomes of Alzheimer's disease therapy with acetylcholinesterase inhibitors and memantine. Expert Opin. Drug Saf. 2014;13:759–74.

261. Wattmo C, Wallin ÅK, Londos E, Minthon L. Predictors of long-term cognitive outcome in Alzheimer's disease. Alzheimers. Res. Ther. 2011;3:23.

262. Ritchie CW, Ames D, Clayton T, Lai R. Metaanalysis of Randomized Trials of the Efficacy and Safety of Donepezil, Galantamine, and Rivastigmine for the Treatment of Alzheimer Disease. Am. J. Geriatr. Psychiatry. 2004;12:358–69.

263. Wattmo C, Wallin ÅK, Londos E, Minthon L. Long-term Outcome and Prediction Models of Activities of Daily Living in Alzheimer Disease With Cholinesterase Inhibitor Treatment. Alzheimer Dis. Assoc. Disord. 2011;25:63–72.

264. Wattmo C, Wallin AK, Londos E, Minthon L. Risk Factors for Nursing Home Placement in Alzheimer's Disease: A Longitudinal Study of Cognition, ADL, Service Utilization, and Cholinesterase Inhibitor Treatment. Gerontologist. 2011;51:17–27.

265. Wattmo C, Londos E, Minthon L. Cholinesterase inhibitors do not alter the length of stay in nursing homes among patients with Alzheimer's disease: a prospective, observational study of factors affecting survival time from admission to death. BMC Neurol. BioMed Central; 2016;16:156.

266. Cooper C, Ketley D, Livingston G. Systematic review and meta-analysis to estimate potential recruitment to dementia intervention studies. Int. J. Geriatr. Psychiatry. 2014. p. 515–25.

267. Farlow MR, Grossberg GT, Sadowsky CH, Meng XY, Velting DM. A 24-Week, Open-Label Extension Study to Investigate the Long-term Safety, Tolerability, and Efficacy of 13.3 mg/24 h Rivastigmine Patch in Patients With Severe Alzheimer Disease. Alzheimer Dis. Assoc. Disord. 2015;29:110–6.

268. Traynor V, Pritchard E, Dewing J. Illustrating the importance of including the views and experiences of users and carers in evaluating the effectiveness of drug treatments for dementia. Dementia. 2004;

269. Jansen J, Naganathan V, Carter SM, McLachlan AJ, Nickel B, Irwig L, et al. Too much medicine in older people? Deprescribing through shared decision making. BMJ. British Medical Journal Publishing Group; 2016;353:i2893.

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270. Reeve E, To J, Hendrix I, Shakib S, Roberts MS, Wiese MD. Patient barriers to and enablers of deprescribing: a systematic review. Drugs and Aging. 2013;30:793–807.

271. Psaty BM, Burke SP. Protecting the Health of the Public — Institute of Medicine Recommendations on Drug Safety. N. Engl. J. Med. 2006;355:1753–5.

272. Ioannidis JPA. Why most published research findings are false. PLoS Med. 2005;2:e124.

273. Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Review of deprescribing processes and development of an evidence based, patient-centred deprescribing process. Br. J. Clin. Pharmacol. 2014;78:738–47.

274. Reeve E, Denig P, Hilmer SN, Ter Meulen R. The Ethics of Deprescribing in Older Adults. J. Bioeth. Inq. 2016;1–10.

275. Tjia J, Givens J. Ethical framework for medication discontinuation in nursing home residents with limited life expectancy. Clin. Geriatr. Med. 2012;28:255–72.

276. Barnett N, Kelly O. Deprescribing: is the law on your side? Eur. J. Hosp. Pharm. 2017;24:21–5.

277. Warren LA, Shi Q, Young TK, Borenstein A, Martiniuk A. Prevalence and incidence of dementia among Indigenous populations: a systematic review. Int. Psychogeriatrics. 2015;27:1959–70.

278. Smith K, Flicker L, Lautenschlager NT, Almeida OP, Atkinson D, Dwyer A, et al. High prevalence of dementia and cognitive impairment in Indigenous Australians. Neurology. Lippincott Williams & Wilkins; 2008;71:1470–3.

279. Lo Giudice D, Smith K, Fenner S, Hyde Z, Atkinson D, Skeaf L, et al. Incidence and predictors of cognitive impairment and dementia in Aboriginal Australians: A follow-up study of 5 years. Alzheimer's Dement. 2016;12:252–61.

280. Jacklin KM, Walker JD, Shawande M. The emergence of dementia as a health concern among first nations populations in Alberta, Canada. Can. J. Public Heal. 2013;104.

281. Cooper C, Tandy AR, Balamurali TBS, Livingston G. A Systematic Review and Meta-Analysis of Ethnic Differences in Use of Dementia Treatment, Care, and Research. Am. J. Geriatr. Psychiatry. 2010;18:193–203.

282. Mehta K, Yin M, Resendez C, Yaffe K. Ethnic differences in acetylcholinesterase inhibitor use for Alzheimer disease. Neurology. 2005;

283. Maxwell CJ, Stock K, Seitz D, Herrmann N. Persistence and Adherence with Dementia Pharmacotherapy: Relevance of Patient, Provider, and System Factors. Can. J. Psychiatry. SAGE PublicationsSage CA: Los Angeles, CA; 2014;59:624–31.

284. Page A. Personal experience in rural Western Australia. Aust. Pharm. 2014;January:66–8.

285. Smith K, Flicker L, Shadforth G, Carroll E, Ralph N, Atkinson D, et al. "Gotta be sit down and worked out together": Views of aboriginal caregivers and service providers on ways to improve dementia care for aboriginal Australians. Rural Remote Health. 2011;11.

286. Roe CM, Anderson MJ, Spivack B. Use of Anticholinergic Medications by Older Adults with Dementia. J. Am. Geriatr. Soc. Blackwell Science Inc; 2002;50:836–42.

287. Gnjidic D, Hilmer SN, Hartikainen S, Tolppanen A-M, Taipale H, Koponen M, et al. Impact of

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high risk drug use on hospitalization and mortality in older people with and without Alzheimer's disease: a national population cohort study. PLoS One. 2014;9:e83224.

288. Mitchell SL, Kiely DK, Hamel MB. Dying with advanced dementia in the nursing home. Arch Intern Med. 2004;164:321–6.

289. Giron MS, Wang HX, Bernsten C, Thorslund M, Winblad B, Fastbom J. The appropriateness of drug use in an older nondemented and demented population. J Am Geriatr Soc. 2001/04/13 ed. 2001;49:277–83.

290. Salahudeen MS, Duffull SB, Nishtala PS. Impact of anticholinergic discontinuation on cognitive outcomes in older people: a systematic review. Drugs Aging. 2014;31:185–92.

291. Lu C, Tune LE. Chronic exposure to anticholinergic medications adversely affects the course of Alzheimer disease. Am. J. Geriatr. psychiatry. 2003;11:458–61.

292. Yaffe K, Boustani M. Benzodiazepines and risk of Alzheimer's disease. BMJ. 2014;349.

293. de Gage SB, Bégaud B, Bazin F, Verdoux H, Dartigues J-F, Pérès K, et al. Benzodiazepine use and risk of dementia: prospective population based study. BMJ. 2012;345:e6231.

294. Kouladjian L, Gnjidic D, Chen TF, Mangoni AA, Hilmer SN. Drug Burden Index in older adults: theoretical and practical issues. Clin. Interv. Aging. 2014;9:1503.

295. Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. Am. J. Psychiatry. 2012;169:946–53.

296. Cabrera E, Sutcliffe C, Verbeek H, Saks K, Soto-Martin M, Meyer G, et al. Non-pharmacological interventions as a best practice strategy in people with dementia living in nursing homes. A systematic review. Eur. Geriatr. Med. 2015. p. 134–50.

297. Commonwealth Senate Standing Committee on Community Affairs. Care and management of younger and older Australians living with dementia and behavioural and psychiatric symptoms of dementia (BPSD). 2014.

