Cholinesterase Inhibitor Discontinuation in Patients With Alzheimer's Disease: A Meta-Analysis of Randomized Controlled Trials

Jordana O'Regan, MSc[a,b]; Krista L. Lanctôt, PhD[a,b,c]; Graham Mazereeuw, PhD[a,b]; and Nathan Herrmann, MD, FRCPC[a,c,*]

ABSTRACT

Objective: This meta-analysis examined the effects of cholinesterase inhibitor (ChEI) discontinuation in patients with Alzheimer's disease (AD).

Data Sources: Electronic records up to March 2014 were searched from MEDLINE, Embase, PsycINFO, Cochrane Library, Allied and Complementary Medicine Database, and Cumulative Index to Nursing and Allied Health Literature. Search terms included *Alzheimer's disease* and *cholinesterase inhibitors,* plus *discontinuation* or *cessation* or *tapering* or *withdrawal*. There were no language limits.

Study Selection: Randomized, double-blind, placebo-controlled studies investigating the effect of ChEI discontinuation on patients with AD according to standardized criteria (eg, National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association, *DSM-IV*) and presenting measurable results of neuropsychological testing were included.

Data Extraction: Demographics, setting, ChEI treatment length, discontinuation protocol, follow-up duration, study outcomes, and dropouts during the double-blind phase were extracted.

Results: Of 1,430 records returned, 18 were reviewed. Five ChEI discontinuation randomized controlled trials (N = 321 continued and N = 332 discontinued, following patients for 1.5–24 months) were analyzed. Discontinued patients demonstrated a significant worsening of cognition (standard mean Mini-Mental State Examination difference: −0.29 [95% CI, −0.45 to −0.13], N = 300 continued/307 discontinued, $P < .001$), a significant worsening of neuropsychiatric symptoms (standard mean Neuropsychiatric Inventory difference: −0.32 [−0.51 to −0.12], N = 199/211, $P = .001$), and significantly higher dropout rates (risk ratio [RR] = 1.33 [1.11–1.59], N = 321/332, $P = .002$) compared to those who continued. No difference in adverse events was observed (RR = 1.01 [0.85–1.20], N = 314/326, $P = .92$).

Conclusions: ChEI discontinuation may have negative effects on cognition and neuropsychiatric symptoms, a finding corroborated by a higher incidence of trial dropout.

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[a]Neuropsychopharmacology Research Group, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[b]Departments of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada
[c]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
**Corresponding author:* Nathan Herrmann, MD, Neuropsychopharmacology Research Group, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Ste FG08, Toronto, Ontario, Canada, M4N 3M5 (nathan.herrmann@sunnybrook.ca).

Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disorder, characterized by cognitive impairment and functional decline. It is the most prevalent form of dementia, accounting for 60%–70% of all dementias, and is estimated to impact 35.6 million people globally.[1]

Currently, the symptoms of AD are treated with second-generation cholinesterase inhibitors (ChEIs), such as donepezil, rivastigmine, and galantamine, as well as the *N*-methyl-D-aspartate receptor antagonist memantine. ChEIs are currently indicated for use in mild to moderately severe stages of AD; however, donepezil and the rivastigmine transdermal patch have received additional approval for the treatment of severe AD in the United States and Canada. Memantine has also been approved for use in moderate to severe AD.

Meta-analyses of randomized controlled trials (RCTs) have shown that ChEI treatment provides modest benefits for cognition, neuropsychiatric symptoms, and function for up to 1 year.[2,3] Large population-based studies have revealed that patients are typically maintained on these medications for much longer periods of time, with one study finding that patients were using ChEIs for 2 to 3 years on average and, in over half of observed cases, until death.[4] In light of this, various clinical practice guidelines have recommended that ChEIs should be administered until a therapeutic benefit is no longer evident, after which these medications should be discontinued.[5,6] However, literature addressing the definition of a clinically relevant therapeutic benefit and the effects of ChEI discontinuation is limited. There is some evidence from open-label trials supporting the long-term cognitive effects of ChEIs,[7,8] although evidence from double-blind RCTs is lacking due, in part, to the ethical limitations of conducting lengthy RCTs. It is also important to note that ChEI use has been associated with increased risk of nausea, vomiting, weight loss, syncope, and bradycardia, all of which may be cause for concern in a frail elderly population.[2,3,9] Ultimately, it is unclear how long these medications remain effective and whether patients in more advanced stages of AD derive sufficient benefit to justify the potential adverse effects associated with continued use. In light of this uncertainty, we conducted a meta-analysis to summarize the effects of ChEI discontinuation on cognition, neuropsychiatric symptoms, and adverse events in mild, moderate, and severe AD.

