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## **Withdrawal of Antidementia Drugs in Older People: Who, When and How?**

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1 **Withdrawal of antideementia drugs in older people: who, when and how?**

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4

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8

9 **Abstract**

10 The evidence base to guide withdrawal of antideementia medications in older people with dementia is limited;  
11 while some randomised controlled studies have considered discontinuation of cholinesterase inhibitors, no such  
12 studies examining discontinuation of the N-Methyl-D-aspartate receptor antagonist memantine have been  
13 conducted to date. The purpose of this opinion article was to summarise the existing evidence on withdrawal of  
14 cholinesterase inhibitors and memantine, to highlight the key considerations for clinicians when making these  
15 prescribing decisions and to offer guidance as to when and how treatment might be discontinued. Until the  
16 evidence-base is enhanced by the findings of large scale randomised controlled discontinuation trials of ChEIs  
17 and memantine which use multiple, clinically relevant cognitive, functional and behavioural outcome measures,  
18 clinicians' prescribing decisions involve balancing the risks of discontinuation with side-effects and costs of  
19 continued treatment. Such decisions must be highly individualised and patient-centred.

20

21 **Key Points**

- 22 • The evidence base to guide discontinuation of antideementia medications is limited; there is a pressing  
23 need to conduct large scale randomised placebo-controlled discontinuation trials of cholinesterase  
24 inhibitors and memantine
- 25 • In the absence of a significant body of evidence, clinicians' decisions to discontinue an antideementia  
26 medication are highly individualised for each patient, and involve a consideration of risks of  
27 discontinuation versus side-effects and cost of continuing therapy
- 28 • If discontinuation is to be attempted, clinicians should taper the dose slowly and carefully monitor the  
29 patient for clear signs of cognitive, functional or behavioural decline.

30

## 31 **1. Introduction**

32

33 Dementia is a global public health concern; it has been estimated that 46.8 million people worldwide were living  
34 with dementia in 2015, and that this number will rise to 74.7 million in 2030 and 131.5 million in 2050 [1].

35 Dementia is primarily a condition of old age, its incidence increasing exponentially as age increases [1,2].

36 Medications approved for the treatment of dementia do not provide a cure; they can only delay disease

37 progression and alleviate symptoms [3,4]. They comprise cholinesterase inhibitors (ChEIs) and N-methyl-D-

38 aspartate (NMDA) receptor antagonists. Three available ChEIs are widely prescribed in clinical practice:

39 donepezil, rivastigmine and galantamine. Loss of cholinergic neurons is known to be an early feature in the

40 pathophysiology of Alzheimer's disease [5,6]; these agents exert their mechanism of action by preventing

41 acetylcholine breakdown at synaptic clefts [7]. They have received regulatory approval in Europe and the

42 United States for treatment of mild - moderate Alzheimer's disease and, in addition, are approved by the US

43 Food and Drug Administration for more advanced dementia [8 9]. Drug agencies in other jurisdictions have yet

44 to approve ChEIs for use in severe Alzheimer's disease. Rivastigmine is also licensed for treatment of mild to

45 moderate Parkinson's Disease dementia in the UK and the USA. Memantine is currently the only NMDA

46 receptor antagonist available. Licensed for treatment of moderate-severe Alzheimer's disease in North America,

47 Europe and Australia [10], its mechanism of action is uncertain, but it is thought to block the excitatory activity

48 of the toxic neurotransmitter glutamate [11] believed to contribute to the pathogenesis of Alzheimer's disease

49 [12] without interfering with the physiological actions required for memory and learning [13, 14].

50

51 There is uncertainty regarding long-term efficacy of antidementia drugs; most randomized controlled trials

52 (RCTs) are of no longer than 6 months in duration [15]. However, a number of long-term observational

53 controlled studies have provided evidence of long-term effects which suggest ChEI treatment should be

54 continued throughout all stages of Alzheimer's disease [16,17]. One prospective study of 641 patients conducted

55 over 20 years reported that a longer, more persistent treatment duration was associated with clinically significant

56 increased cognitive, global and functional performance [18]. Another prospective study of 790 patients followed

57 over three years demonstrated that a higher mean ChEI dose was associated with slower functional decline [19].