298. Declercq T, Petrovic M, Azermai M, Vander Stichele R, De Sutter AI, van Driel ML, et al. Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia. Cochrane Database Syst Rev. 2013;3:CD007726.

299. Huntley JD, Gould RL, Liu K, Smith M, Howard RJ. Do cognitive interventions improve general cognition in dementia? A meta-analysis and meta-regression. BMJ Open. British Medical Journal Publishing Group; 2015;5:e005247.

300. Forbes D, Thiessen EJ, Blake CM, Forbes SSSC, Forbes SSSC, Cendoroglo MS, et al. Exercise programs for people with dementia. Blake CM, editor. Sao Paulo Med. J. Chichester, UK: John Wiley & Sons, Ltd; 2014;132:195–6.

301. Fleming R, Purandare N. Long-term care for people with dementia: environmental design guidelines. Int. Psychogeriatrics. 2010;22:1084–96.

302. Winkelmayer WC, Fischer MA, Schneeweiss S, Wang PS, Levin R, Avorn J. Underuse of ACE Inhibitors and Angiotensin II Receptor Blockers in Elderly Patients With Diabetes. Am. J. Kidney Dis. 2005;46:1080–7.

303. Tan ECK, Jokanovic N, Koponen MP, Thomas D, Hilmer SN, Bell JS. Prevalence of analgesic

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use in people with and without dementia or cognitive impairment in aged care facilities: a systematic review and meta-analysis. Curr Clin Pharmacol. Bentham Science Publishers; 2015;10:194–203.

304. Nelson JC, Devanand DP. A Systematic Review and Meta-Analysis of Placebo-Controlled Antidepressant Studies in People with Depression and Dementia. J. Am. Geriatr. Soc. Blackwell Publishing Inc; 2011;59:577–85.

305. Conklin J, Farrell B, Ward N, McCarthy L, Irving H, Raman-Wilms L, et al. Developmental evaluation as a strategy to enhance the uptake and use of deprescribing guidelines: protocol for a multiple case study. Implement. Sci. BioMed Central; 2015;10:91.

306. Farrell B, Conklin J, Irving H, McCarthy L, Pizzola L, Pottie K, et al. Deprescribing guidelines for the elderly: preliminary outcomes of a developmental evaluation. NAPCRG. 2014;New York, .

307. Thompson W, Hogel M, Li Y, Thavorn K, O'Donnell D, McCarthy L, et al. Effect of a Proton Pump Inhibitor Deprescribing Guideline on Drug Usage and Costs in Long-Term Care. J. Am. Med. Dir. Assoc. 2016;17:673.e1–673.e4.

308. Liang L, Bernhardsson S, Vernooij RWM, Armstrong MJ, Bussières A, Brouwers MC, et al. Use of theory to plan or evaluate guideline implementation among physicians: a scoping review. Implement. Sci. 2017;12:26.

309. Gagliardi AR, Alhabib S. Trends in guideline implementation: a scoping systematic review. Implement. Sci. 2015;10:54.

310. Gagliardi AR, Marshall C, Huckson S, James R, Moore V. Developing a checklist for guideline implementation planning: review and synthesis of guideline development and implementation advice. Implement. Sci. 2015;10:19.

311. Grimshaw J, Thomas R, MacLennan G, Fraser C, Ramsay CR, Vale L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol. Assess. (Rockv). 2004;8:1–72.

312. Aminoff BZ, Purits E, Noy S, Adunsky A. Measuring the suffering of end-stage dementia: Reliability and validity of the Mini-Suffering State Examination. Arch. Gerontol. Geriatr. 2004;38:123–30.

313. Mitchell SL, Miller SC, Teno JM, Davis RB, Shaffer ML. The Advanced Dementia Prognostic Tool (ADEPT): A Risk Score to Estimate Survival in Nursing Home Residents with Advanced Dementia. J Pain Symptom Manag. 2010;40:639–51.

314. Burns A [Ed], Winblad B [Ed]. Severe dementia. Sev. dementia. John Wiley & Sons; 2006. p. 246.

315. Brown MA, Sampson EL, Jones L, Barron AM. Prognostic indicators of 6-month mortality in elderly people with advanced dementia: A systematic review. Palliat. Med. 2013;27:389–400.

316. Rikkert MO, Tona K. Validity, reliability, and feasibility of clinical staging scales in dementia: a systematic review. Am. J. 2011;

317. NHMRC Partnership Centre for Dealing with Cognitive and Related Functional Decline in Older People. Implementing guideline recommendations into practice A companion document for the Clinical Practice Guidelines and Principles of Care for People with Dementia. Sydney;

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2016.

318. Michie S. Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual. Saf. Heal. Care. 2005;14:26–33.

319. Schrijvers G, Hoorn A van, Huiskes N. The Care Pathway Concept: concepts and theories: an introduction. Int. J. Integr. Care. 2012;12:7.

320. Graham I, Logan J, Harrison M. Lost in knowledge translation: time for a map? J. Contin. 2006;

321. American Geriatrics Society. Choosing wisely—five things physicians and patients should question: part 2 [Internet]. 2014 [cited 2017 Feb 27]. Available from: http://www.americangeriatrics.org/files/documents/5things_list_PART.pdf

322. Qaseem A, Snow V, Cross JT, Forciea MA, Hopkins R, Shekelle P, et al. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann. Intern. 2008;148:370–8.

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Glossary

Acetylcholinesterase inhibitors	A class of medications used to treat the symptoms of dementia. They work by inhibiting the breakdown of acetylcholine—an important neurotransmitter that is reduced in people with dementia (the so-called 'cholinergic hypothesis'). Acetylcholinesterase inhibitors approved for use in clinical practice in Australia and Canada are rivastigmine, donepezil and galantamine.
Adverse drug reaction (ADR)	An undesirable effect (harmful or unpleasant reaction) from administration of a medication. Also known as '**side effects**'.
AGREE II	An international tool that is used to assess the quality and transparency of a clinical practice guideline. It evaluates the methodological development of the guideline and can be used to inform the methodological strategy for development of guidelines and how the information ought to be reported.
Alzheimer's disease (AD)	Alzheimer's disease is the most common type of dementia. It is a progressive condition involves symptoms of impaired memory, thinking, behavior, emotions and function.
Antipsychotics	A class of medication used to manage the symptoms of psychosis or mood disorders. Also known as neuroleptics and major tranquilizers.
Behavioural and psychological symptoms of dementia	This term describes a number of behavioural and psychological symptoms which can occur in people with dementia. They may include agitation, aggression, anxiety, depressive mood, restlessness, wandering, sexual disinhibition, vocalisations, hallucinations and delusions. The most common validated tool used to measure behavioural and psychological symptoms of dementia is the Neuropsychiatric Inventory (NPI). These symptoms are also known as 'responsive symptoms' – this terminology is generally preferred by consumer organisations.
Care staff	A person employed to provide personal, physical and emotional support to individuals in need of this assistance (for example, older adults). Often have certificate level qualifications. Care staff provides professional care for a person with dementia, often in the community or in a long-term care facility. Care staff are different from carers as they are paid for their services.

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Carer	Individuals, typically a family member or friend, who provide ongoing, everyday care for a person with dementia (or any individual requiring support). A carer is different from care staff as they provide their support in a non-professional and unpaid manner. Also known as a **caregiver**.
Cognitive function	Cognitive function relates to thoughts, knowledge, memory, attention, language and judgement. The most common tools used to measure cognitive function in people with dementia include the MMSE and ADAS-Cog.
Comorbidity	The presence of two or more medical conditions (diseases or disorders) in a single individual.
Consensus-based recommendation	Recommendations formulated based on systematic review findings that are inconclusive or of low quality (that is, insufficient to be classed as EBR).
Consumer	In this guideline a consumer is a person with dementia and their carer/family.
Dementia	Describes a syndrome that is characterised by a progressive loss in cognition, function and behaviour.
Dementia with Lewy Bodies (DLB)	A type of dementia characterized by symptoms of both Alzheimer's disease and Parkinson's disease. It is a progressive neurodegerative disease caused by the abnormal deposition of alpha-synuclein protein in specific areas of the brain that are responsible for movement, behavior, and cognition.
Deprescribing	Deprescribing is the structured withdrawal of an inappropriate medication, supervised by a healthcare professional. It may also involve tapering and dose reduction. The purpose of 'deprescribing' is to improve the overall risk–benefit profile of medication use in individuals through withdrawal of inappropriate medications in a safe and effective manner.
Drug-disease interactions	Where administration of a medication can lead to exacerbation of a medical condition in that individual.
Drug-drug interaction	Where co-administration of two or more medications leads to an alteration in the activity of one or more of those medications. Drug-drug interactions may lead to clinically significant results (reduced efficacy of the medication, or increased risk of harm).
Dual treatment/therapy	Co-administration of both a cholinesterase inhibitor and memantine in an individual.

