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

Technical Report

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

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Developing organisations:

The University of Sydney, NHMRC Partnership Centre: Dealing with Cognitive and Related Functional Decline in Older People (Cognitive Decline Partnership Centre) and Bruyère Research Institute, Deprescribing Guidelines in the Elderly Project

Contents

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.

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 (such as, 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.

This guideline does not dictate the type of professional (based on training, qualifications and experience) who is suitable to conduct deprescribing (with appropriate consultation, such as with family members). 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 of the full Guideline.

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 (medications currently approved and marketed in Australia and Canada). This guideline 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. People with dementia who are not taking one of the above listed medications are not covered by this guideline.

Clinical research questions

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

Box 1: PICOS 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 and psychological 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 (of person with dementia and their carer)
Study design	Primary study design of interest: blinded randomised controlled trial Additional study designs included in systematic review[±]: non-randomised controlled studies (cohort and case controlled) OR pilot/feasibility interventional studies OR before–after interventional studies (controlled and uncontrolled) OR observational, prospective or retrospective before and after studies

[†] This was our ideal control population; however, because we found no studies that included this control population for memantine discontinuation in a preliminary scoping review, we also included studies without this control.

[±] We proposed that non-randomised controlled trials and other study designs may provide additional information to inform the recommendations and/or the clinical considerations section. No randomised controlled trials were identified for memantine; thus, these other study types were used for this medication.

Method of Systematic Review

The systematic review was registered on PROSPERO prior to beginning the review (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016053544).

Date of search

July 2016

Databases searched

PubMed, EMBASE, International Pharmaceutical Abstracts, PsycINFO, Scopus, Cochrane Library (including the Cochrane Central Register of Controlled Trials) and Clinicaltrials.gov.

Search terms

Three categories of search terms (concepts) were used:

1. Key words and MeSH terms related to deprescribing (e.g. withdrawal, discontinuation, cessation) **AND**
2. Key words and MeSH terms related to the condition which these medications are prescribed for (e.g. dementia) **AND**
3. Key words and MeSH terms related to ChEIs and memantine (including generic drug names and brand names)

Full search strategy all databases is provided in Appendix 1: Search terms.

Note: no population groups were specified in the search strategy. A separate search was conducted to inform the care of Aboriginal and Torres Strait Islander people and other indigenous and minority populations as outlined in the 'Clinical Considerations' section of the main guideline document.

Limitations

No limitations were used in the search strategy. Where non-English articles were considered potentially relevant for inclusion, colleagues with fluency in this language were identified to assist. These individuals are noted in the Administrative Report.

Inclusion/exclusion criteria

Inclusion criteria

- Original research
- Study type: Randomised controlled trials OR non-randomised controlled studies (cohort and case controlled) OR pilot/feasibility interventional studies OR before-after interventional studies (controlled and uncontrolled) OR observational, prospective or retrospective before and after studies
- Age ≥ 18 years' old
- Participants must be taking donepezil, rivastigmine, galantamine, tacrine (included in systematic review but not considered relevant for the guideline) or memantine
- Target medication must have been prescribed for > 1 week prior to withdrawal/dose reduction (could be initiated prior to study or within study) – at a dose which is at least minimum effective dose (defined by the Australian Medicines Handbook [1])
- Outcomes must be measured > 1 week after withdrawal or dose reduction
- Outcomes (as stipulated below) must be measured **before and after** discontinuation/dose reduction (must be measured at a specific point consistent across participants, e.g. at time of discontinuation and 6 weeks after discontinuation).

Exclusion criteria

- Study type: Case reports/case series OR pharmaco-epidemiological studies where prevalence of use only is reported (i.e. number of participants who stopped versus continued, or where before/after participants are not matched)
- Animal studies
- Studies conducted in healthy volunteers (as defined by the manuscript)
- Studies which conduct a medication review with discontinuation of multiple medications (which may or may not include ChEIs and memantine), unless data on discontinuation of these medications is presented separately
- Participants switched immediately to another medication for the same condition (for example, another ChEI or memantine) with no washout period (or where data not presented at point of discontinuation and prior to initiation of another medication)

- Studies which compare continuers to discontinuers, including those which measure outcomes before and after, but where measurement of outcomes is not a consistent time point relative to time of discontinuation across participants. (For example, outcomes measured on all participants at the start and end of a 12 month period – with data split based on whether or not participants discontinued the medication at any point during the 12 month period.)