58

59 Although long-term ChEI treatment appears to have beneficial effects on global, cognitive and functional

60 outcomes, it has been associated with adverse events, the consequences of which may be extremely serious for

61 this frail patient population. These include gastrointestinal side-effects such as nausea, vomiting and anorexia  
62 [20-22]. Involuntary weight loss has been described in case reports [22], and although subsequent observational  
63 studies suggest that ChEI treatment does not increase risk of weight loss in patients with Alzheimer's Disease  
64 [23, 24], it has been argued that individual patients may be at risk [25]. There are also concerns that ChEIs may  
65 increase gastric acid production. One cohort study reported that upper gastrointestinal bleeding was not  
66 associated with use of ChEIs [26], but it has again been suggested that this does not mean that individual  
67 patients will not experience these problems if these medications are prescribed [25]. Of particular concern are  
68 the reports of adverse cardiovascular events; prescribing of ChEIs has been reported to be associated with a  
69 statistically significant increased risk of bradycardia leading to hospitalisation, syncope, pacemaker insertion  
70 and hip fracture [27-30]. There have also been case reports of QT interval prolongation with torsade de pointes  
71 ventricular tachycardia [31]. It has therefore been argued that patients taking ChEIs should be asked about  
72 presyncope or syncope and have their pulse examined for bradycardia as a matter of routine [32]. One small  
73 study of hospitalised older people suggested that ChEIs increased the risk of pulmonary disorders [33], although  
74 a much larger population-based study did not demonstrate an increase in serious pulmonary complications in  
75 older people with chronic obstructive pulmonary disease who were also receiving a ChEI [34]. In addition to the  
76 adverse events detailed above, predictable from a knowledge of the pharmacology of ChEIs [25], unpredictable  
77 and rare adverse events have also been reported. One case report has suggested that Pisa syndrome,  
78 characterised by abnormal flexion of the body and head to one side with slight rotation of the trunk, may be  
79 associated with ChEI treatment, although causality remains to be confirmed [35].

80

81 Given the benefits of, and adverse effects associated with, ChEI therapy discussed above, there is considerable  
82 uncertainty among clinicians surrounding how long it should be continued [36], and if and when to discontinue  
83 treatment, particularly as dementia progresses and patients approach end of life [37, 38]. Some clinical practice  
84 guidelines provide little direction regarding optimal treatment duration and emphasise the modest effects of  
85 currently available drugs [39-41]. Others suggest that ChEIs should be prescribed at all stages of Alzheimer's  
86 disease, and recommend discontinuation only if there are issues with tolerability or if clinical benefit is no  
87 longer apparent [42-44]. Conversely, however, discontinuation may reduce the risk of adverse events, minimise  
88 polypharmacy, and reduce caregiver burden and cost of care [45]. The clinical picture is further complicated by  
89 reports of discontinuation syndrome on ceasing treatment [46,47].

90

91 Similarly, there is limited evidence regarding long-term efficacy of memantine [48]. Most trials have utilised  
92 durations ranging from 12 weeks to 6 months [49-55], although several follow-up and open-label extension  
93 studies have reported clinically relevant benefits for patients treated for one or two years [10,56]. There is  
94 uncertainty over efficacy in end-stage dementia [57] and when to discontinue treatment [48]. Prolonged  
95 treatment is not without risks; there have been case reports of serious adverse effects, including loss of  
96 consciousness and/or seizure-like episodes [58]. Discontinuation of memantine, as with ChEIs, may minimise  
97 polypharmacy and reduce caregiver burden, cost of care and the risk of adverse events. This uncertainty serves  
98 to make clinical decisions regarding discontinuing memantine complex.

99

100 In this article we will examine the evidence base available to guide withdrawal of antedementia agents,  
101 highlighting the key considerations for clinicians when making prescribing decisions. We will offer guidance to  
102 support clinicians in making these decisions, based on the currently available evidence, and will discuss research  
103 priorities for future work in this area.