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Evidence-based recommendation	Recommendation formulated based on the findings of the systematic review.
First Nations	The predominant indigenous peoples of Canada.
Frontotemporal Dementia (FTD).	A type of dementia that is characterized by progressive, irreversible damage to the frontal and temporal regions of the brain. This damage can lead to changes in personality, behavior, and cognitive function.
General Practitioner	A medical practitioner who works in primary care and provides routine medical care to patients by assessing and treating a wide variety of medical conditions, rather than specialising in one specific area of medicine. Also known as **Primary Care Physician, Family Physician**.
Generic medication	A medication that is therapeutically equivalent to a brand name medication. It must be similar in strength, dosage form, route of administration, and intended use.
Global change	An assessment of the total change in symptoms and/or condition of a person with dementia across different symptoms domains; including cognition, behaviour and function. The most common tools used to assess global change in people with dementia include the GCI-C and the CIBIC-Plus.
GRADE	The Grading of Recommendations, Assessment, Development and Evaluation is a comprehensive and explicit approach used to rate the quality of evidence and strength of recommendations that are made.
Inappropriate medication	A medication whose potential harms to the individual outweigh its potential benefits, and/or is no longer indicated for the treatment of a condition or are not in alignment with their treatment goals.
Indigenous	Ethnic groups which have historical ties to a territory and identify with the culture of the original inhabitants. Indigenous people have specific rights based on their territorial connections that are not given to ethnic groups that have colonized the area more recently. In Australia, this refers to Aboriginal and Torres Strait Islander Australians.
Meta-analysis	A statistical analysis that is used to combine the results of multiple studies to identify common effect or variation in findings.

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Mild cognitive impairment (MCI)	An intermediate state between the expected decline in cognitive function associated with normal aging and the decline associated with early dementia. The changes observed in MCI may be severe enough to be noticed, however these changes typically do not interfere with a person's normal daily functioning.
Multimorbidity	The presence of two or more medical conditions in an individual.
N-methyl-D-aspartate (NMDA) receptor antagonist, memantine	NMDA receptor antagonists are thought to act through prevention of excitatory amino acid neurotoxicity, which is implicated in the pathogenesis of AD. Memantine is the only NMDA receptor antagonist approved for use in people with dementia in Australia and Canada.
Nurse practitioners, registered nurses and enrolled nurses with endorsement	There are multiple categories of nurses in Australia and Canada which have various levels of training (qualifications) and responsibilities. In Australia nurse practitioners, registered nurses and enrolled nurses with endorsement may have administration of medications within their scope of practice. In Canada nurse practitioners, registered nurses and licensed practical nurses (also known as licensed vocational nurses) may have administration of medications within their scope of practice. Nurse practitioners have expanded roles which may include prescribing medications.
Person-centered care	Care that is based on the active involvement of individuals and their families in the management of their care. Person-centered care focuses on viewing the patient as a whole and considering their values and circumstances when making care related decisions.
Pharmaceutical Benefits Scheme (PBS)	A program implemented by the Australian government that aims to provide greater access to necessary medications by offering financial aid in the form of subsidies.
PICO framework	A framework used in evidence based medicine to formulate a clinical question. It ensures that the clinical question is directly related to the individual or population, involves the interventions and comparators in question, and examines the outcome of interest.
Placebo	A substance that is pharmaceutically inactive and provides no therapeutic effect. Placebos are often given to participants in clinical research trials as a control to observe if a perceived improvement is due to the participant's expectations rather than the treatment.

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Practice Point (PP)	A recommendation that is based on expert opinion rather than being derived from a systematic review of evidence (outside the scope of the clinical questions of the systematic review). They are provided to support the EBR and CBR.
Prescribing cascade	Where one medication is prescribed to treat the side effect of another medication.
Primary progressive aphasia (PPA)	A type of progressive cognitive impairment commonly associated with neurodegenerative diseases such as Alzheimer's Disease. PPA is characterized by a gradual decline in language capabilities, including the ability to produce and understand speech.
Quality of life (QoL)	A subjective measure of the well-being of a person and how satisfied they are with their life. QOL measurements consider factors such as life circumstances, the burden of illnesses, and the person's level of functioning.
Randomized controlled trials (RCTs)	A study design in which participants are randomly assigned to either an intervention or control group. The intervention group receives the intervention that is being studied and the control group receives the standard or placebo treatment. This is done to examine the effect of specific interventions on a specific outcome. Aside from the intervention they receive, participants should be similar in all other aspects.
Residential care	Refers to the supportive care that is provided to individuals with complex health care needs who are living in long-term care facilities.
Stakeholder	A person who has an interest or role in a specific organisation or service.
Strong recommendation	A strong recommendation is provided when all or most individuals would be best served with that course of action, and the outcomes align with their values and preferences.
Systematic review	A type of literature review that uses explicit and predefined methodologies to identify, critically appraise, and summarize relevant research studies for the purpose of answering a specific clinical question.
Taper	The gradual dose reduction of a medication for the purpose of discontinuation.

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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.
Validated tool	A survey or questionnaire that has been determined to be able to accurately measure what it intends to measure.
Vascular dementia	A type of dementia that occurs when the blood supply in the brain is impaired and results in cognitive decline. Persons with vascular dementia may experience difficulty with memory, thinking, and reasoning, which may interfere with daily activities.
Weak recommendation	A weak recommendation reflects that consideration of the individual's values and preferences and treatment goals is required before proceeding with the recommended course of action (such as the individual's preference on competing interests).

List of acronyms

AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale—Cognitive
ADR	Adverse Drug Reaction
ADWE	Adverse Drug Withdrawal Event
AIDS	Acquired Immune Deficiency Syndrome
CBR	Consensus-based Recommendations
CGI-I	Clinical Global Impressions of Improvement
CGI-S	Clinical Global Impressions of Severity
CGI-C	Clinical Global Impressions of Change
ChEI	Cholinesterase Inhibitor
CI	Confidence Interval
CIBIC-Plus	Clinician's Interview-based Impression of Change Plus Caregiver Input
CNS	Central Nervous System
COI	Conflict of Interest
CPS	Cognitive Performance Scale

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DEMQOL-Proxy	Health Related Quality of Life in dementia (proxy reported by a carer).
DRS	Dementia Rating Scale
EBR	Evidence-based Recommendations
FAST	Functional Assessment Stage Tool
FTD	Frontotemporal Dementia
GAS	Goal Attainment Scaling
GDT	Guideline Development Team
INR	International Normalised Ratio
LBD	Lewy Body Dementia
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
NHMRC	National Health and Medical Research Council
NIHR-HTA	National Institute for Health Research—Health Technology Assessment
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory – Nursing Home
NPZ8	Battery of 8 neuropsychological performance tests
NMDA	N-methyl-D-aspartate
PBS	Pharmaceutical Benefits Scheme
PDD	Parkinson's Disease Dementia
PP	Practice Points
PPA	Primary Progressive Aphasia
QALY	Quality-adjusted Life Year
QUALID	Quality of Life in Late Stage Dementia
RCT	Randomised Controlled Trial
SMD	Standardised Mean Difference
TDF	Theoretical Domains Framework
UK	United Kingdom
US	United States

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Appendix 1: Guideline Development Team

Process and criteria for selecting members

We recruited Guideline Development Team (GDT) members who were one or more of the following: content experts, end-users, methodology experts or consumers. We sought to include healthcare professionals who are involved in the prescription and/or monitoring/management of prescriptions of cholinesterase inhibitors and/or memantine (end-users). At a minimum, we intended our GDT to have at least one member of the following groups: general practitioner (family physician, primary care physician), geriatrician, pharmacist and nurse. This guideline was developed as a partnership between Australian and Canadian institutions and therefore we intended to have a balance of members from both countries.