Outcome(s) of interest

Primary outcomes

- Cognition
- Behavioural symptoms
- Global change in condition/dementia stage (as 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)

Secondary outcomes

- Person/carer relevant outcomes
    - Individual symptom monitoring
    - Goal attainment
    - Satisfaction with treatment
    - Carer burden/distress
    - Patient choices/wishes – advanced care outcomes
- Mortality
- Hospitalisation
- ED room visits
- Health services utilisation
- Residential aged care facility admission
- Functional outcomes (including disability)
- Benefits of withdrawal (reversal of adverse drug reactions)
- Adverse drug withdrawal events
- Cost benefits and/or cost effectiveness

Data extraction (selection and coding)

Three reviewers were involved in screening titles/abstracts (ER, LKO, CL). ER screened all abstracts while LKO and CL screened half each, ensuring each title was screened independently by two people. Any title which was deemed as potentially included by one or more reviewers had its full text retrieved. Full texts were then reviewed independently by two reviewers for inclusion (similarly to the screening process, ER reviewed all the full texts and LKO and ES reviewed half each). If discrepancies occurred, a third, senior team member (SH) reviewed the discrepancies and determined inclusion.

Data extracted (independently by two reviewers) included:

- Article details (title, authors, year of publication)
- Sponsor/funder details/conflicts of interest
- Study type
- Important study inclusion/exclusion criteria
- Population (type and severity of dementia/other condition, place of residence, age range and mean)
- Medication withdrawn – including duration of use prior to withdrawal/dose reduction
- Process of withdrawal (taper vs. abrupt cessation)
- Outcomes measured (as per list above), including timing after withdrawal and results

Data extraction for meta-analysis

Data that was to be included in the meta-analysis was extracted directly from each article and the online supplementary material where possible (by two individuals independently). We contacted the authors of the original articles and those of a previous meta-analysis [2] to retrieve missing data for some of the articles. Following this, some information was still missing but was extracted from graphs in two of the original articles [3,4] using the digitize [5] package in R [6]. Two of the studies [3,7] used the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) and not the Mini-mental State Examination (MMSE). We converted ADAS-Cog scores to MMSE scores using the formula from Doraiswamy et al.[8] as was done in a previous meta-analysis [2].

Strategy for data synthesis

Studies were grouped according to type of study and synthesised descriptively. Meta-analyses of the randomised controlled trials of continuation versus discontinuation were conducted for cognitive and neuropsychiatric symptom outcomes.

The meta-analysis for cognitive outcomes was performed using R (version 3.3.2) [6]. We calculated standardised mean differences (SMD) and 95% confidence intervals using a random effects model. We used I^2 as a measure of inconsistency. We followed the same procedure and conducted a meta-analysis on the three studies that included the Neuropsychiatric Inventory (NPI) as an outcome.

Analysis of subgroups or subsets

In analysis, studies were grouped based on the indication for use (approved versus non-approved indications) and duration of use prior to discontinuation (<12 months versus ≥ 12 months, long term use definition [9]).

Specifically, with our meta-analysis we conducted two sensitivity analyses: one with the six studies which all included participants with AD (excluded the article by Kertesz [10] as the population in this study did not have an approved indication for use of ChEIs) and one with three studies with long term users of ChEIs (duration of use prior to discontinuation ≥ 12 months).

Risk of bias and quality assessment

Risk of bias assessment was conducted by two authors independently (ER and WT) using one of the two tools: Cochrane Risk of Bias (RoB) [11] (randomized controlled trials), ROBINS-I [12] (all other study types). For the randomised controlled trials we considered sample size calculations and pharmaceutical company influence as 'other bias'.

GRADE recommendations were followed to determine the quality of the evidence [13]. For each of our primary outcomes, we first assessed the risk of bias, inconsistency, indirectness, imprecision and other considerations. Each of these were then determined to have a very serious, serious, or not serious impact on the quality of the outcome. The risk of bias was assessed by reviewing the Cochrane Risk of Bias and the ROBINS-I tool results. To summarise the risk of bias across studies, we considered the risk of bias of each study in the context of their level of contribution to the estimated magnitude of effect (especially where a meta-analysis was conducted) [14]. The sources of bias for each of the outcomes are reported as footnotes in the table. Inconsistency was assessed via heterogeneity (p-values and I^2) for the outcomes of ChEI discontinuation which had a meta-analysis conducted. For the outcomes that we could not conduct a meta-analysis (ChEI global assessment of change and quality of life, and all memantine outcomes), inconsistency was assessed by considering whether the same result

was found across studies in direction, magnitude (i.e. point estimates) and significance (including overlap of confidence intervals) [15]. Indirectness was assessed by reviewing the inclusion criteria of the studies (i.e. the population) and the relevance of the tools used to measure change to person-centred outcomes. In particular, indication for use (e.g. approved versus non-approved indications), age of participants, and exclusion criteria (such as requiring a carer and/or being in 'good health') were considered and compared with the wider population of people with dementia [16]. Imprecision was determined by examining the confidence interval of the meta-analysis or the individual studies which reported such a result (where a meta-analysis was not able to be conducted) [17]. We determined that it would be appropriate to consider the role that pharmaceutical companies played in each of the included studies (e.g. as a funder, employer of authors etc). This was reported, but was not considered in the overall assessment of the quality for each outcome (described as follows).