104

## 105 2. Search Methodology

106

107 A literature search was conducted using MEDLINE (1950–April 2016), EMBASE (1980– April 2016), Web of  
108 Science (1981– April 2016), International Pharmaceutical Abstracts (1970– April 2016) and the Cochrane  
109 Library of Systematic Reviews (1999–April 2016). The search terms used were ‘cholinesterase inhibitor(s)’,  
110 ‘acetylcholinesterase inhibitor(s)’, ‘donepezil’, ‘rivastigmine’, ‘galantamine’, ‘NMDA receptor antagonist’,  
111 ‘memantine’, ‘discontinue’, ‘discontinuation’, ‘withhold(ing)’, ‘withheld’, ‘withdraw’, ‘withdrawal’,  
112 ‘cessation’, ‘reducing’, ‘tapering’, ‘stopping’, ‘dementia’, ‘older’, ‘old’, ‘elderly’, ‘aged’ and combinations  
113 thereof. Only articles in the English language were selected. No attempt was made to reject papers on the basis  
114 of methodology, e.g. not a randomized controlled trial, as some studies were descriptive in nature or were papers  
115 that were classified as commentaries. One hundred and sixteen references have been included in this paper.

116

## 117 3. Discontinuing cholinesterase inhibitors

118

119 To date there has been limited research into whether discontinuation of antedementia medications leads to  
120 clinically significant cognitive and behavioural decline [41]. This is, however, gaining research interest,  
121 illustrated by the increasing numbers of RCTs in recent years detailed in Table 1.

122

123 INSERT TABLE 1 HERE

124

125 It must be noted that the trials summarised in Table 1 examined ChEIs, not memantine, and that duration of  
126 ChEI therapy prior to randomisation varied significantly. Furthermore, the majority of these studies were funded  
127 by the pharmaceutical industry, which must be borne in mind when interpreting the findings. The authors of  
128 these studies varied in their recommendations; Holmes et al. reported that discontinuation of ChEI treatment  
129 may lead to behavioural decline [59]. Johannsen et al. suggested that patients may benefit from continued  
130 therapy and that decisions to discontinue ChEIs should be carefully considered, based on evaluations of the  
131 impact on multiple symptom domains and not on cognition alone [60]. They argued that decline may not  
132 necessarily reflect lack of benefit, as the decline observed may be less than that which would have occurred  
133 without treatment, and that discontinuation may be counter-productive given the potential for loss of therapeutic  
134 response during washout between treatments.

135

136 The authors of the DOMINO-AD trial concluded that perceived benefits of continuing treatment are unclear, but  
137 consideration of the potential risks of withdrawal should inform clinicians' decisions [61]. Gaudig et al. argued  
138 that their findings corroborated previous work suggesting that long-term galantamine treatment may delay time  
139 to nursing home placement [63,83]. They concluded that sustained, uninterrupted therapy yielded clinical  
140 benefits; over the course of two 6-week withdrawal studies, patients continuing galantamine maintained the  
141 improvements in cognitive function they exhibited in the original parent studies. Scarpini et al. [64]  
142 acknowledged that the analysis of their primary cognitive outcome measure, the ADAS-cog/11, was  
143 underpowered, but argued that their data provided supporting evidence that galantamine is well tolerated when  
144 used long-term and that treatment should be continued in patients observed to benefit from galantamine therapy.  
145 They concluded that interruption of therapy should be undertaken with caution and that treatment should only be  
146 discontinued in the event of adverse effects.

147

148 A recent meta-analysis of studies investigating ChEI discontinuation in patients with Alzheimer's disease [84]  
149 included five of the studies described above [59-61,63,64]. Data from cognitive outcome measures were  
150 extracted from all included studies; ADAS-cog/11 scores were converted to MMSE scores. Neuropsychiatric  
151 symptoms, measured using the NPI, were extracted for three of the included studies [59-61]. Quality of included  
152 studies was analysed using items from the Newcastle-Ottawa Scale [85] and the Cochrane Collaboration's risk  
153 of bias assessment tool [86]. The authors reported that patients discontinuing ChEIs demonstrated significant  
154 worsening of cognition from baseline to the endpoint of the study compared to those continuing treatment. They  
155 reported no significant heterogeneity or publication bias. For the studies reporting neuropsychiatric outcomes,  
156 patients discontinuing ChEIs demonstrated worsening of neuropsychiatric symptoms, again with no significant  
157 heterogeneity or publication bias. Adverse event incidence and study dropout were similar between continuation  
158 and discontinuation groups. The authors suggested that the deteriorations in cognition and neuropsychiatric  
159 symptoms may have clinical relevance and are important considerations for clinicians when deciding whether to  
160 discontinue therapy. They stressed the highly individualised nature of this decision, suggesting that factors such  
161 as side-effects, current cognitive and functional status and caregiver preference must be considered.