To recruit potential content experts, end-users and methodology experts, we used the networks of the people involved in the submission of the fellowship/project.

Where possible, potential conflicts of interest (COIs) were reviewed prior to inviting members (for example, recent publications reviewed for COIs). All potential members were invited via email which briefly explained the aim of the guideline and the process involved in development. If a potential member declined, they were asked to suggest another person in their place. If they expressed an interest in participating, they were provided with more information (via email or in person) and they were asked to complete the COI form.

GDT members received no reimbursement for their involvement. Travel costs were covered to attend the first GDT meeting.

Consumer involvement in the GDT

We sought to recruit two consumer representatives to be on the GDT: a current/past carer of a person with dementia and a person with dementia. The carer was recruited through the NHMRC Cognitive Decline Partnership Centre (Australia) and the person with dementia was recruited through the Alzheimer Society of Nova Scotia. As GDT members they were involved throughout the development process. The carer representative was present at the first GDT team meeting where the scope of the guideline was determined and provided ongoing input to the guideline and recommendations via email/telephone communication. The person with dementia was not able to be recruited until after the first meeting (setting the scope) had occurred, as such they did not participate in this meeting. During the development phase the person with dementia provided input via one-on-one meetings with the guideline lead in a place that was suitable to them. Other communication occurred via email and telephone contact.

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GDT members and others involved in guideline development

Table 8: GDT members, roles and affiliations

Name	Discipline/role/expertise	Organisational affiliation(s)
Emily Reeve *Guideline coordinator and lead*	NHMRC-ARC Dementia Research Development Fellow Pharmacist	NHMRC Cognitive Decline Partnership Centre, Kolling Institute of Medical Research, Northern Clinical School, Sydney Medical School, University of Sydney, NSW, Australia Geriatric Medicine Research, Faculty of Medicine, Dalhousie University and Nova Scotia Health Authority, NS, Canada Adjunct Appointee, College of Pharmacy, Faculty of Health Professions, Dalhousie University, NS, Canada
Sarah Hilmer	Geriatrician and Clinical Pharmacologist Professor of Geriatric Pharmacology and Head of Department, Clinical Pharmacology and Senior Staff Specialist, Royal North Shore Hospital	NHMRC Cognitive Decline Partnership Centre, Kolling Institute of Medical Research, Northern Clinical School, Sydney Medical School, University of Sydney, NSW, Australia Departments of Clinical Pharmacology and Aged Care, Royal North Shore Hospital, NSW, Australia
Lynn Chenoweth	Professor of Nursing Professor of Aged and Extended Care Nursing Adjunct Professor	Centre for Healthy Brain Ageing, University of NSW, NSW, Australia Faculty of Health Sciences, University of Macau, Macau, China School of Nursing, The Notre Dame University, NSW, Australia
Lyntara Quirke	Consumer representative: carer	Consumer Network, Alzheimer's Australia, ACT, Australia Bribie-Moreton Hospice Health Service, QLD, Australia Rotary Club Bribie Island, QLD, Australia Dementia Training Australia, Australia
Parker Magin	General practitioner Director Conjoint Professor	NSW and ACT Research and Evaluation Unit, GP Synergy, NSW, Australia Discipline of General Practice, School of Medicine and Public Health, University of Newcastle, NSW, Australia

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Barbara Farrell	Pharmacist Methodology expert in deprescribing guideline development	Bruyère Research Institute, ON, Canada Department of Family Medicine, University of Ottawa, ON, Canada School of Pharmacy, University of Waterloo, ON, Canada
Mary Gorman	General practitioner, aged care specialty	Faculty of Medicine, Dalhousie University, NS, Canada
Nathan Herrmann	Geriatric psychiatrist Head, Division of Geriatric Psychiatry	Division of Geriatric Psychiatry, Sunnybrook Health Sciences Centre, ON, Canada Faculty of Medicine, University of Toronto, ON, Canada
Graeme Bethune	General practitioner, aged care specialty Medical Director of Veterans' Services	Veterans' Services, Nova Scotia Health Authority, NS, Canada Hydrostone Medical Centre, NS, Canada
Wade Thompson	Pharmacist in residential aged care services Methodology expert in deprescribing guideline development process	Medisystem Pharmacy, ON, Canada Bruyère Research Institute, ON, Canada School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, ON, Canada
Ingrid Sketris	Pharmacist Methodology expert in systematic reviews and pharmacoepidemiology	College of Pharmacy, Faculty of Health Professions, Dalhousie University, NS, Canada
Faye Forbes	Consumer: person with dementia	Alzheimer's Society of Canada (board member)

Table 9: Non-GDT members involved in guideline development

Name	**Profession/discipline** *Role in the guideline development process*	**Organisational affiliation(s)**
Lisa Kouladjian O'Donnell	Pharmacist Postdoctoral Research Associate *Reviewer for systematic review (title/abstract screening, full text screening and eligibility assessment, and data extraction)*	NHMRC Cognitive Decline Partnership Centre, Kolling Institute of Medical Research, Northern Clinical School, Sydney Medical School, University of Sydney, NSW, Australia
Judith Godin	Researcher *Conducting meta-analysis of the*	Nova Scotia Health Authority, NS, Canada Geriatric Medicine Research, Faculty of

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	systematic review	Medicine, Dalhousie University, NS, Canada
Caitlin Lees	Medical doctor, research student *Second reviewer for systematic review (title/abstract screening)*	Maritime Resident Doctors, PGY3 Internal Medicine & Clinician Investigator Program, Dalhousie University, NS, Canada
Emma Squires	Research assistant *Data extraction of systematic review (full text screening and eligibility assessment, and data extraction)*	Geriatric Medicine Research, Nova Scotia Health Authority, NS, Canada
Ivanka Hendrix	Senior clinical pharmacist, postgraduate research fellow *Reviewed Dutch-language article for potential inclusion in the systematic review*	Department of Pharmacy, Queen Elizabeth Hospital, Woodville, SA, Australia School of Nursing and Adelaide Geriatrics Training and Research with Aged Care (GTRAC), School of Medicine, University of Adelaide, SA, Australia NHMRC Centre of Research Excellence: Frailty Trans-Disciplinary Research to Achieve Health Ageing, SA, Australia

We also wish to thank Robin Parker, Academic librarian at Dalhousie University, Nova Scotia, Canada for assistance in developing the search strategy for the systematic review.

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Appendix 2: Summary of Findings and Evidence to Recommendations Tables

Table 10: GRADE Summary of Findings—Cholinesterase Inhibitors

Quality assessment							Effect	Quality
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Cognitive Function								
7 [54–56,59,60,62,63]	Placebo-controlled randomised discontinuation versus continuation	Serious risk of bias [1,2, 3, 4, 5]	No serious inconsistency [6]	Serious indirectness [7, 8, 9, 10, 11]	No serious imprecision	5/7 studies were funded by pharmaceutical companies	Significantly greater decrease in cognitive function in those who discontinued versus those who continued. Standardised mean difference = 0.38, 95% CI = 0.22–0.53.	⊕⊕OO LOW
Global assessment of change or dementia stage								
3 [59,62,63]	Placebo-controlled randomised discontinuation versus continuation	Serious risk of bias [2, 3, 4, 5]	No serious inconsistency	Serious indirectness [8, 9]	No serious imprecision [12]	2/3 studies were funded by pharmaceutical companies	No significant difference between groups in global change assessments. Unable to pool results due to variability of tools used. CGI-C = 3.6 ± 1.1 (discontinuation) versus 3.4 ± 1.2 (continuation), p = 0.55 [62]. 'No difference was seen between treatment groups concerning mean values of the CIBIC-plus scale.' Data not provided [59]. 'Only a trend in favor of galantamine appeared in the overall group (CGI-S) … The CGI-I did not show significant difference between any of the galantamine-treated and the placebo groups.' Data not provided [63].	⊕⊕OO LOW
Behaviour								
5 [55,56,60,62,63]	Placebo-controlled randomised discontinuation versus continuation	Serious risk of bias [2, 3, 4, 5]	No serious inconsistency [13]	Serious indirectness [8, 9, 11]	Depends on meta-analysis	3/5 studies were funded by pharmaceutical companies	Non-significantly greater change in NPI scores in discontinuation versus continuation group. Meta-analysis of three studies with available data using the NPI [55,56,63]: standardised mean difference = 0.20, 95% CI = −0.24–0.65. Two studies not included in meta-analysis: NPI-NH: 3.6 ± 12.6 (discontinuation) versus −1.1 ± 8.9, p = 0.24 [62].	⊕⊕OO LOW