The GRADE approach results in the assessment of the quality of the evidence to be high, moderate, low or very low. Studies with a RCT design (ChEI studies) began at a high quality of evidence, while non-RCT studies (memantine studies) started at a low quality of evidence. While some of the memantine studies contained an RCT design of treatment versus placebo, the withdrawal aspect (of which the relevant results were extracted) was not randomised. Therefore we considered it appropriate to start these studies at a low quality. This assessment was then downgraded depending whether there were serious (-1 level) or very serious (-2 levels) concerns about the risk of bias, inconsistency, indirectness and/or imprecision. The quality could be upgraded if there was a large effect, evidence of a dose response or if all plausible residual confounding would either reduce a demonstrated effect or would suggest a spurious effect if no effect had been observed [13]. Once this had been conducted for each outcome, the lowest rating of quality (across outcomes) was assigned to the recommendations which resulted from that set of evidence.

The above described process was conducted by ER and reviewed by WT with discussion to gain consensus.

Results of the Systematic Review

A total of 5,849 records were retrieved (after removal of duplicates) from our search strategy. Of these, 272 were determined to be potentially eligible and had their full text retrieved and reviewed. Forty-five studies were eligible for inclusion in this review (including one additional study identified through hand-searching of reference lists):

- 7 randomised controlled trials of continuation versus discontinuation of ChEIs (donepezil, rivastigmine and galantamine)
- 32[†] studies of ChEI discontinuation (not classified as a randomised controlled trial of continuation versus discontinuation), including one on tacrine discontinuation (not used for the guideline)
- 1 study of ChEI dose reduction
- 8[†] studies of memantine discontinuation (not classified as a randomised controlled trial of continuation versus discontinuation)

[†] 3 studies involved discontinuation of ChEI and/or memantine and are included in both counts.

Using the highest available quality of evidence for each of the medication classes (ChEIs and memantine), we used the 7 randomised controlled trials of continuation versus discontinuation of ChEIs to primarily inform development of the ChEI recommendations. No randomised controlled trials of continuation versus discontinuation of memantine were identified. Thus we included the 8 studies of outcomes after memantine withdrawal; open discontinuation of memantine versus discontinuation of placebo (following a placebo controlled randomised controlled trial: 4 studies), before versus after interventional studies (2 studies) and non-randomised observational studies of continuation versus discontinuation (2 studies). See 'Summary of Findings' the full Guideline for further details.

Table 1 (ChEIs) and Table 2 (memantine) provide details on the study design, outcomes, level of evidence, findings of the meta-analysis (where performed) and other relevant information. Table 3, Table 4 and Table 5 show the results of the risk of bias assessment of the ChEI and memantine studies.

For each of the outcomes of the ChEI studies, the quality of the evidence was downgraded by two levels from high quality to low quality. The downgrades were based on serious risk of bias (-1) and serious indirectness (-1). The main risks of bias arose from unclear randomisation, allocation concealment and blinding of personnel conducting the outcome assessments as well as attrition bias and selective reporting of results. The major concerns relating to indirectness were the use of tools which may not assess person-relevant outcomes, age of participants lower than that of the wider population of people with dementia and exclusion criteria based

on comorbidities and comedications (i.e. the population in the study may not be a good representation of the wider population of users). For the outcomes of the memantine studies, the quality of the evidence was downgraded one level from low to very low quality (limited ability to downgrade by only one level as very low is the lowest category). Again, the main concerns were related to risk of bias and serious indirectness as well as imprecision. The risk of bias arose from lack of blinding, deviations from original interventions and large numbers of dropouts (especially uneven numbers of dropouts). Use of inappropriate comparators, participants with non-supported indications and large proportions of potentially eligible participants not included/enrolled contributed to concerns about indirectness. Imprecision was influenced by the small sample sizes of the majority of studies, which led to large confidence intervals/standard deviations. Additionally, one of the studies was published as a conference abstract only and another used a non-validated measure for outcomes. These assessments were consistent across all outcomes, therefore the overall rating of the quality of evidence for the outcomes of ChEI discontinuation was low and memantine discontinuation was very low. Footnotes in Table 1 and Table 2 detail these concerns and which outcomes they are relevant to.

Table 1: 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 [3,7,10,18–21] 949 participants	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 among those who discontinued versus those who continued. SMD 0.40 (95% CI = 0.23–0.57).	⊕⊕OO LOW
Global assessment of change or dementia stage								
3 [7,10,18] 213 participants	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 because of 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 [10,18–21] 699 participants	Placebo-controlled randomised discontinuation versus continuation	Serious risk of bias [2, 3, 4, 5]	No serious inconsistency [13]	Serious indirectness [8, 9, 11]	No serious imprecision	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]: SMD = 0.20, 95% CI = -0.24–0.65. Two studies not included in meta-analysis: NPI-NH: 3.6 ± 12.6 (discontinuation) versus	⊕⊕OO LOW

						-1.1 ± 8.9, p = 0.24 [62]. 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 [18,21] 335 participants	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 seven 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/CI reported in one study.