162

163 Most recently, the pilot trial conducted by Herrmann et al. reported no significant differences in CGI-C score  
164 [71] between continuation and placebo groups in the occurrence of adverse events, or in any of the secondary  
165 outcome measures, suggesting that ChEI discontinuation does not result in clinical worsening, and is safe and  
166 well-tolerated in institutionalized patients with moderate to severe dementia who have been treated for at least  
167 two years [45]. The results of this pilot trial did not replicate the findings of the DOMINO-AD trial [61];  
168 treatment allocation was not observed to have a significant effect on change in cognition, function or global  
169 status over the eight-week study period. The authors suggested that this may be due to differences in setting and  
170 participant characteristics, and acknowledged that the study was underpowered to detect a difference in CGI-C;  
171 clinical deterioration in the discontinuation group was numerically greater than in the continuation group and the  
172 authors argued that statistically significant differences may have been detected with a larger sample size, though  
173 they speculated as to the clinical relevance of such a difference. They observed that baseline scores of psychosis  
174 correlated with clinical worsening when ChEIs were discontinued, and suggested that clinicians should closely  
175 monitor patients with psychotic symptoms when attempting discontinuation.

176

177 These trials, outlined above and in Table 1, add to the evidence base which includes studies employing other  
178 design methodologies; Daiello et al. undertook a retrospective cohort study of 178 nursing home residents with a  
179 diagnosis of Alzheimer's or non-Alzheimer's dementia, treated with ChEIs [87]. The cohort was divided into a  
180 continuation group, who were prescribed continuous ChEI therapy for > 9 months, and a discontinuation group  
181 (for whom there were no prescription claims for ChEIs for a minimum of 60 days after a stable regimen of  
182 treatment). Each patient who discontinued therapy was matched with  $\geq 1$  member of the continuation cohort.  
183 The primary outcome measures were change in total Depression Rating Scale (DRS) [88] and Aggressive  
184 Behavior Scale (ABS) [89] between baseline and the last Minimum Data Set (MDS) assessment. The authors  
185 reported that behavioural worsening, demonstrated by an increase in the mean change in ABS score, occurred in  
186 the discontinuation cohort but not in the continuation cohort, and that the difference between groups was  
187 statistically significant. There was no significant difference between continuation and discontinuation cohorts in  
188 change in mood symptoms on the DRS. Analysis of secondary outcomes indicated that patients in the  
189 discontinuation group exhibited significantly more episodes of repetitive questioning and repetitive health  
190 complaints and spent significantly less time in leisure-related activities than patients in the continuation cohort.  
191 These findings must be interpreted in light of the retrospective nature of the study and the limitations in the data  
192 set; it was not possible to determine reasons for discontinuation or rule out discontinuation due to an accelerated  
193 worsening of symptoms.

194

195 Attitudes of prescribers to discontinuing ChEIs have also been examined. Herrmann et al. conducted an online  
196 survey of geriatric psychiatrists, neurologists, and geriatricians (n=27) to determine opinions and consensus  
197 regarding circumstances in which ChEIs should be discontinued [90], the majority of whom agreed or strongly  
198 agreed that ChEIs should be discontinued if requested by a patient (with capacity) or a substitute decision-maker  
199 (if the patient is not considered to have capacity), or in the presence of severe adverse events. There was greater  
200 uncertainty on issues related to effectiveness, particularly regarding what constituted "greater than expected  
201 decline". Clinicians were reluctant to base decisions on any single measure of cognition, behaviour or function;  
202 the MMSE in particular was perceived to be of little value. Studies considering medication appropriateness have  
203 employed Delphi consensus methods to determine clinician opinion. Farrell et al. defined ChEIs as a drug class  
204 in need of evidence-based guidelines for deprescribing, arguing that in many cases a specialist initiates  
205 treatment, and a primary care practitioner has little guidance on how to determine ongoing need [91]. Consensus  
206 panels of experts in US [92] and UK [93] studies considered ChEIs to be "never appropriate" or "rarely



207 appropriate” for people with advanced dementia and a short life expectancy, respectively. A recent Delphi panel  
208 study in Canada did not reach a consensus regarding ChEI appropriateness in severe dementia [94], reflecting  
209 continued uncertainty, which is also evident in the variation of prescribing rates. A number of studies have  
210 reported that ChEIs are prescribed for between 7 % and 36% of people with severe dementia in the US and  
211 Europe [95 -97].

