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CURRENT OPINION

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

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

Key Points

The evidence base to guide discontinuation of antidementia medications is limited; there is a pressing need to conduct large-scale, randomised placebo-controlled discontinuation trials of cholinesterase inhibitors and memantine.

In the absence of a significant body of evidence, clinicians' decisions to discontinue antidementia medication are highly individualised for each patient, and involve a consideration of risks of discontinuation versus side effects and cost of continuing therapy.

If discontinuation is to be attempted, clinicians should taper the dose slowly and carefully monitor the patient for clear signs of cognitive, functional or behavioural decline.

1 Introduction

Dementia is a global public health concern; it has been estimated that 46.8 million people worldwide were living with dementia in 2015, and that this number will rise to 74.7 million in 2030 and 131.5 million in 2050 [1]. Dementia is primarily a condition of old age, its incidence increasing exponentially as age increases [1, 2].

Medications approved for the treatment of dementia do not provide a cure; they can only delay disease progression and alleviate symptoms [3, 4]. They comprise cholinesterase inhibitors (ChEIs) and *N*-methyl-D-aspartate (NMDA) receptor antagonists. Three available ChEIs are

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widely prescribed in clinical practice: donepezil, rivastigmine and galantamine. Loss of cholinergic neurons is known to be an early feature in the pathophysiology of Alzheimer's disease [5, 6]; these agents exert their mechanism of action by preventing acetylcholine breakdown at synaptic clefts [7]. They have received regulatory approval in Europe and the US for treatment of mild to moderate Alzheimer's disease and, in addition, are approved by the US Food and Drug Administration for more advanced dementia [8, 9]. Drug agencies in other jurisdictions have yet to approve ChEIs for use in severe Alzheimer's disease. Rivastigmine is also licensed for treatment of mild to moderate Parkinson's disease dementia in the UK and the US. Memantine is currently the only NMDA receptor antagonist available. Licensed for treatment of moderate to severe Alzheimer's disease in North America, Europe and Australia [10], its mechanism of action is uncertain, but it is thought to block the excitatory activity of the toxic neurotransmitter glutamate [11], believed to contribute to the pathogenesis of Alzheimer's disease [12], without interfering with the physiological actions required for memory and learning [13, 14].

There is uncertainty regarding long-term efficacy of antidementia drugs; most randomized controlled trials (RCTs) are of no longer than 6 months in duration [15]. However, a number of long-term observational controlled studies have provided evidence of long-term effects which suggest ChEI treatment should be continued throughout all stages of Alzheimer's disease [16, 17]. One prospective study of 641 patients conducted over 20 years reported that longer, more persistent treatment duration was associated with clinically significant increased cognitive, global and functional performance [18]. Another prospective study of 790 patients followed over 3 years demonstrated that a higher mean ChEI dose was associated with slower functional decline [19].

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

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

Similarly, there is limited evidence regarding long-term efficacy of memantine [48]. Most trials have utilised durations ranging from 12 weeks to 6 months [49–55], although several follow-up and open-label extension studies have reported clinically relevant benefits for patients treated for 1–2 years [10, 56]. There is uncertainty over efficacy in end-stage dementia [57] and when to discontinue treatment [48]. Prolonged treatment is not without risks; there have been case reports of serious adverse effects, including loss of consciousness and/or seizure-like episodes [58]. Discontinuation of memantine, as with ChEIs, may minimise polypharmacy and reduce caregiver burden, cost of care and the risk of adverse events. This

uncertainty serves to make clinical decisions regarding discontinuing memantine complex.

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

2 Search Methodology

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

3 Discontinuing Cholinesterase Inhibitors

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

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

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

A recent meta-analysis of studies investigating ChEI discontinuation in patients with Alzheimer's disease [84] included five of the studies described above [59–61, 63, 64]. Data from cognitive outcome measures were extracted from all included studies; ADAS-cog/11 scores were converted to MMSE (Mini Mental State Examination) scores. Neuropsychiatric symptoms, measured using the NPI (Neuropsychiatric Inventory), were extracted for three of the included studies [59–61]. Quality of included studies was analysed using items from the Newcastle-Ottawa Scale [85] and the Cochrane Collaboration's risk of bias assessment tool [86]. The authors reported that patients discontinuing ChEIs demonstrated significant worsening of cognition from baseline to the endpoint of the study compared with those continuing treatment. They reported no significant heterogeneity or publication bias. For the studies reporting neuropsychiatric outcomes, patients discontinuing ChEIs demonstrated worsening of neuropsychiatric symptoms, again with no significant heterogeneity or publication bias. Adverse event incidence and study dropout were similar between continuation and discontinuation groups. The authors suggested that the deteriorations in cognition and neuropsychiatric symptoms may have clinical relevance and are important