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							NPI = 2.3 points lower with continuation versus discontinuation; 95% CI, −1.1–5.7, p = 0.08 (not included in meta-analysis as this figure represents pooled data of those who also initiated memantine) [60].	
Quality of Life								
2 [60,62]	Placebo-controlled randomised discontinuation versus continuation	Serious risk of bias [2, 4, 5]	No serious inconsistency	Serious indirectness [8, 9]	No serious imprecision		No significant difference between groups in quality of life measures. QUALID = 0.3 ± 3.1 (discontinuation) versus −0.1 ± 4.8, p = 0.92 [62]. DEMQOL-Proxy = −1.6 (95% CI −4.7–1.4) continued versus discontinued (pooled data of those who also initiated memantine) [60].	⊕⊕OO LOW

95% CI = 95% Confidence Interval, CGI-I = Clinical Global Impressions of Improvement, CGI-S = Clinical Global Impressions of Severity, CGI-C = Clinical Global Impressions of Change, CIBIC-Plus = Clinician's Interview-based Impression of Change Plus Caregiver Input, NPI = Neuropsychiatric Inventory, NPI-NH = Neuropsychiatric Inventory—Nursing Home, QUALID = Quality of Life in Late-stage Dementia, DEMQOL-Proxy = Health-related Quality of Life in Dementia (Proxy Reported by a Carer).

[1] Unclear randomisation process in one or more studies.

[2] Unclear allocation concealment in one or more studies.

[3] Unclear if personnel conducting assessments were blinded in one or more studies.

[4] Risk of attrition bias (imbalance of dropouts) and use of observed case analysis in one or more studies.

[5] Possible selective reporting of outcomes in one or more studies.

[6] Meta-analysis heterogeneity results: I^2 = 16% (all 7 studies).

[7] Tools to assess cognitive function may not be related to person-centred outcomes.

[8] Inclusion/exclusion criteria in one or more studies limit generalisability (for example, participants had to be in 'good health' and living in the community).

[9] All except one study involved people with AD (the seventh study was for a non-supported indication), and thus cannot be generalised to use outside of AD (such as PDD and DLB).

[10] Mean age of participants in the majority of studies was lower than the mean age of users of cholinesterase inhibitors/people with dementia (80 versus 75, 89, 78, 77, 73, 63 and 74).

[11] Duration of use prior to discontinuation of < 6 months in one or more studies limits generalisability.

[12] No standard deviation/confidence interval reported in one study.

[13] Meta-analysis heterogeneity results: I^2 = 67% (3 studies). Variability due to study which included participants with a non-approved indication.

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Table 11: Evidence to Recommendations—Cholinesterase Inhibitors

Question: Does deprescribing compared to continuation of cholinesterase inhibitor use result in benefit or harms?		
Population: Adults > 18 years old		
Intervention: Deprescribing (complete cessation) of cholinesterase inhibitors		
Setting: Primary care, residential care and hospital		
Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence (CoE) *Is there high or moderate certainty of evidence* Yes☐ No ☒	**CoE:** Low Our systematic review identified seven placebo-controlled randomised discontinuation versus continuation studies. Due to the study design (randomised controlled trial), the quality was originally rated as high, but was downgraded two levels due to risk of bias and indirectness. In particular, there were concerns about attrition bias, selective reporting of outcomes and pharmaceutical company sponsorship. Regarding imprecision, the main outcome measured (cognitive function) may be considered a surrogate measure for person-centred outcomes, there were strict inclusion criteria (younger population in most studies than the general population of people with dementia), and there was short duration of use prior to discontinuation in many of the studies.	
Balance of benefits and harms Is there certainty that the	Meta-analysis showed an increased risk of cognitive decline in those who discontinued versus those who continued. The magnitude of this effect is unclear due to different follow-up	**Indication and prior duration of use may affect the balance of risk and harms.** Is the baseline risk for benefit of **deprescribing** similar

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benefits of **deprescribing** outweigh the harms? Yes☐ No ☒	periods in the different studies, but can be estimated to be of modest clinical importance. There was a non-significant worsening in behavioural outcomes (NPI) in those who discontinued versus those who continued; however, this difference may not be clinically important. There was no significant difference observed in global change assessments or quality of life measures reported. Potential benefits of discontinuation of ChEIs include reduced use of psychotropic medications, reduced costs and reduced caregiver burden (found in non-RCT discontinuation versus continuation studies). Other unstudied benefits include reduced pill burden and reduction in the harms associated with polypharmacy.	across subgroups? Yes ☒ No ☐ Benefit from deprescribing is likely to be similar across all groups. Is the baseline risk for harm from **deprescribing** similar across subgroups? Yes☐ No ☒ **Indication:** In non-approved indications, there appears to be a minimal risk associated with deprescribing.
Is there certainty that the benefits of **continued use** outweigh the harms? Yes☐ No ☒	The benefit of ChEIs for cognition and global outcomes is modest and there are limited data on the long-term efficacy (> 12 months). There are a lack of unbiased data on the risk of harm from long-term use in a representative population. As such, there is no certainty that the benefits of continued use beyond 12 months outweigh the harms.	Is the baseline risk for benefit of **continued use** similar across subgroups? Yes☐ No ☒ **Indication:** There are different expected benefits depending on the indication in which it is being used, and severity of dementia (see 'Benefits'). **Duration of use:** The strongest and greatest evidence for benefit is in the first six to 12 months of use. Is the baseline risk for harm from **continued use** similar across subgroups?

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		Yes ☒ No ☐ The potential for harm is similar across indications and duration of use (although limited evidence on risks associated with long-term use). Potential for harm may vary in the individual depending on age, comorbidities, co-medications and frailty. Should there be separate recommendations for subgroups? Yes ☒ No ☐
Values and preferences Is there confidence in the estimate of relative importance of outcomes and individual preferences? Yes☒ No ☐	In general, younger and older adults would like to take fewer medications. Medication administration for people with dementia is burdensome to carers and nurses/care staff, and may be distressing for people with dementia, especially those with swallowing difficulties. While there may be concerns about discontinuing ChEIs, the consumer expectation for benefit of these medications is not in concordance with the evidence (see Consumer Values and Preferences section). Additionally, many of the outcomes highly valued by individuals/carers (such as quality of life and function) are understudied. Quality of life and global change (observable change in status) were not altered by discontinuation. None of the discontinuation studies captured individual/carer preferences/satisfaction.	**Perspective taken:** Individual's perspective—we have taken the view that people with dementia and their carers find medication administration burdensome and would trial stopping medications if their doctor said it was possible. We assume that if people with dementia/carers have realistic expectations of the true benefits of the medication, reduction in polypharmacy burden will likely outweigh potential ongoing benefits Sources of values and preferences: Non-systematic literature review. Source of variability, if any: Cannot estimate. Method for determining values satisfactory for this recommendation? Yes☒ No ☐ All critical outcomes measured? Yes☐ No ☒