212

#### 213 **4. Discontinuing memantine**

214

215 To the best of the author’s knowledge, no randomised controlled studies have been published to date which  
216 examine memantine discontinuation. A small pilot study into the safety and tolerability of memantine in  
217 Parkinson’s Disease Dementia reported a slightly greater deterioration in cognitive function six weeks after  
218 discontinuation (assessed using the Dementia Rating Scale [98]) when compared with placebo, though this was  
219 not statistically significant [99]. When global outcomes were examined using CIBIC-Plus [72], significantly  
220 more patients taking memantine deteriorated compared to those treated with placebo, and the magnitude of this  
221 deterioration was significantly greater, demonstrated by a significantly higher CIBIC-Plus score, suggesting that  
222 continued treatment with memantine may be needed to maintain global level of functioning. Fillit et al.  
223 conducted a retrospective chart review of 113 nursing home residents to examine the effect of memantine  
224 discontinuation, and reported significant worsening of overall health status for patients in whom memantine was  
225 stopped, compared to those treated continuously [100]. They reported an average emergence of approximately 1  
226 to 2 new symptoms, or worsening of 3 to 4 existing symptoms, within 2 to 3 months of discontinuation for each  
227 patient who discontinued memantine treatment, compared with continuously treated patients, and suggested that  
228 the negative effects of discontinuation may increase over time. An extension trial of memantine in dementia  
229 with Lewy Bodies and Parkinson’s disease dementia reported that recurrence of symptoms occurred more  
230 frequently upon drug withdrawal in patients receiving memantine than in those taking placebo, with significant  
231 global deterioration measured by the CGI-C [101]. The authors suggested that treatment-associated benefits are  
232 rapidly lost following memantine withdrawal.

233 Despite these findings, and due to the lack of RCTs in this area, there remains uncertainty over when to  
234 discontinue treatment [48] and over efficacy in end-stage dementia [57]. This is reflected in the Delphi  
235 consensus studies considering medication appropriateness, in which memantine has been categorised as “never

236 appropriate” [92] or “sometimes appropriate” [93] for people with advanced dementia and a short life  
237 expectancy. In a further study, no consensus was reached regarding appropriateness in severe dementia [94].

238

## 239 **5. Guidance for discontinuation of antedementia medications in clinical practice**

240 Clinicians who provide care for people with dementia are faced with the complex task of attempting to  
241 extrapolate this limited and somewhat contradictory evidence base to the individual patient presenting for  
242 treatment [102]. Decisions to cease treatment are further complicated by the view (albeit held by a minority) that  
243 cholinesterase inhibitors and memantine may have neuroprotective or disease-modifying effects [103-108]. The  
244 American Geriatrics Society Choosing Wisely Workgroup suggests that clinicians should consider ChEI  
245 discontinuation if the cognitive, behavioural and functional goals of treatment are not met [109]. Other guidance  
246 suggests determining benefit by considering whether treatment meets goals based on symptoms that patients and  
247 their families define as important [102, 110]. This highly individualised, patient-centred approach has been  
248 advocated by others [25,60,84]. Hogan suggested that treatment benefit may manifest only as a slowed  
249 progression, and that this should be considered by physicians when deciding whether to discontinue treatment  
250 [25]. A recent consensus conference in Canada noted that discontinuing ChEIs may lead to worsening cognition  
251 and function, and recommended that risks should be balanced with known side-effects and costs of continuing  
252 treatment [43]. The circumstances in which treatment should be discontinued have been described as follows  
253 [43,90,111]:

254

- 255 1. When the patient/caregiver decides to stop (after being advised on the risks and benefits of stopping  
256 treatment
- 257 2. When the patient refuses to take the medication
- 258 3. When there are issues with patient compliance which cannot be reasonably resolved
- 259 4. When the patient’s cognitive, functional or behavioural decline is worse on treatment
- 260 5. When there are intolerable side-effects likely to be caused by the ChEI
- 261 6. When comorbidities make treatment risky or futile (for example, terminal illness)
- 262 7. Where there is no clinically meaningful benefit to continuing therapy.
- 263 8. When dementia has progressed to a severely impaired stage (Global Deterioration Scale stage 7,  
264 development of swallowing difficulties.