Table 1 Characteristics of ChEI discontinuation studies

Study	ChEI studied	Duration of ChEI therapy prior to withdrawal study	Sample	Design	Outcome measures	Study findings	Study funder
Holmes et al. [59]	Donepezil	3 months	Community-dwelling patients with mild–moderate AD exhibiting marked neuropsychiatric symptoms. Age ≥55 year, NINCDS-ADRDA probable or possible AD ≥6 month duration, MMSE 11–27	24-week double-blind placebo-controlled withdrawal study. Patients treated with 5 mg/day donepezil for 6 week followed by 10 mg/day for 6 week in open-label phase, before being randomised to placebo ($n = 55$) or 10 mg/day ($n = 41$) for 6 week. If no marked cognitive deterioration observed (loss of >2 points on MMSE compared with baseline), treatment was continued for a further 6 week	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 with continued improvements in patients continuing treatment; the difference in NPI scores between discontinuation and continuation groups was maintained at 6.2 points at week 6 and 12. NPI-D scores showed a consistent difference of 2.7 points and 2.8 points at week 6 and 12, respectively. Although statistically significant, these differences were not considered clinically significant	Pfizer/Eisai
Johannsen et al. [60]	Donepezil	3–6 months	Outpatients with mild–moderate AD for whom clinical benefit initially uncertain Age ≥50 year, DSM-IV and NINDS-ADRDA probable or possible AD, MMSE 10–26	12-week double-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 week	Primary measure: ADAS-cog/11 Secondary measures MMSE, NPI, DAD	Statistically 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, $p = 0.1$)	Pfizer/Eisai
Howard et al. [61, 62]	Donepezil	At least 3 months	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 week	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 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	UK Medical Research Council and the Alzheimer's Society

Table 1 continued

Study	ChEI studied	Duration of ChEI therapy prior to withdrawal study	Sample	Design	Outcome measures	Study findings	Study funder
Gaudig et al. [63]	Galantamine	3 months	Outpatients with mild–moderate AD NINDS-ADRDA probable AD Study 1: MMSE 10–22 and a score of ≥18 on the ADAS-cog/11 Study 2: MMSE 11–24 and score of ≥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 week. Patients taking 24 mg/day galantamine had active treatment discontinued and received placebo for 6 week ($n = 198$). In study 2 [66], patients receiving placebo in the parent trial continued placebo for 6 week ($n = 47$), and those taking 24 or 32 mg/day galantamine were randomised to a withdrawal group and received placebo for 6 week ($n = 39$), or a continuation group in which galantamine was continued at the dose assigned in the parent trial ($n = 32$)	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. 6 week 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/d demonstrated a mean improvement of 0.6 points in ADAS-cog/11 ($p = 0.451$) compared with 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	Janssen Pharmaceuticals NV, Janssen EMEA Medical Affairs
Scarpini et al. [64]	Galantamine	12 months	Outpatients with mild–moderate AD Age ≥50 year, 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 month	Primary measure: time to deterioration (deterioration in ADAS-cog/11 score of ≥ 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 ≥4 between treatment groups (HR 1.66, 95 % CI 0.78–3.54, $p = 0.19$)	Janssen Cilag GmbH/Janssen EMEA