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		The majority of the discontinuation studies did not measure important person-centred outcomes, including activities of daily living, quality of life and carer burden.
Resource implications *Are the resources worth the expected benefit?* Yes☒ No ☐	Cost-effective analyses on the use of ChEIs are based on data from relatively short-term use among younger and healthier participants with less severe stage of dementia than the real-world population of people with dementia. They often presume that the medications are discontinued on admission to a residential care facility. Depending on drug costs and other variables, these medications are not always considered cost-effective. There will be a reduction in cost associated with discontinuation of the medication; however, this will need to be balanced against possible increased clinician visits due to monitoring and possible re-occurrence of symptoms. A single cost-effectiveness study on deprescribing ChEIs has been published. No significant difference in costs was identified, but continuation was concluded to be cost-effective due to difference in quality-adjusted life year outcomes. There are significant limitations to this study that restrict its generalisability.	Feasibility: Is the intervention generally available? Yes☒ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes☒ No ☐ While there may be an initial increase in costs due to increased clinician visits, this may be offset in the long term through discontinuation of ongoing prescription and medication administration costs. Is there lots of variability in resource requirements across settings? Yes☒ No ☐ Deprescribing guidelines and implementation were felt to have relatively low resource requirements and feasibility in primary care and long-term care. However, resource requirements for monitoring after discontinuation may be different depending whether the person lives in the community with a carer, at home with professional care services, or in a residential care facility. In the community, unpaid carers may conduct the monitoring, although may require additional visits with a clinician. In the residential care setting, there may be increased use of paid healthcare professionals, but may not need to attend external appointments. Without further studies, it is not possible to

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		know whether these different settings will amount to different resource requirements. Additionally, drug price may differ by country/setting/over time.
Overall strength of recommendation: STRONG	Evidence of harm with discontinuation is low quality, with a small effect size in cognitive outcomes (no/minimal change in person-centred outcomes, such as function and quality of life, which carers value highly) in mostly non-generalisable populations. Two recommendations are provided with details about indication and duration of use to exclude those individuals who are at the greatest risk of harm due to discontinuation. The recommendation is also based on limitations in both the benefits and harms of long-term use. Also considered is the societal cost of inappropriate continuation of ChEIs and the feasibility of this intervention in primary care and long-term care. We assume that if consumers are provided with education on the potential benefits and harms of continuing versus the potential benefits and harms of discontinuing, with the knowledge that discontinuation was a trial, the majority would be open to the possibility of trial deprescribing. However, we acknowledge that this assumption is not based on prospective evidence.	
Values and assumptions	The recommendations place a high value on minimising polypharmacy and inappropriate medication use in a population that is particularly susceptible to medication harm (older adults with dementia). Through the development of this guideline and development of tools to assist implementation, we believe that the recommendations will be acceptable to stakeholders and feasible to implement. We also assume that the final decision to discontinue the medication will be made through shared decision making with the individual/family, taking into account individual values and preferences and the potential for benefit and harm. Additionally, discontinuation should be conducted with monitoring and re-initiation of the medication if necessary (see Clinical Considerations).	

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Table 12: GRADE Summary of Findings—Memantine

Quality assessment							Effect	Quality
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Cognitive function								
3 [74,84,86]	Open withdrawal of memantine versus withdrawal of placebo (randomised controlled trial study of treatment versus placebo, followed by discontinuation of both groups)	Serious risk of bias [1, 2, 3, 4]	No serious inconsistency	Very serious indirectness [5, 6, 7]	Serious [8, 9]	Two of the studies had some funding from pharmaceutical companies and the third did not report sponsorship	None of the studies found a significant difference between memantine and placebo discontinuation in cognitive outcome measures. Indication (n, tool): AIDS Dementia Complex (94, NPZ8): NPZ8 % score difference from baseline—placebo discontinuation (Median, 95% CI) 24 (−91–125) at end of treatment to 26 (−48–171) four weeks later. Memantine discontinuation 28 (−234–363) at end of treatment to 35 (−82–444) four weeks later. Difference from baseline (prior to any treatment) between the two groups, p = 0.54 [86]. Mild cognitive impairment (39, ADAS-Cog): 'surprisingly the COMBI group did not show a cognitive decline after medication (memantine) was tapered' (Figure 3—data not provided) [74]. PDD (24, MMSE): 'Statistically significant differences between groups on the … MMSE were not observed'. Placebo discontinuation MMSE = 20.9 (6.0) at end of drug treatment to 18.5 (6.7) six weeks later. Memantine discontinuation MMSE = 19.9 (6.3) at end of drug treatment to 16.9 (7.2) six weeks later [84].	⊕OOO VERY LOW
1 [87]	Open discontinuation of memantine before versus after	Serious risk of bias [1, 2, 10]	No serious inconsistency	Very serious indirectness [5, 6, 7, 11]	Serious [7, 8]	Study funded by a pharmaceutical company	Improvement in verbal learning and memory measures upon discontinuation. Indication (n, tool): Postmenopausal women at risk of dementia (17, neuropsychological test battery of cognitive skills): 'Examination of neuropsychological changes 6 months after discontinuation of memantine showed significant improvements in the Auditory Consonant Trigrams (ACT) 18-s delay (b =	⊕OOO VERY LOW

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							−1.085, 95% CI −2.146 to −0.024, p = 0.046), the CVLT-II total (b = −4.189, 95% CI −8.050 to −0.328, p = 0.035), the CVLT-II short delay-free recall (b = −0.418, 95% CI −0.760 to −0.077, p = 0.020), the CVLT-II long delay-free recall (b = −0.527, 95% CI −0.868 to −0.187, p = 0.005), the DKEFS Color-Word inhibition (b = −0.451, 95% CI −0.848 to −0.055, p = 0.028), the Color Trails 1 (b = 6.571, 95% CI 2.433 to 10.709, p = 0.004), the WMS-III Logical Memory 1 (b = −2.062, 95% CI −2.964 to −1.160, p < 0.001) and the WMS-III Logical Memory 2 (b = −1.345, 95% CI −2.232 to −0.459, p = 0.006).' [87]	
1 [67]	Non-randomised continuation versus discontinuation of memantine	Serious risk of bias [1, 12]	No serious inconsistency	Very serious indirectness [5, 7]	Serious [8, 13]	Conference abstract, results pertain to discontinuation of either memantine or ChEI	No difference between groups. Indication (n, tool): Advanced dementia (42, CPS): 'Over 18 months there continued to be no difference in any of the other measures [including CPS] between the two groups' [67].	⊕OOO VERY LOW
Global assessment of change or dementia stage								
2 [84,85]	Open withdrawal of memantine versus withdrawal of placebo (randomised controlled trial study of treatment versus placebo, followed by discontinuation of both groups)	Serious risk of bias [1, 2, 4]	No serious inconsistency	Very serious indirectness [5, 6, 11]	Serious [7, 14]	One of the studies was funded by a pharmaceutical company	No difference in change between groups of dementia stage or global change scores. In both studies, significantly more participants who had discontinued memantine had a worsening of their condition or recurrence of symptoms than those who had been on placebo. Indication (n, tool): PDD (24, DRS and CIBIC-Plus): Mean change in DRS: −2.7 points (memantine discontinuation) versus 1.0 point (placebo discontinuation), p = 0.7. Percentage deterioration after discontinuation = 70% (memantine) versus 29% (placebo), p = 0.04 [84]. PPD or DLB (44, CGIC and 'recurrence of symptoms'): CGIC change after discontinuation = 1.4 ± 1.2 (memantine) versus 0.8 ± 1.4 (placebo) Significant deterioration during washout within the memantine group (p<0.001) but not placebo group (p=0.06). No difference in change between the groups (p value not provided). 'No significant intergroup difference of change was detected (Mann–Whitney U-test)'. Fourteen out of 24 (58%) experienced recurrence of symptoms in the memantine discontinuation group versus five out of	⊕OOO VERY LOW