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

Table 2: GRADE Summary of Findings - Memantine

Quality assessment							Effect	Quality
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Cognitive function								
3 [22–24] 158 participants	Open withdrawal of memantine versus withdrawal of placebo (RCT 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]. MCI (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	⊕OOO VERY LOW

							[84].	
1 [25] 17 participants	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 = -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].	⊕OOO VERY LOW
1 [26] 42 participants	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 and 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 [24,27] 69 participants	Open withdrawal of memantine versus withdrawal of	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	No difference in change between groups of dementia stage or global change scores. In both studies, significantly more participants	⊕OOO VERY LOW

	placebo (RCT study of treatment versus placebo, followed by discontinuation of both groups)					pharmaceutical company	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, CGI-C and 'recurrence of symptoms'): CGI-C change after discontinuation = 1.4 ± 1.2 (memantine) versus 0.8 ± 1.4 (placebo). Significant deterioration during washout in the memantine group (p < 0.001), but not in the 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%) participants experienced recurrence of symptoms in the memantine discontinuation group, compared with five out of 20 participants (25%) in the placebo discontinuation group, p = 0.04 [85].	
2 [26,28] 563 participants	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 and results pertain to discontinuation of either memantine or ChEI One of the studies was	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	⊕OOO VERY LOW

						funded by a pharmaceutical company	worsening of one to two symptoms).	
Behaviour								
1 [24] 25 participants	Open withdrawal of memantine versus withdrawal of placebo (RCT 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 [29] 24 participants	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 [26] 42 participants	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 and 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 because of 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 because of 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.

Table 3: Risk of bias assessment of ChEI studies (Cochrane Risk of Bias assessment tool)

	Random sequence generation (selection bias)	**Allocation concealment** (selection bias)	**Blinding of participants and personnel** (performance bias)	**Blinding of outcome assessment** (detection bias)	**Incomplete outcome data addressed** (attrition bias)	**Selective reporting** (reporting bias)	**Other bias**
Gaudig 2011	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Holmes 2004	Low	Low	Unclear	Unclear	High	Unclear	Low
Howard 2012	Low	Low	Low	Low	Unclear	High	High
Johannsen 2006	Low	Unclear	Unclear	Unclear	High	Unclear	High
Scarpini 2011	Low	Unclear	Unclear	Unclear	High	High	High
Herrmann 2016	Low	Unclear	Low	Low	Unclear	Unclear	Low
Kertesz 2008	Low	Unclear	Low	Low	Low	High	Unclear

Table 4: Risk of bias assessment of memantine RCTs (Cochrane Risk of Bias assessment tool)

	Random sequence generation (selection bias)	**Allocation concealment** (selection bias)	**Blinding of participants and personnel** (performance bias)	**Blinding of outcome assessment** (detection bias)	**Incomplete outcome data addressed** (attrition bias)	**Selective reporting** (reporting bias)	**Other bias**
Johansson 2011	Low	Low	Low	Unclear	High	High	High
Leroi 2009	Unclear	Unclear	High	High	Unclear	Low	Unclear
Peters 2012	Unclear	High	High	High	Unclear	High	High
Schiffito 2007	Low	Unclear	Unclear	Unclear	High	Low	High

Table 5: Risk of bias assessment of memantine non-RCTs (ROBINS-I)

	Bias due to confounding	Bias in selection of participants onto the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Wroolie 2009	Serious	Serious	Low	Serious	Serious	Serious	Low
Cros 2013	Serious	Low	Low	Serious	Low	Serious	Low
Burns 2010	Serious	Low	Low	NI	NI	Serious	NI
Fillit 2010	Serious	Serious	Low	Low	NI	Serious	Low

NI=No Information

Method of review of harms

A review of reviews was conducted to inform the section on the potential harms of ChEIs and memantine. To conduct this review of harms, we searched PubMed with terms related to ChEIs and memantine, adverse drug reactions (ADRs) and systematic reviews to identify relevant reviews on the potential harms of these medications. Additionally, we used reference lists of national guidelines (see Apendix 3 in the full Guideline) and searched the Cochrane library for the most recent meta-analyses that presented the harms of donepezil, rivastigmine, galantamine and/or memantine (search strategy: cholinesterase inhibitor, donepezil, rivastigmine, galantamine or memantine, limited to the past 10 years). We considered all ChEIs to be equal in potential toxicity and only utilised reviews/studies of specific ChEIs if no grouped studies were identified.