Clinical Points

- The effectiveness of cholinesterase inhibitors (ChEIs) for symptoms of Alzheimer's disease (AD) has been established over the short term, but the long-term effectiveness is unclear. Given the potential negative side effects of ChEIs, it is clinically important to determine if their benefits outweigh their side effects over the long term in AD patients.
- This article demonstrates that discontinuation from a ChEI after prolonged stable use is associated with a clinically relevant deterioration of cognitive function and neuropsychiatric symptoms but no change in adverse events in AD patients. Therefore, ChEI discontinuation in AD outpatients must be approached cautiously, on a case-by-case basis.

METHOD

Search Strategy and Selection Criteria

Literature was searched using Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), PsycINFO, the Cochrane Library, Allied and Complementary Medicine Database, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) up to March 2014. Search terms included *Alzheimer's disease* and *cholinesterase inhibitors* (exploded to include *donepezil* or *rivastigmine* or *galantamine*) plus *discontinuation* or *cessation* or *tapering* or *withdrawal*. The search was then repeated using the keywords as Medical Subject Headings (MeSH). Reference lists of retrieved studies were searched for additional reports.

Reports of original work investigating the effect of ChEI discontinuation on patients with AD according to standardized criteria (eg, National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA][10]) were included. Included studies were required to be double-blind placebo-controlled RCTs and to present measurable results of neuropsychological testing. Studies were not limited by language.

Data Extraction

Two independent reviewers examined each retrieved article for eligibility. Results were compared between reviewers, and disagreements were settled by consensus with a third reviewer. The methods and results sections of each included article were examined, and all participant and study characteristics (eg, setting, prior treatment/medications, discontinuation protocol, duration of follow-up, study outcomes, and dropouts during the double-blind phase) were extracted. Data that could not be retrieved from online reports were sought directly through contact with study authors.

Evaluation of Quality Reporting

Selected studies were analyzed for reporting quality by 2 independent raters using items from the Newcastle-Ottawa Scale[11] and the Cochrane Collaboration's risk of bias assessment tool.[12] These items addressed key methodological and reporting criteria relevant to included studies.

Statistical Analysis

Data from measures of cognitive function such as the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) were extracted from the included studies. ADAS-cog/11 scores were statistically converted to MMSE scores[13] for those studies not reporting MMSE scores. Neuropsychiatric symptoms, as measured by the Neuropsychiatric Inventory (NPI), were also extracted from 3 of the included studies.[14,15]

Standardized mean differences (SMDs) and 95% confidence intervals were calculated using a fixed-effects model.[16] Fixed-effects models are appropriate when significant heterogeneity (diversity in characteristics) among the studies is not present.[17] Heterogeneity among combined results was evaluated with a Q statistic, calculated in a χ^2 analysis. To determine the impact of heterogeneity, inconsistency was assessed using an I^2 index.[18] Meta-regressions were performed with study participant characteristics to identify potential influencers of discontinuation effects. Effect sizes, heterogeneity, risk of publication bias (Egger test[19]), and meta-regressions were calculated using Stata (Release 10.1, StataCorp, Texas).

The clinical impact of meta-analytic results was estimated by converting SMDs for each outcome into their respective test score units. SMDs represent the difference between treatment groups on a particular test as a fraction of that test's standard deviation. Accordingly, weighted averages of MMSE and NPI test standard deviations across the included studies were calculated. SMDs for each outcome were then converted into MMSE or NPI score units using the following equation: test score = SMD of test × weighted standard deviation of test. Dropouts were defined as any patient who did not complete the trial, and differences between treatment groups were calculated using a risk ratio. For cognitive and neuropsychiatric outcomes, the intent-to-treat population was used.