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							20 (25%) in the placebo discontinuation group, p = 0.04 [85].	
2 [67,88]	Non-randomised continuation versus discontinuation of memantine	Serious risk of bias [1, 12, 15, 16]	No serious inconsistency	Very serious indirectness [5]	Serious [8, 13, 14]	Conference abstract, results pertain to discontinuation of either memantine or ChEI One of the studies was funded by a pharmaceutical company	Indication (n, tool): Advanced dementia (42, FAST): 'Over 18 months there continued to be no difference in any of the other measures [including FAST] between the two groups' [67]. Nursing home residents (521, total AD symptom score): In adjusted analyses, there was a difference between groups of 1.36 ± 0.23 (equivalent to the emergence or worsening of one to two symptoms in the discontinuation group than in the continuation group).	⊕OOO VERY LOW
Behaviour								
1 [84]	Open withdrawal of memantine versus withdrawal of placebo (randomised controlled trial study of treatment versus placebo, followed by discontinuation of both groups)	Serious risk of bias [1]	No serious inconsistency	Very serious indirectness [5, 6, 11]	Serious [8, 9, 14]	One of the studies was funded by a pharmaceutical company	No difference in change in NPI between memantine and placebo discontinuation groups. Indication (n, tool): PDD (25, NPI): 'Statistically significant differences between groups on the NPI total and sub-scores (not shown) … were not observed'. Placebo discontinuation NPI = 13.5 (12.4) at end of drug treatment to 19.6 (11.0) six weeks later. Memantine discontinuation NPI = 11.5 (11.5) at end of drug treatment to 18.2 (14.6) six weeks later [84].	⊕OOO VERY LOW
1 [78]	Open discontinuation of memantine before versus after	Serious risk of bias [1, 10, 4]	No serious inconsistency	Very serious indirectness [5]	Serious [8]	Results pertain to discontinuation of either memantine or ChEI Authors declare COIs with pharmaceutical companies	Indication (n, tool): Late-stage dementia (18, NPI): No change in total NPI score before versus after (18.8 ± 14.4 to 20.4 ± 10.0, p = 0.47); however, significant worsening in apathy sub-score (increased 4.16 to 6.70, p = 0.048) [78].	⊕OOO VERY LOW
1 [67]	Non-randomised continuation versus discontinuation of memantine	Serious risk of bias [1, 12]	No serious inconsistency	Very serious indirectness [5]	Serious [8, 13]	Conference abstract, results pertain to discontinuation of either memantine or ChEI	Indication (n, tool): Advanced dementia (42, NPI): 'Over 18 months there continued to be no difference in any of the other measures [including NPI] between the two groups' [67].	⊕OOO VERY LOW
Quality of life								

0	No evidence available							

95% CI = 95% Confidence Interval, NPZ8 = Battery of eight neuropsychological performance tests, MCI = Mild Cognitive Impairment, ADAS-Cog = Alzheimer's Disease Assessment Scale—Cognitive subscale, PDD = Parkinson's Disease Dementia, MMSE = Mini-Mental State Examination, CPS = Cognitive Performance Scale, DRS = Dementia Rating Scale, CGI-C = Clinical Global Impressions of Change, CIBIC-Plus = Clinician's Interview-based Impression of Change Plus Caregiver Input, FAST = Functional Assessment Stage Tool, AD = Alzheimer's disease, NPI = Neuropsychiatric Inventory.

[1] Participants and personal/assessors were not blinded to discontinuation in one or more studies

[2] Large number of dropouts/uneven dropouts, did not complete final assessment after discontinuation.

[3] Discontinuation not part of original study design (one study).

[4] Possible/unclear selective reporting of outcomes.

[5] Inappropriate comparator/no comparator or potential for bias due to confounding

[6] Use in non-supported indications, and different populations (indications) in each study.

[7] Tools to assess cognitive function may not be related to person-centred outcomes.

[8] Small sample size.

[9] Wide confidence intervals/standard deviations.

[10] Potential for bias due to deviations from intended interventions

[11] Relatively small proportion of potential participants were eligible for inclusion and/or consented to inclusion.

[12] Participants self-selected for discontinuation.

[13] Full results not published (conference abstract only).

[14] Non-validated measure used (recurrence of symptoms as per case note review or 'Total AD symptom change' score generated from case note review).

[15] Confounding factor not fully accounted for (of the group that was reported to have discontinued for 'non-medical' reasons, 40% had unknown reasons).

[16] Unclear timing of measurements before and after discontinuation.

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Table 13: Evidence to Recommendations—Memantine

Question: Does deprescribing compared to continuing memantine use result in benefits or harms?		
Population: Adults > 18 years old		
Intervention: Deprescribing (complete cessation) of memantine		
Setting: Primary care, residential care and hospital		
Decision domain	Summary of reason for decision	Subdomains influencing decision
Certainty of evidence (CoE) *Is there high or moderate certainty of evidence?* Yes☐ No ☒	CoE: Very low No blinded, placebo-controlled RCTs of discontinuation versus continuation identified. Therefore, none of the studies were adequately designed to answer the question. A variety of study types, comparators and outcomes assessed in a large variety of participant populations were found. Significant limitations to the studies included insufficient sample sizes, lack of appropriate control and lack of blinding.	
Balance of benefits and harms Is there certainty that the benefits of **deprescribing** outweigh the harms? Yes☐ No ☒	Potential benefits of discontinuation of ChEIs include reduced use of psychotropic medications and removal of adverse drug reactions. Other unmeasured benefits include reduced pill burden, reduced costs, and reduction in the harms associated with polypharmacy. The very low quality of evidence limits the ability to clarify the benefits and harms of deprescribing memantine. The majority of studies and outcomes	**Indication for memantine treatment** Is the baseline risk for benefit of **deprescribing** similar across subgroups? Yes ☒ No ☐ Benefit from deprescribing is likely to be similar across all groups. Is the baseline risk for harm from **deprescribing** similar across subgroups Yes☐ No ☒

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	measured demonstrated no harm following discontinuation. Two studies found that a greater number of participants discontinuing memantine experienced a worsening of overall symptoms than did those discontinuing placebo. From the identified studies, in populations with established indications (AD) and indications with some evidence of benefit (PDD and LBD), there may be a return of condition when stopping the medication prior to 12 months of use. For indications without evidence to support a benefit, there appeared to be no harm in deprescribing.	In studies with participants with AD, PDD and DLB and treatment duration < 12 months, there may be some potential for harm (return of symptoms). In non-supported indications (prevention of dementia, AIDS Dementia Complex, advanced dementia) and use for > 12 months, the potential for harm appears to be less.
Is there certainty that the benefits of **continued use** outweigh the harms? Yes☐ No ☒	The benefit of memantine on cognition and global outcomes is modest and there are limited data on the long-term efficacy (> 12 months). While the risk of harm of memantine use appears to be minimal, long-term data in a representative population are lacking. As such, there is no certainty that the benefits of continued use outweigh the harms.	Is the baseline risk for benefit of **continued use** similar across subgroups? Yes☐ No ☒ The strongest evidence for benefit of memantine is for the indication AD. There is limited evidence of a benefit on overall condition in PDD and DLB. There is no, or negative, evidence of a benefit of memantine use in other indications. Is the baseline risk for harm from **continued use** similar across subgroups Yes ☒ No ☐ Should there be separate recommendations for subgroups? Yes ☒ No ☐

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Values and preferences Is there confidence in the estimate of relative importance of outcomes and individual preferences? Yes☒ No ☐	In general, younger and older adults would like to take fewer medications. Medication administration for people with dementia is burdensome to carers and nurses/care staff, and may be distressing to people with severe dementia, especially those with swallowing difficulties. People with dementia value independence and remaining at home. However, memantine is indicated in people with severe dementia, where these may no longer be treatment goals. Some individuals/carers may prefer to continue the medication due to a high level of hope that is placed on the medication and fear associated with discontinuation. None of the discontinuation studies captured individual/carer preferences, although one of the studies only conducted discontinuation with people who were willing to have the medication stopped.	**Perspective taken:** Individual's perspective—we have taken the view that people with dementia and their carers find medication administration burdensome and would stop medications if their doctor said it was possible. We assume that where individuals/carers have realistic expectations of the true benefits of the medication, reduction in polypharmacy burden will likely outweigh potential ongoing benefits Sources of values and preferences: Non-systematic literature review. Source of variability, if any: Cannot estimate. Method for determining values satisfactory for this recommendation? Yes☒ No ☐ All critical outcomes measured? Yes☐ No ☒ The majority of the discontinuation studies did not measure important person-centred outcomes, including activities of daily living, quality of life and carer burden.
Resource implications *Are the resources worth the expected benefit?* Yes☒ No ☐	Cost-effective analyses on the use of memantine do not always indicate a benefit. There will be a reduction in cost associated with discontinuation of the medication; however, this will need to be balanced against possible increased clinician visits due to monitoring and possible re-occurrence of	Feasibility: Is the intervention generally available? Yes☒ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes☒ No ☐