265

266 The authors of these guidelines acknowledge the difficulties in determining if an adverse event is related to the  
267 treatment and in determining lack of clinically relevant benefit in this population; they suggest that an  
268 assessment of the probability that the adverse event is related to the ChEI [112] is necessary, although the  
269 difficulties in applying criteria developed for this purpose to older people with adverse drug reactions, and the  
270 lack of a method validated specifically for use in older people with multiple co-morbidities and medications,  
271 complicate this assessment [113]. The authors further recommend that clinical judgement should form the basis  
272 of determining lack of benefit rather than ceasing treatment when a patient reaches a certain score on a cognitive  
273 outcome or when they are institutionalised [57,114]. Many outcome measures used in studies of anticholinergic  
274 medications have limitations; the MMSE, although simple to administer in clinical practice, lacks sensitivity in  
275 determining rate of change in cognition and progression to severe dementia [115,116]; the ADAS-cog scale  
276 appears to be more sensitive to change but is more time-consuming to administer [4]. In addition to measures of  
277 cognitive function, functional abilities and behavioural and psychological symptoms should be considered, and  
278 an overall assessment of severity using the global deterioration scale (GDS) or functional assessment staging  
279 (FAST) undertaken to monitor disease progression and to determine treatment discontinuation [4,57]. Such an  
280 individualised approach should also monitor patients' specific sets of symptoms and considers management  
281 goals and potential benefits when deciding on discontinuation.

282

283 When a decision is made to stop therapy, tapering of the dose and monitoring the patient for evidence of  
284 significant decline during the next 1 – 3 months have been advocated [25,43,45,84]. If such decline occurs,  
285 reinstatement of therapy should be considered.

286

287 Although no such guidance is available to support clinicians to discontinue memantine, the circumstances in  
288 which treatment should be stopped, and the caution to be exercised in terms of dose tapering and monitoring  
289 patients for significant decline, are similar.

290

## 291 **6. Future research priorities**

292

293 Clinical practice guidelines should be based on controlled discontinuation trials [90]. While some small scale  
294 studies examining discontinuing ChEIs have been conducted, there is a pressing need for large-scale double-

295 blind RCTs examining the impact of discontinuing these medications on multiple clinically relevant cognitive,  
296 functional and behavioural outcomes for patients. Furthermore, to the best of the author's knowledge, no such  
297 studies examining discontinuation of memantine exist. The evidence-base for discontinuing memantine requires  
298 significant research attention.

299

## 300 **7. Conclusion**

301

302 This article examines the limited evidence base available to guide withdrawal of antedementia agents and  
303 highlights the pressing need for large scale randomised controlled discontinuation trials which use multiple,  
304 clinically relevant cognitive, functional and behavioural outcome measures. Until the evidence-base is enhanced  
305 by the findings of such studies, clinicians' prescribing decisions involve balancing risks of discontinuation with  
306 side-effects and costs of continued treatment. Such decisions must be highly individualised and patient-centred.

307

## 308 **Compliance with ethical standards**

309

310

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312

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314

315

## 316 **Conflict of interest**

317

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320

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Author/Year	ChEI studied	Duration of ChEI therapy prior to withdrawal study	Sample	Design	Outcome Measures	Study Findings	Study funder
Holmes et al. 2004 [59]	Donepezil	3 mo	Community-dwelling patients with mild-moderate AD exhibiting marked neuropsychiatric symptoms. Age $\geq$ 55y, NINCDS-ADRDA probable or possible AD $\geq$ 6 mo duration, MMSE 11 -27	24- week double-blind placebo-controlled withdrawal study. Patients treated with 5 mg/day donepezil for 6 weeks followed by 10 mg/day for 6 weeks in open label phase, before being randomised to placebo (n=55) or 10 mg/day (n=41) for 6 weeks. If no marked cognitive deterioration observed (loss of > 2 points on MMSE compared with baseline), treatment was continued for a further 6 weeks.	Primary measure: NPI Secondary measure: NPI-D	Patients who discontinued donepezil 10 mg following open label treatment demonstrated significant worsening of NPI and NPI-D scores compared to continued improvements in patients continuing treatment; the difference in NPI scores between discontinuation and continuation groups was maintained at 6.2 points at weeks 6 and 12. NPI-D scores showed a consistent difference of 2.7 points and 2.8 points at weeks 6 and 12 respectively. Although statistically significant, these differences were not considered clinically significant.	Pfizer/Eisai
Johannsen et al.	Donepezil	3-6 mo	Outpatients with	12-week double-	Primary measure:	Statistically	Pfizer/Eisai