RESULTS

Literature Search Results

The initial search strategy yielded 1,430 publications in total. Of these, 16 articles were relevant to AD, ChEIs, and discontinuation. Two articles were found through a manual search of reference lists. A total of 13 articles were excluded as 6 were not double-blind, placebo-controlled RCTs, 3 were reviews, 2 were study protocols, 1 was a commentary, and 1 was a conference abstract of an included study. In total, 5 studies were identified as eligible for this meta-analysis (Supplementary eFigure 1) (Table 1).[14,15,20–22] In Gaudig et al,[21] only the galantamine discontinuation and continuation arms from study 2 met inclusion criteria for this meta-analysis. The risk of study and reporting bias was judged to be low for each of the included studies as they each addressed the majority of bias sources (Supplementary eTable 1). In

Table 1. Summary of Included Study Characteristics

Author/Year	ChEI Studied	Inclusion Criteria	Duration	Previous Duration of ChEI Therapy	Sample Size	Patient Characteristics (ChEI/placebo)[a]	Tapering	Study Endpoints
Gaudig et al, 2011 (Study 2)[21]	GAL	NINCDS-ADRDA probable or possible AD, completed 3 mo of GAL treatment, MMSE 11–24, ≥12 on ADAS-cog/11	6 wk	3 mo	GAL: 32 Placebo: 39	Age (y): 75.3 ± 1.1/76.5 ± 1.3 Gender (% male): 34.4/48.7 ADAS-cog/11: 23.6 ± 2.2/24.9 ± 1.5	Direct discontinuation	Primary: ADAS-cog/11
Holmes et al, 2004[14]	DPZ	Age ≥ 55 y, NINCDS-ADRDA probable or possible AD ≥6 mo duration, community dwelling residents with caregivers, MMSE 10–27, NPI ≥ 11 points from at least 3 domains of behavior, no loss of >2 points on MMSE following open-label phase	3 mo	3 mo	DPZ: 41 Placebo: 55	Age (y): 78.6 ± 1.4/78.8 ± 1.2 Gender (% male): 46/33 MMSE: 21.1 ± 0.9/20.8 ± 0.6 NPI: 14.3 ± 1.4/15.1 ± 1.8	Direct discontinuation	Primary: NPI Secondary: NPI-D
Howard et al, 2012[15]	DPZ	NINCDS-ADRDA probable or possible AD, SMMSE 5–13, community dwelling residents with daily caregivers, prescribed donepezil for at least 3 mo prior to study enrollment and on 10 mg donepezil for the previous 6 wk, no changes in prescription of any psychotropic drugs in the previous 6 wk	12 mo	At least 3 mo (mean = 32.5 ± 4.2)	DPZ: 73 Placebo: 73	Age (y): 77.2 ± 7.5/77.7 ± 8.0 Gender (% male): 30/36 MMSE: 9.0 ± 2.8/9.1 ± 2.4 NPI: 22.3 ± 16.7 /22.9 ± 17.0	Discontinuation after 4 wk of tapering	Primary: SMMSE, BADLS Secondary: NPI, DEMQOL-Proxy, GHQ-12
Johannsen et al, 2006 (phase 2)[22]	DPZ	Age ≥ 50 y, *DSM-IV* and NINCDS-ADRDA probable or possible AD, MMSE 10–26, ambulatory outpatients with sufficient vision and hearing, no decline or change on MMSE, and a PQ answer of "no" following open-label phase	3 mo	3–6 mo	DPZ: 99 Placebo: 103	Age (y): 74.1 ± 7.6/71.4 ± 9.3 Gender (% male): 40.4/36.9 MMSE: 18.8 ± 4.8/18.5 ± 4.8	Direct discontinuation	Primary: ADAS-cog/11 Secondary: MMSE, NPI, DAD
Scarpini et al, 2011[20]	GAL	Age ≥ 50 y, NINCDS-ADRDA probable or possible AD, MMSE 11–24, outpatients, no decline of <4 points on ADAS-cog/11 following open-label phase	24 mo	12 mo	GAL: 76 Placebo: 63	Age (y): 74.5/74.4 Gender (% male): 35.5/46 ADAS-cog/11: 20.4 ± 8.8/23.0 ± 8.7	Direct discontinuation	Primary: time to deterioration (deterioration in the ADAS-cog/11 score of ≥4 points)

[a]Age and outcome scores expressed as mean ±SD (Scarpini et al[20] did not provide standard deviations for age).

Abbreviations: AD = Alzheimer's disease, ADAS-cog/11 = Alzheimer's Disease Assessment Scale-cognitive subscale, BADLS = basic activities of daily living, ChEI = cholinesterase inhibitor, DAD = Disability Assessment for Dementia scale, DPZ = donepezil, GAL = galantamine, GHQ-12 = General Health Questionnaire 12, MMSE = Mini-Mental State Examination, NINCDS-ADRDA = National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association, NPI = Neuropsychiatric Inventory, NPI-D = Neuropsychiatric Inventory-Distress, PQ = Physician Questionnaire, SMMSE = Standardized Mini-Mental State Examination.