The search was conducted on the 16th of Novemeber 2016. The search strategy for PubMed was as follows:

((donepezil* OR galantamine[MeSH Terms] OR galantamin* OR galanthamin* OR memantine[MeSH Terms] OR memantin* OR rivastigmi* OR cholinesterase inhibitors[MeSH Terms] OR anticholinesterase* OR anti-cholinesterase* OR acetylcholinesterase inhibitor* OR cholinesterase inhibitor*) AND ((adverse drug event[MeSH Terms] OR Drug Toxicities [MeSH] OR adverse drug event*[Text Word] OR adverse event*[Text Word] OR adverse drug reaction*[Text Word] OR adverse reaction*[Text Word] OR side effect*[Text Word] OR unwanted effect*[Text Word] OR unwanted reaction*[Text Word] OR ADR*OR toxicit*) OR (cardiovascular* OR bradycardia* OR syncope* OR falls OR falling OR fracture* OR pulmonary OR lung* OR seizure* OR gastrointestinal bleed* OR ulcer* OR gastrointestinal haemorrhage* OR weight loss[Text Word] OR anorexia* OR insomnia* OR Pisa* OR incontinence*)) AND (systematic review*[Text Word]) OR meta analysis*[Text Word] OR meta-analysis*[Text Word] OR narrative review*[Text Word] OR sysrev_methods [sb]))

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Appendix 1: Search terms

Database	Concept 1: withdrawal/deprescribing terms – any of these terms combined with OR	Concept 2: disease terms (dementia expanded) – any of these terms combined with OR	Concept 3: drug names – any of these combined with OR
	Concept 1 AND Concept 2 AND Concept 3 *all fields were searched unless otherwise specified*		
PubMed	deprescription[MeSH Terms] OR deprescri* OR de-prescri* OR discontinu* OR withdraw* OR cessat* OR ceas* OR stop* OR reduc* OR taper* OR witheld* OR washout* OR persistence* OR substance withdrawal syndrome[MeSH Terms] OR adherence, medication[MeSH Terms] OR compliance, patient[MeSH Terms] OR adhere* OR compliance* OR halt* OR suspend* OR terminat* OR decreas*	mild cognitive impairment[MeSH Terms] OR lewy body disease[MeSH Terms] OR frontotemporal dementia[MeSH Terms] OR dementia, vascular[MeSH Terms] OR dementia, multiinfarct[MeSH Terms] OR alzheimer disease[MeSH Terms] OR dementia[MeSH Terms] OR Neurocognitive Disorders[MeSH Terms] OR memory disorder[MeSH Terms] OR lewy* OR alzheimer* OR cognitive deficit*[tw] OR cognition deficit*[tw] OR cognitive declin*[tw] OR cognition declin*[tw] OR memory disorder*[tw] OR mild cognitive impairment*[tw] OR minor neurocognitive	Class: ((((anticholinesterase*) OR anti-cholinesterase*) OR acetylcholinesterase inhibitor*) OR cholinesterase inhibitor*) OR cholinesterase inhibitors[MeSH Terms] Donepezil: ((((E2020) OR donepezil*) OR donezepil*)) OR ((((((((((((((((((((oneza[tw]) OR mazil[tw]) OR memac[tw]) OR memkar[tw]) OR memoboost[tw]) OR memocept[tw]) OR memorit[tw]) OR mensapex[tw]) OR miltus[tw]) OR navazil[tw]) OR nepanizil[tw]) OR nepezil[tw]) OR nepla[tw]) OR niritos[tw]) OR nomi-nox[tw]) OR nopez[tw]) OR nozil[tw]) OR nuo chong[tw]) OR oldinot[tw]) OR onefin[tw]))) OR (((((((((((((((((((((((((((((((((zopitel[tw]) OR palixid[tw]) OR pamigen[tw]) OR paxel[tw]) OR penezil[tw]) OR pezale[tw]) OR pezil[tw]) OR peziled[tw]) OR pezilgen[tw]) OR promemore[tw]) OR rafazil[tw]) OR razil[tw]) OR redumas[tw]) OR remoplix[tw]) OR rewind[tw]) OR ricordo[tw]) OR sai ling si[tw]) OR servonex[tw]) OR sib o hai[tw]) OR sulbenin[tw]) OR symepezil[tw]) OR tactrol[tw]) OR tolerdilan[tw]) OR tonizep[tw]) OR torpezil[tw]) OR valpex[tw]) OR vastia[tw]) OR venaxen[tw]) OR yasnal[tw]) OR yasnoro[tw]) OR zakalmer[tw]) OR zhedon[tw]) OR ziledon[tw]) OR zinocept[tw]) OR zolpezil[tw])) OR ((((((((((((((((((((((((((((lizidra[tw]) OR gai fei[tw]) OR endoclar[tw]) OR epez[tw]) OR eranz[tw]) OR evimal[tw]) OR ezida[tw]) OR fang qing[tw]) OR filosept[tw]) OR fincip[tw]) OR fordesia[tw]) OR fremptel[tw]) OR fu si ke[tw]) OR genezil[tw]) OR hania[tw]) OR jia qi[tw]) OR kibilis[tw]) OR kognezil[tw]) OR labrea[tw]) OR landex[tw]) OR lirpan[tw]) OR lixben[tw])) OR ((dozyl[tw]) OR damzipil[tw]) OR danpezil[tw]) OR davia[tw]) OR dazolin[tw]) OR demelan[tw]) OR dementis[tw]) OR demenza[tw]) OR dentap[tw]) OR depzil[tw]) OR dezira[tw]) OR dilpeze[tw]) OR divare[tw]) OR dizil[tw]) OR dobedipil[tw]) OR doenza[tw])