2006 [60]			mild-moderate AD for whom clinical benefit initially uncertain Age $\geq$ 50y, DSM-IV and NINDS-ADRDA probable or possible AD, MMSE 10-26	blind placebo-controlled withdrawal study. Patients taking donepezil 10 mg/day during open-label study were randomised to continue donepezil (n=99) or were switched to placebo (n=103), for 12 weeks.	ADAS-cog/11 Secondary measures MMSE, NPI, DAD	significant worsening of MMSE (1.13 points, p=0.02) and NPI (3.16 points, p=0.02) in patients discontinuing donepezil. Differences were less than MCIDs for MMSE and NPI. No significant differences observed in ADAS-cog/11 (0.57, p=0.5) or DAD (3.67, p=0.1).	
Howard et al 2012, 2015 [61,62]	Donepezil	At least 3 mo	Community-dwelling patients with moderate-severe AD. NINDS-ADRDA probable or possible AD, MMSE 5-13	Multicentre double-blind randomised placebo-controlled trial. Patients randomised to continue donepezil 10 mg/day (n=73) or were switched to placebo (n=73) for 52 weeks	Primary measures: SMMSE, BADLS Secondary measures: NPI, DEMQOL-Proxy, GHQ-12 (caregiver); risk of nursing home placement	Significant worsening of cognition and function in patients for whom donepezil was withdrawn. Patients assigned to continue donepezil had higher SMMSE scores by an average of 1.9 points and lower BADLS scores by an average of 3.0 points (p<0.001 for both comparisons). The difference in cognitive function exceeded the MCID of 1.4 points on the SMMSE), but the difference in BADLS did not exceed the MCID of 3.5 points. Differences in NPI, DEMQOL-Proxy and GHQ-12 scores	UK Medical Research Council and the Alzheimer's Society

						for patients continuing vs patients discontinuing donepezil were not statistically significant. Donepezil withdrawal associated with increased risk of nursing home placement during the 12 month treatment period, but no significant difference in institutionalisation risk during subsequent 36 month follow-up.	
Gaudig et al 2011 [63]	Galantamine	3 mo	Outpatients with mild-moderate AD. NINDS-ADRDA probable AD Study 1: MMSE 10-22 and a score of $\geq 18$ on the ADAS-cog/11 Study 2: MMSE 11-24 and score of $\geq 2$ on ADAS-cog	Double-blind withdrawal studies including patients who had completed a previous 3-month or 5-month randomised clinical trial investigating the safety and efficacy of galantamine [65,66]. In study 1 [65], patients taking placebo (n=219), 8 mg/day galantamine (n=104) or 16 mg/day galantamine (n=202) continued the assigned treatment for 6 weeks. Patients taking 24mg/day galantamine had active treatment	Primary measure: ADAS-cog/11 Secondary measures: safety and tolerability assessments	For patients in whom cognition improved with galantamine treatment, withdrawal was associated with cognitive decline. Six weeks after stopping treatment, the cognitive function of these patients had deteriorated towards levels observed in patients who had received continuous placebo. In study 1, patients continuously treated with galantamine 16 mg/day demonstrated a mean improvement of 0.6 points in ADAS-cog/11 (p=0.451) compared	Janssen Pharmaceutica NV, Janssen EMEA Medical Affairs