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	symptoms. There were no cost-effectiveness analyses on deprescribing memantine identified.	While there may be an initial increase in costs due to increased clinician visits, this may be offset long term through discontinuation of ongoing prescription and medication administration costs. Is there lots of variability in resource requirements across settings? Yes☒ No ☐ Deprescribing guidelines and implementation were felt to have relatively low resource requirements and feasibility in primary care and long-term care. However, resource requirements for monitoring after discontinuation may be different, depending whether the person lives in the community with a carer, receives at-home professional care services, or is in a residential care facility. In the community, unpaid carers may conduct the monitoring, although may require additional visits with a clinician. In the residential care setting, there may be increased use of paid healthcare professionals, but may not need to attend external appointments. Without further studies, it is not possible to know whether these different settings will amount to different resource requirements. Additionally, drug price may differ by country/setting/over time.
Overall strength of recommendation: STRONG	This strength is based on the lack of evidence of significant harms associated with discontinuation versus continuation, and lack of evidence of benefit of continued use of memantine, the societal cost of inappropriate memantine use, and the feasibility of this intervention in primary care and long-term care.	
Values and assumptions	The recommendations place a high value on minimising polypharmacy and inappropriate medication use in a population that is particularly susceptible to medication harm (older adults with dementia). Through developing this guideline and developing tools to assist implementation, we believe that the recommendations will be acceptable to stakeholders and feasible to implement.	

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	We also assume that the final decision to discontinue the medication will be made through shared decision making with the individual/family, taking into account individual values and preferences and the potential for benefit and harm. Additionally, discontinuation should be conducted with monitoring and re-initiation of the medication if necessary (see Clinical Considerations).

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Appendix 3: Other Relevant Guidelines

Search strategy for identifying relevant guidelines

Guidelines were included if they were less than 10 years old, were reported to follow a guideline development process, were national (not based on a single institution) and were the most current from the developing organisation. We searched for guidelines for the following countries: Australia, Canada, the US and the UK. We conducted targeted searches using Google and Google Scholar with relevant keywords. We also searched the Australian NHMRC Clinical Practice Guideline Portal, Canadian Medical Association Clinical Practice Guideline Portal, National Guidelines Clearinghouse, National Institute of Health and Clinical Excellence (NICE) and Guidelines International Network (GIN). We also identified a systematic review of dementia guidelines published in 2015 [95], and several of the guidelines appeared in our systematic review of the outcomes of deprescribing ChEIs and/or memantine.

Deprescribing recommendations contained within national treatment guidelines

Table 14: Recommendations regarding deprescribing in previously developed guidelines

Country (reference)	Year	Developing organisation	Specific recommendation on when to stop
Australia [89]	2016	Developed by the NHMRC Partnership Centre for Dealing with Cognitive and Related Functional Decline in Older People; Recommendations approved by the National Health and Medical Research Council (NHMRC)	'People who have been prescribed an acetylcholinesterase inhibitor or memantine should be reviewed within a short time (e.g., one month) for evaluation of adverse effects and dose titration and within six months, to determine whether there is a clinically meaningful response to treatment. Review and consideration of de-prescribing is recommended at regular intervals including at the time of admission to residential care.' *(This recommendation is listed as a 'Practice Point: A recommendation that is outside the scope of the search strategy for the systematic evidence review and is based on expert opinion'.)*
Canada [91]	2012	Canadian Consensus Conference	'Recommendations regarding discontinuation of cholinesterase inhibitors • Discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer's disease may lead to worsening of cognitive function and greater functional impairment as compared to continued therapy (Grade 2B). This must be balanced with the risk for known

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			side-effects and drug costs if therapy continues. It is suggested that cholinesterase inhibitors be discontinued when: a) The patient and/or their proxy decision-maker decide to stop after being appraised of the risks and benefits of continuation and discontinuation; b) The patient is sufficiently non-adherent with the medication that continued prescription of it would be useless, and it is not possible to establish a system for the administration of the medication to rectify the problem; c) The patient's rate of cognitive, functional, and/or behavioural decline is greater on treatment compared to that prior to being treated; d) The patient experiences intolerable side effects that are definitely or probably related to the cholinesterase inhibitor; e) The comorbidities of the patient make continued use of the agent either unacceptably risky or futile (e.g., terminally ill); f) The patient's dementia progresses to a stage (e.g., Global Deterioration Scale stage 7) where there would be no clinically meaningful benefit from continued therapy. • When a decision has been made to discontinue therapy because of a perceived lack of effectiveness, it is suggested that the dose be tapered before stopping the agent and that the patient be monitored over the next 1-3 months for evidence of an observable decline. If this occurs, it is suggested that consideration be given to reinstating therapy (Grade 2C).'
UK [92]	2006 (updated September 2016)	National Collaborating Centre for Mental Health, in partnership with the Social Care Institute for Excellence, commissioned by	'Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.'

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		the National Institute for Health and Care Excellence (NICE)	
UK [93]	2011	British Association for Psychopharmacology	Nil.
US [94]	2007 (updated in 2014)	American Psychiatric Association	'If the benefit of a medication is unclear, a brief medication-free trial may be used to assess whether continued treatment is worthwhile.' 'It is uncertain how long patients should be treated with cholinesterase inhibitors.' 'In practice, the decision whether to continue treatment with cholinesterase inhibitors is a highly individualized one. Reasons that patients choose to stop taking these medications include side effects, adverse events, lack of motivation, lack of perceived efficacy, and cost. Individual patients may be observed to have some stabilization of symptoms or slowing of their decline. Under these circumstances, a physician might consider continuing the medication. Conversely, a patient who is declining rapidly despite taking cholinesterase inhibitors may be considered a medication nonresponder, and the medication can be discontinued. Discontinuation of cholinesterase inhibitor medication during placebo-controlled trials after 12–24 weeks has been associated with a regression of cognitive improvement to the level of the associated placebo group. Whether resumption of the cholinesterase inhibitor reverses this symptomatic worsening is unclear. Some patients have shown pronounced deterioration within several weeks of discontinuing cholinesterase inhibitors and improvement when the medication has been restarted. In contrast, the results of one study suggested that donepezil-treated patients who had treatment interrupted for 6 weeks and then restarted treatment never regained cognition back

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			to the level achieved before medication discontinuation.' *This guideline does not contain succinct recommendations (but rather presents a literature review). The quotes above are a representation of the content of this guideline regarding deprescribing.*
US [322]	2008 (reaffirmed April 2013)	American College of Physicians and the American Academy of Family Physicians	'Evidence is insufficient to determine the optimal duration of therapy. A beneficial effect, if any, would generally be observed within 3 months on the basis of duration of trials. This effect could be an improvement or stabilization. In addition, no evidence demonstrates when it is appropriate to stop the treatment if the patient becomes unresponsive or shows decline in various domains of dementia. However, if slowing decline is no longer a goal, treatment with memantine or a cholinesterase inhibitor is no longer appropriate.'
International [90]	2011	World Federation of Societies of Biological Psychiatry	'The end of treatment should depend on an individual decision (Level C3, Grade 4). It should be discontinued if there are significant adverse effects or after consensus with patients and relatives/caregivers/legal representatives (Level C3, Grade 4).' 'Any significant deterioration in the patient's condition should lead to a rigorous re-assessment of the diagnosis and a work-up on potential intercurrent diseases, but not automatically to discontinuation of anti-dementia drugs. All patients on long-term treatment should be reassessed at least every 6 months (Level C3, Grade 4).'

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