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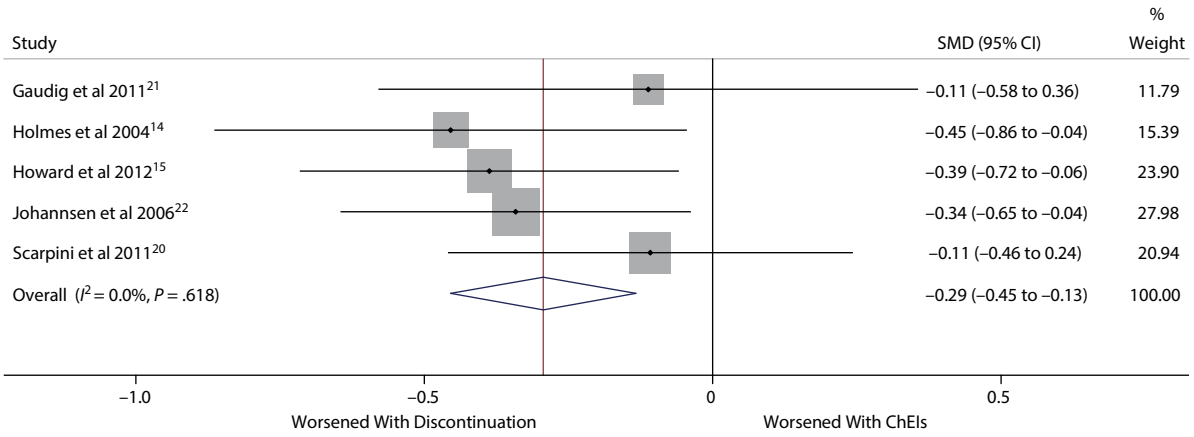
Figure 1. Effects of Cholinesterase Inhibitor (ChEI) Discontinuation on Global Cognitive Performance (Mini-Mental State Examination score) Over Trial Duration[a]



[a]Effect sizes are calculated using standardized mean differences (SMDs) in a fixed-effects model. Summary statistics: n = 300 ChEI continuation groups/307 ChEI discontinuation groups; SMD = −0.29 (−0.45 to −0.13), Z = 3.56, P < .001; heterogeneity: Q = 2.62, df = 4, I^2 = 0.0%, P = .618.

Table 2. Results of Meta-Regression Analyses Between Treatment Effect Size and Selected Study Characteristics

Outcome	No. of Studies	Mean Age		% Male		Previous Duration of ChEI Therapy		Duration of Follow-Up		Baseline Severity (MMSE)	
		B (95% CI)	*P*	*B* (95% CI)	*P*	*B* (95% CI)	*P*	*B* (95% CI)	*P*	*B* (95% CI)	*P*
MMSE	5	−0.03 (−0.15 to 0.09)	.50	0.03 (−0.05 to 0.10)	.35	−0.00 (−0.03 to 0.02)	.76	0.01 (−0.02 to 0.04)	.46	0.01 (−0.04 to 0.07)	.51
NPI	3	−0.00 (−0.52 to 0.51)	.94	−0.03 (−0.50 to 0.43)	.55	0.01 (−0.09 to 0.10)	.54	0.02 (−0.2 to 0.31)	.55	−0.02 (−0.27 to 0.24)	.52

Abbreviations: ChEI = cholinesterase inhibitor, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory.

all included studies, participants were randomly assigned to continue or discontinue ChEIs (receiving placebo) and were blind to their treatment allocation.

The mean length of follow-up across the included studies was 42 weeks. Changes in MMSE scores ranged from an increase of 1.6 points to a decrease of 5.6 points over that time. The average standard deviation of MMSE change scores was 4.8. Changes in NPI scores ranged from an increase of 3.3 points to a decrease of 2.9 points over a mean of 42 weeks. The average standard deviation of NPI change scores was 10.2.

Effects of ChEI Discontinuation on Cognition

AD patients discontinuing a ChEI demonstrated a significant worsening of cognition (MMSE) from baseline to study endpoint compared to patients who continued a ChEI (Figure 1). There was no significant heterogeneity (Figure 1) or publication bias (Egger test: t = −0.56, P = .62) detected across the included studies. There were no associations between discontinuation effects and study or participant characteristics (Table 2).