Table 1 continued

Study	ChEI studied	Duration of ChEI therapy prior to withdrawal study	Sample	Design	Outcome measures	Study findings	Study funder
Herrmann et al. [45]	Donepezil, galantamine or rivastigmine (oral)	At least 2 years	Patients with moderate to severe AD residing in long-term care Age ≥55 year, NINDS-ADRDA probable AD, DSM-IV criteria for primary degenerative dementia, SMMSE score ≤15	8-week randomised double-blind placebo-controlled pilot trial. Patients were randomised with a 1:1 ratio balanced by ChEI to 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 week and then continued on placebo for a further 6 week	Primary measure: CGI-C Secondary measures: cognitive function (SMMSE, SIB), behavioural status (NPI-NH, CMAI, AES), function (ADCS-ADL-sev), quality of life (QUALID), safety and tolerability	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)

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, *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]

considerations for clinicians when deciding whether to discontinue therapy. They stressed the highly individualised nature of this decision, suggesting that factors such as side effects, current cognitive and functional status and caregiver preference must be considered.

Most recently, the pilot trial conducted by Herrmann et al. reported no significant differences in CGI-C (Clinician's Global Impression of Change) score [71] between continuation and placebo groups in the occurrence of adverse events, or in any of the secondary outcome measures, suggesting that ChEI discontinuation does not result in clinical worsening, and is safe and well tolerated in institutionalised patients with moderate to severe dementia who have been treated for at least 2 years [45]. The results of this pilot trial did not replicate the findings of the DOMINO-AD trial [61]; treatment allocation was not observed to have a significant effect on change in cognition, function or global status over the 8-week study period. The authors suggested that this may be due to differences in setting and participant characteristics, and acknowledged that the study was underpowered to detect a difference in CGI-C; clinical deterioration in the discontinuation group was numerically greater than in the continuation group and the authors argued that statistically significant differences may have been detected with a larger sample size, though they speculated as to the clinical relevance of such a difference. They observed that baseline scores of psychosis correlated with clinical worsening when ChEIs were discontinued, and suggested that clinicians should closely monitor patients with psychotic symptoms when attempting discontinuation.

These trials, outlined above and in Table 1, add to the evidence base which includes studies employing other design methodologies; Daiello et al. undertook a retrospective cohort study of 178 nursing home residents with a diagnosis of Alzheimer's or non-Alzheimer's dementia, treated with ChEIs [87]. The cohort was divided into a continuation group, who were prescribed continuous ChEI therapy for >9 months, and a discontinuation group (for whom there were no prescription claims for ChEIs for a minimum of 60 days after a stable regimen of treatment). Each patient who discontinued therapy was matched with one or more member of the continuation cohort. The primary outcome measures were change in total Depression Rating Scale (DRS) [88] and Aggressive Behavior Scale (ABS) [89] between baseline and the last Minimum Data Set (MDS) assessment. The authors reported that behavioural worsening, demonstrated by an increase in the mean change in ABS score, occurred in the discontinuation cohort but not in the continuation cohort, and that the difference between groups was statistically significant. There was no significant difference between continuation and discontinuation cohorts in change in mood symptoms

on the DRS. Analysis of secondary outcomes indicated that patients in the discontinuation group exhibited significantly more episodes of repetitive questioning and repetitive health complaints and spent significantly less time in leisure-related activities than patients in the continuation cohort. These findings must be interpreted in light of the retrospective nature of the study and the limitations in the data set; it was not possible to determine reasons for discontinuation or rule out discontinuation due to an accelerated worsening of symptoms.

Attitudes of prescribers to discontinuing ChEIs have also been examined. Herrmann et al. conducted an online survey of geriatric psychiatrists, neurologists and geriatricians ($n = 27$) to determine opinions and consensus regarding circumstances in which ChEIs should be discontinued [90], the majority of whom agreed or strongly agreed that ChEIs should be discontinued if requested by a patient (with capacity) or a substitute decision maker (if the patient is not considered to have capacity), or in the presence of severe adverse events. There was greater uncertainty on issues related to effectiveness, particularly regarding what constituted "greater than expected decline". Clinicians were reluctant to base decisions on any single measure of cognition, behaviour or function; the MMSE in particular was perceived to be of little value. Studies considering medication appropriateness have employed Delphi consensus methods to determine clinician opinion. Farrell et al. defined ChEIs as a drug class in need of evidence-based guidelines for deprescribing, arguing that in many cases a specialist initiates treatment, and a primary care practitioner has little guidance on how to determine ongoing need [91]. Consensus panels of experts in US [92] and UK [93] studies considered ChEIs to be 'never appropriate' or 'rarely appropriate' for people with advanced dementia and a short life expectancy, respectively. A recent Delphi panel study in Canada did not reach a consensus regarding ChEI appropriateness in severe dementia [94], reflecting continued uncertainty, which is also evident in the variation of prescribing rates. A number of studies have reported that ChEIs are prescribed for between 7 and 36 % of people with severe dementia in the US and Europe [95–97].