		disorder*[tw] OR major neurocognitive disorder*[tw] OR dement* OR amnesi* OR lewy body disease[MeSH Terms]) OR mild cognitive impairment[MeSH Terms])	OR dolizi[tw]) OR domethan[tw]) OR donaccord[tw]) OR donacept[tw]) OR donasure[tw]) OR donaz[tw]) OR donecept[tw]) OR donecil[tw]) OR donecleus[tw]) OR donectil[tw]) OR donefix[tw]) OR donegal[tw]) OR donelet[tw]) OR donelinn[tw]) OR donemed[tw]) OR donep[tw]) OR donepes[tw]) OR donepex[tw]) OR donepil[tw]) OR doneprion[tw]) OR donept[tw]) OR doneratio[tw]) OR donesan[tw]) OR donespes[tw]) OR donester[tw]) OR donesyn[tw]) OR donezel[tw]) OR donezil[tw]) OR donila[tw]) OR donnox[tw]) OR donopez[tw]) OR donpethon[tw]) OR donpex[tw]) OR donzeimer[tw]) OR dopaben[tw]) OR dopezil[tw]) OR dorent[tw]) OR dospelin[tw]) OR dospelin[tw]) OR dozept[tw]) OR dozil[tw]) OR dozilax[tw])) OR done[tw])))) OR ((((((((((cristaclar[tw]) OR calofra[tw]) OR cebrocal[tw]) OR cenipil[tw]) OR ciclodin[tw]) OR cogiton[tw]) OR cognezil[tw]) OR concorda[tw]) OR covolos[tw]) OR crialix[tw])))) OR ((((((((((((((((((((((((((azepezil[tw]) OR a rui si[tw]) OR adonep[tw]) OR aldomer[tw]) OR aldonil[tw]) OR alizil[tw]) OR alkimus[tw]) OR almer[tw]) OR aloxtra[tw]) OR alzaimax[tw]) OR alzancer[tw]) OR alzdone[tw]) OR alzedon[tw]) OR alzepezil[tw]) OR alzepil[tw]) OR alzhedon[tw]) OR alzil[tw]) OR alzim[tw]) OR apo-doperil[tw]) OR arazil[tw]) OR aricep*[tw]) OR aridon[tw]) OR aridon[tw]) OR ariknow[tw]) OR aripez[tw]) OR aripil[tw]) OR arizil[tw]) OR arizime[tw]) OR arypez[tw]) OR asenta[tw]) OR aurobral[tw]))) Galantamine: ((((galantamine[MeSH Terms]) OR galantamin*) OR galanthamin*) OR ((((((((((((((((((((((((zoroflog[tw]) OR jin kang ling li[tw]) OR kuroment[tw]) OR lotprosin[tw]) OR luventa[tw]) OR lycoremine[tw]) OR masparen[tw]) OR memo-farmellas[tw]) OR memolos[tw]) OR memoton[tw]) OR nivalin[tw]) OR nivalina[tw]) OR numencial[tw]) OR oxygal[tw]) OR proneurax[tw]) OR qi er neng[tw]) OR razadyne[tw]) OR reminyl[tw]) OR riminyl[tw]) OR shi wei bao[tw]) OR trezor[tw]) OR yi you li ning[tw]) OR zaptron[tw])))) OR ((((((((((((((((((intelec[tw]) OR aneprosil[tw]) OR apo-galant[tw]) OR beklamen[tw]) OR bergal[tw]) OR elmino[tw]) OR flashemel[tw]) OR galamed[tw]) OR galamer[tw]) OR galantagen[tw]) OR galantex[tw]) OR galantyl[tw]) OR galanyl[tw]) OR galema[tw]) OR galnora[tw]) OR galsya[tw]) OR gamine[tw]) OR gatalin[tw]) OR hui min[tw]) Memantine:

			(((((memantine[MeSH Terms]) OR memantin*) OR ((((((((((((((((((zimerz[tw]) OR namenda[tw]) OR nemdatine[tw]) OR neumantine[tw]) OR polmatine[tw]) OR precel[tw]) OR prilben[tw]) OR pronervon[tw]) OR sades[tw]) OR tonibral[tw]) OR tormoro[tw]) OR valios[tw]) OR vilimen[tw]) OR vivimex[tw]) OR viximem[tw]) OR xapimant[tw]) OR xeimer[tw]) OR zenmem[tw]) OR zider[tw])) OR ((((((((((((((((((((((((((((((mizazir[tw]) OR mantomed[tw]) OR marbodin[tw]) OR marixino[tw]) OR maruxa[tw]) OR maxiram[tw]) OR melanda[tw]) OR melutrin[tw]) OR mema[tw]) OR memabix[tw]) OR memaneurin[tw]) OR memanxa[tw]) OR memanzaks[tw]) OR memary[tw]) OR memax[tw]) OR memicar[tw]) OR memigmin[tw]) OR memikare[tw]) OR memixa[tw]) OR memorelnoojerone[tw]) OR memorix[tw]) OR memotec[tw]) OR memox[tw]) OR mentadem[tw]) OR mentixa[tw]) OR mentra[tw]) OR merital[tw]) OR mevitan[tw]) OR mexia[tw]) OR mimetix[tw]) OR mirvedol[tw])) OR ((((((lucidex[tw]) OR fentina[tw]) OR fixrem[tw]) OR korint[tw]) OR lindex[tw])))) OR ((((((((((((((((((((((((((((ezemantis[tw]) OR abixa[tw]) OR adaxor[tw]) OR admenta[tw]) OR akatinol[tw]) OR almenta[tw]) OR alzant[tw]) OR alzeim[tw]) OR alzer[tw]) OR alzia[tw]) OR alzmex[tw]) OR axura[tw]) OR biomentin[tw]) OR ceramin[tw]) OR cissor[tw]) OR clomenac[tw]) OR cogito[tw]) OR conexine[tw]) OR dantex[tw]) OR demax[tw]) OR denigma[tw]) OR ebitex[tw]) OR ebix[tw]) OR ebixa[tw]) OR emaxin[tw]) OR eutebrol[tw]))) Rivastigmine: ((((rivastigmi*) OR ((((((((((((((((((((luneste[tw]) OR alapril[tw]) OR alcenorm[tw]) OR altigmin[tw]) OR alzest[tw]) OR alzigmine[tw]) OR balaxon[tw]) OR demelora[tw]) OR divasmin[tw]) OR donadox[tw]) OR emerpand[tw]) OR escapar[tw]) OR evertas[tw]) OR exelon[tw]) OR impalon[tw]) OR ivagalmin[tw]) OR kerstipon[tw]) OR kivas[tw]) OR lasium[tw])))) OR ((((((((((prometax[tw]) OR mentazac[tw]) OR mnimoran[tw]) OR nervopan[tw]) OR newvastig[tw]) OR niddastig[tw]) OR nimvastid[tw]) OR orivast[tw]) OR permente[tw]) OR probrain[tw])) OR ((((((((((((((((((((((((((((((symelon[tw]) OR remizeral[tw]) OR rimane[tw]) OR rimans[tw]) OR ristart[tw]) OR ristidic[tw]) OR rivadem[tw]) OR rivagmin[tw]) OR rivamer[tw]) OR rivaldo[tw]) OR rivaller[tw]) OR rivalong[tw]) OR rivamylan[tw]) OR rivanel[tw]) OR rivarem[tw]) OR rivarious[tw]) OR rivarlau[tw]) OR rivaset[tw]) OR rivasmina[tw]) OR rivasmine[tw]) OR

			rivastach[tw]) OR rivastinol[tw]) OR rivastinorm[tw]) OR rivaxe[tw]l) OR rivaxon[tw]) OR riveka[tw]) OR rivetal[tw]) OR rivoder[tw]) OR r-stigmin[tw]) OR sairv[tw]) OR signelon[tw]) OR somniton[tw]) OR srivasmine[tw])) OR (((((((zeemine[tw]) OR telomens[tw]) OR tigma[tw]) OR vasri[tw]) OR vastigma[tw]) OR vastigmex[tw]) OR velastina[tw]) OR voleze[tw]) Tacrine: ((((((tacrine[MeSH Terms]) OR tacrin*) OR cognex[tw]) OR talem[tw])) OR cognitiv[tw]) OR tetrahydroaminoacridin* Combination brand names: (((((((megingo[tw]) OR neuroplus[tw]) OR tonibral[tw]) OR ebicomb[tw]) OR ginkorem[tw]) OR valprex[tw])))) OR (((namzaric[tw]) OR arizex[tw]) OR donamen[tw])
Embase Via OVID	exp drug withdrawal/ exp treatment withdrawal/ exp withdrawal syndrome/ exp medication compliance/ deprescri*.mp OR de-prescri*.mp OR discontinu*.mp OR withdraw*.mp OR cessat*.mp OR ceas*.mp OR stop*.mp OR taper*.mp OR withheld*.mp OR washout*.mp OR persistence*.mp OR adhere*.mp OR compliance*.mp OR halt*.mp OR suspend*.mp OR terminat*.mp OR	exp dementia/ exp mild cognitive impairment/ lewy*.mp OR alzheimer*.mp OR cognitive deficit*.ti,ab OR cognition deficit*. ti,ab OR cognitive declin*. ti,ab OR cognition declin*. ti,ab OR memory disorder*. ti,ab OR mild cognitive impairment*. ti,ab OR minor neurocognitive disorder*. ti,ab OR major neurocognitive disorder*. ti,ab OR dement*.mp OR amnesi*.mp	exp cholinesterase inhibitor/ exp memantine/ anticholinesterase* OR anti-cholinesterase*.ti,ab OR acetylcholinesterase inhibitor*.ti,ab OR cholinesterase inhibitor*.ti,ab OR (E2020 OR donepezil* OR donezepil*).mp OR (oneza OR mazil OR memac OR memkar OR memoboost OR memocept OR memorit OR mensapex OR miltus OR navazil OR nepanizil OR nepezil OR nepla OR niritos OR nomi-nox OR nopez OR nozil OR nuo chong OR oldinot OR onefin OR zopitel OR palixid OR pamigen OR paxel OR penezil OR pezale OR pezil OR peziled OR pezilgen OR promemore OR rafazil OR razil OR redumas OR remoplix OR ricordo OR sai ling si OR servonex OR sib o hai OR sulbenin OR symepezil OR tactrol OR tolerdilan OR tonizep OR torpezil OR valpex OR vastia OR venaxen OR yasnal OR yasnoro OR zakalmer OR zhedon OR ziledon OR zinocept OR zolpezil OR lizidra OR gai fei OR endoclar OR epez OR eranz OR evimal OR ezida OR fang qing OR filosept OR fincip OR fordesia OR fremptel OR fu si ke OR genezil OR hania OR jia qi OR kibilis OR kognezil OR labrea OR landex OR lirpan OR lixben OR dozyl OR damzipil OR danpezil OR davia OR dazolin OR demelan OR dementis OR demenza OR dentap OR depzil OR dezira OR dilpeze OR divare OR dizil OR