				<p>discontinued and received placebo for 6 weeks (n=198). In study 2 [66], patients receiving placebo in the parent trial continued placebo for 6 weeks (n=47), and those taking 24 mg/day or 32 mg/day galantamine were randomised to a withdrawal group and received placebo for 6 weeks (n=39), or a continuation group in which galantamine was continued at the dose assigned in the parent trial (n=32).</p>		<p>to the baseline of the parent trial, while patients who had received continuous placebo demonstrated a 2.9 point deterioration in ADAS-cog/11 (p=0.003). Patients switched from galantamine to placebo demonstrated a statistically significant deterioration of 2.4 points (p=0.001). These differences were less than the MCID of 4 points. In study 2, patients who had received continuous galantamine exhibited a mean improvement of 1.5 points in ADAS-cog/11 (p=0.187), while patients who had switched from galantamine to placebo or who had received continuous placebo demonstrated mean deteriorations of 0.1 (p=0.968) and 0.9 (p=0.366) respectively. Again, these differences were less than the MCID.</p>	
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Scarpini et al 2011 [64]	Galantamine	12 mo	Outpatients with mild-moderate AD Age $\geq 50$ y, NINDS-ADRDA probable or possible AD, MMSE 11-24, no decline of $< 4$ points following open-label phase	Randomised, double-blind placebo-controlled trial. Patients randomised to continue 16 mg/day galantamine (n=76) or to discontinue active treatment and take placebo (n=63) for up to 24 months	Primary measure: time to deterioration (deterioration in ADAS-cog/11 score of $\geq 4$ points) Secondary efficacy measures: CIBIC-plus scores, safety and tolerability assessments	Patients who responded to galantamine in the open-label phase of the study and in whom treatment was continued were less likely to discontinue the study prematurely for any reason or due to lack of efficacy than patients in whom galantamine was discontinued. Patients taking placebo were more likely to discontinue treatment prematurely than those taking galantamine for any reason (HR 1.76, 95% CI 1.10-2.81, p=0.02) or lack of efficacy (HR 1.80, 95% CI 1.02-3.18, p=0.04); no statistically significant difference was observed for change in ADAS-cog $\geq 4$ between treatment groups (HR 1.66, 95% CI 0.78-3.54, p=0.19)	Janssen Cilag GmbH/ Janssen EMEA
Herrmann et al 2016 [45]	Donepezil, galantamine or rivastigmine (oral)	At least 2y	Patients with moderate to severe AD residing in long-term care Age $\geq 55$ y, NINDS-ADRDA probable AD, DSM-IV criteria	8-week randomised, double-blind placebo-controlled pilot trial. Patients were randomised with a 1:1 ratio balanced by ChEI to	Primary measure: CGI-C Secondary measures: cognitive function (SMMSE, SIB), behavioural status	No significant difference in CGI-C score, adverse events or any secondary outcome measure, between continuation and placebo groups	Alzheimer's Society of Canada/Coleman Fund (internal funding)



			for primary degenerative dementia, SMMSE score $\leq 15$	continue receiving their ChEI (n=21) at their current dose, or to receive placebo (discontinuation; n=19). Patients discontinuing were tapered off ChEIs over 2 weeks and then continued on placebo for a further 6 weeks	(NPI-NH, CMAI, AES), function (ADCS-ADL-sev), quality of life (QUALID), safety and tolerability		
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Abbreviations: AD Alzheimer's Disease, ADAS-cog/11 Alzheimer's Disease Assessment Scale cognitive subscale [67], ADCS-ADL-sev Alzheimer's Disease Cooperative Study-Activities of Daily Living-severe [68], AES Apathy Evaluation Scale [69], BADLS Bristol Activities of Daily Living Scale [70], CGI-C Clinician's Global Impression of Change [71], ChEI Cholinesterase inhibitor, CI Confidence Interval, CIBIC-plus Clinician's Interview-Based Impression of Change Plus Caregiver Input [72] CMAI Cohen-Mansfield Agitation Inventory [73], DAD Disability Assessment for Dementia [74], DEMQOL-Proxy assessment of health-related quality of life by caregiver [75], DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, GHQ-12 General Health Questionnaire (caregiver) [76], HR Hazard Ratio, MCID Minimum Clinically Important Difference, mo month, MMSE Mini Mental State Examination [77], NINDS-ADRDA National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association, NPI Neuropsychiatric Inventory ) [78] , NPI-D Neuropsychiatric Inventory-Distress ) [78], QUALID Quality of Life in Late-Stage Dementia [79] , SIB Severe Impairment Battery [80], SMMSE Standardised Mini Mental State Examination [81,82], y year