4 Discontinuing Memantine

To the best of the author's knowledge, no RCTs have been published to date that examine memantine discontinuation. A small pilot study into the safety and tolerability of memantine in Parkinson's disease dementia reported a slightly greater deterioration in cognitive function 6 weeks after discontinuation (assessed using the DRS [98]) when compared with placebo, though this was not statistically significant [99]. When global outcomes were examined using CIBIC-Plus (Clinician's Interview-Based Impression of Change Plus Caregiver Input) [72], significantly more patients taking memantine deteriorated compared with those treated with placebo, and the magnitude of this deterioration was significantly greater, demonstrated by a significantly higher CIBIC-Plus score, suggesting that continued treatment with memantine may be needed to maintain global level of functioning. Fillit et al. conducted a retrospective chart review of 113 nursing home residents to examine the effect of memantine discontinuation, and reported significant worsening of overall health status for patients in whom memantine was stopped, compared with those treated continuously [100]. They reported an average emergence of approximately one to two new symptoms, or worsening of three to four existing symptoms, within 2–3 months of discontinuation for each patient who discontinued memantine treatment, compared with continuously treated patients, and suggested that the negative effects of discontinuation may increase over time. An extension trial of memantine in dementia with Lewy bodies and Parkinson's disease dementia reported that recurrence of symptoms occurred more frequently upon drug withdrawal in patients receiving memantine than in those taking placebo, with significant global deterioration measured by the CGI-C [101]. The authors suggested that treatment-associated benefits are rapidly lost following memantine withdrawal.

Despite these findings, and due to the lack of RCTs in this area, there remains uncertainty over when to discontinue treatment [48] and over efficacy in end-stage dementia [57]. This is reflected in the Delphi consensus studies considering medication appropriateness, in which memantine has been categorised as 'never appropriate' [92] or 'sometimes appropriate' [93] for people with advanced dementia and a short life expectancy. In a further study, no consensus was reached regarding appropriateness in severe dementia [94].

5 Guidance for Discontinuation of Antidementia Medications in Clinical Practice

Clinicians who provide care for people with dementia are faced with the complex task of attempting to extrapolate this limited and somewhat contradictory evidence base to the individual patient presenting for treatment [102]. Decisions to cease treatment are further complicated by the view (albeit held by a minority) that ChEIs and memantine may have neuroprotective or disease-modifying effects [103–108]. The American Geriatrics Society Choosing Wisely Workgroup suggests that clinicians should consider ChEI discontinuation if the cognitive, behavioural and

functional goals of treatment are not met [109]. Other guidance suggests determining benefit by considering whether treatment meets goals based on symptoms that patients and their families define as important [102, 110]. This highly individualised, patient-centred approach has been advocated by others [25, 60, 84]. Hogan suggested that treatment benefit may manifest only as a slowed progression, and that this should be considered by physicians when deciding whether to discontinue treatment [25]. A recent consensus conference in Canada noted that discontinuing ChEIs may lead to worsening cognition and function, and recommended that risks should be balanced with known side effects and costs of continuing treatment [43]. The circumstances in which treatment should be discontinued have been described as follows [43, 90, 111].

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

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

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

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

6 Future Research Priorities

Clinical practice guidelines should be based on controlled discontinuation trials [90]. While some small-scale studies examining discontinuing ChEIs have been conducted, there is a pressing need for large-scale double-blind RCTs examining the impact of discontinuing these medications on multiple clinically relevant cognitive, functional and behavioural outcomes for patients. Furthermore, to the best of the author's knowledge, no such studies examining discontinuation of memantine exist. The evidence base for discontinuing memantine requires significant research attention.

7 Conclusion

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

Compliance with Ethical Standards

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