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			riveka OR rivetal OR rivoder OR “r-stigmin” OR sairv OR signelon OR somniton OR srivasmine OR zeemine OR telomens OR tigma OR vasri OR vastigma OR vastigmex OR velastina OR voleze OR tacrin* OR tetrahydroaminoacridin* OR cognex OR talem OR cognitiv OR megingo OR neuroplus OR tonibral OR ebicomb OR ginkorem OR valprex OR namzaric OR arizex OR donamen)
Clinicaltrials.gov	deprescribing OR de-prescribing OR discontinue OR discontinuation OR withdrawal OR cessation OR washout	Not limited by condition	"cholinesterase inhibitor" OR "acetylcholinesterase inhibitor" OR donepezil OR galantamine OR rivastigmine OR tacrine OR memantine

Appendix 2: Evidence to Recommendations Tables

Table 6: Evidence to Recommendations—Cholinesterase Inhibitors

Question: Does deprescribing compared with 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. As a result of the study design (RCT), the quality was originally rated as high, but was downgraded two levels because of 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 benefits of **deprescribing** outweigh the harms? Yes☐ No ☒ Is there certainty that the benefits of **continued use** outweigh the harms?	Meta-analysis showed an increased risk of cognitive decline among those who discontinued versus those who continued. The magnitude of this effect is unclear because of different follow-up 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 the 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. The benefit of ChEIs for cognition and global outcomes is modest and there are limited data on the long-term efficacy (> 12 months). There is a lack of unbiased data on the risk of harm from	**Indication and prior duration of use may affect the balance of risk and harms.** 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 ☒ **Indication:** In non-approved indications, there appears to be a minimal risk associated with deprescribing. 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').

Yes☐ No ☒	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.	**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? 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	**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

	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.	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 ChEIs are based on data from relatively short-term use among younger and healthier participants with a less severe stage of dementia than the real-world population of people with dementia. They often presume that the medications are discontinued upon admission to a residential care facility. Depending on drug costs and other variables, these medications are not always considered cost-effective.	Feasibility: Is the intervention generally available? Yes☒ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing resources from or not allocating resources to other interventions? Yes☒ No ☐ While there may be an initial increase in costs because of increased clinician visits, this may be offset in the long term through discontinuation

	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 because of monitoring and possible reoccurrence 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 because of difference in QALY outcomes. There are significant limitations to this study that restrict its generalisability.	of ongoing prescription and medication administration costs. Is there a lot 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 potentially no 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:	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	

STRONG	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 because of 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 is 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).

Table 7: Evidence to Recommendations—Memantine

Question: Does deprescribing compared with 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?	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.	**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.

Yes☐ No ☒	The very low quality of evidence limits the ability to clarify the benefits and harms of deprescribing memantine. The majority of studies and outcomes 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 DLB), 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.	Is the baseline risk for harm from **deprescribing** similar across subgroups? Yes☐ No ☒ 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 and 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	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

	certainty that the benefits of continued use outweigh the harms.	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 ☐
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 because of a high level of hope that is placed on the medication and fear associated with discontinuation. None of the discontinuation studies	**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?

	captured individual/carer preferences, although one of the studies only conducted discontinuation with people who were willing to have the medication stopped.	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 because of monitoring and possible reoccurrence of symptoms. There were no cost-effectiveness analyses on deprescribing memantine identified.	Feasibility: Is the intervention generally available? Yes☒ No ☐ Opportunity cost: Is this intervention and its effects worth withdrawing resources from or not allocating resources to other interventions? Yes☒ No ☐ While there may be an initial increase in costs because of increased clinician visits, this may be offset long term through discontinuation of ongoing prescription and medication administration costs. Is there a lot 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 potentially no 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. 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).	