Effects of ChEI Discontinuation on Neuropsychiatric Symptoms

Three of the 5 included studies[14,15,22] reported data on neuropsychiatric symptoms (NPI). AD patients who discontinued a ChEI demonstrated a worsening of neuropsychiatric symptoms from baseline to study endpoint compared to those who continued ChEI use (Figure 2). There was no significant heterogeneity (Figure 2) or publication bias (Egger test: t = −0.78, P = .58) detected across the included studies. There were no associations between discontinuation effects and study or participant characteristics (Table 2).

Safety and Tolerability of ChEI Discontinuation

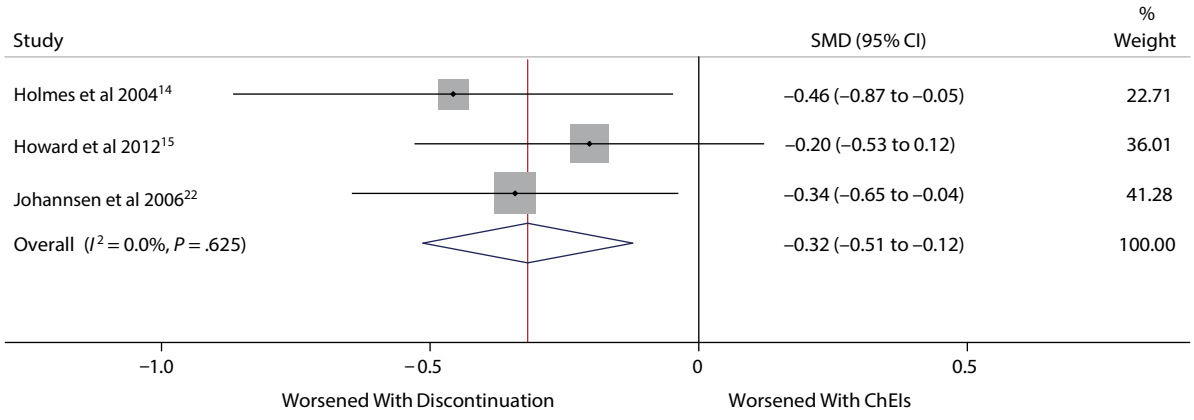
The ChEI discontinuation groups had a significantly greater proportion of dropouts (any reason) than the ChEI continuation groups from baseline to study endpoint (Table 3). Adverse event incidence and study dropout due to death were similar between continuation and discontinuation groups. No significant heterogeneity or publication bias was detected across the included studies (Table 3).

Three studies described the nature of the adverse events.[15,21,22] The most commonly reported adverse events included falls, nausea, diarrhea, respiratory infection, urinary tract infection, confusion, headache, dizziness, agitation, tremor, and vomiting.

Clinical Relevance of MMSE and NPI Outcomes

The SMD between the continuation and discontinuation groups on the MMSE was −0.29, indicating that the discontinuation groups declined an additional 1.4 MMSE points (−0.29 SMD × 4.8 MMSE average SD) relative to the continuation group over the 42-week mean follow-up time. In terms of an absolute rate of decline estimated over 52 weeks, the discontinuation groups experienced a mean decline of −2.6 MMSE points, while continuation

Figure 2. Effects of Cholinesterase Inhibitor (ChEI) Discontinuation on Neuropsychiatric Symptoms (Neuropsychiatric Inventory score) Over Trial Duration[a]



[a]Effect sizes are calculated using standardized mean differences (SMDs) in a fixed-effects model. Summary statistics: n = 199 ChEI continuation groups/211 ChEI discontinuation groups; SMD = −0.32 (−0.51 to −0.12), Z = 3.19, P = .001; heterogeneity: Q = 0.94, df = 4, I^2 = 0.0%, P = .625.

Table 3. Safety and Tolerability Outcomes Between Treatment and Placebo Groups Within the Included Studies

Outcome	No. of Studies	N (treatment/ placebo)	Comparative Outcome				Heterogeneity			
			RR	95% CI	Z	P	Q	df	P	I^2 (%)
Adverse event	5	314/326	1.01	0.85–1.20	0.10	.92	3.88	4	.42	0.0
Dropout	5	321/332	1.33	1.11–1.59	3.15	.002	1.62	4	.81	0.0
Dropout due to death	3	248/238	1.53	0.80–2.95	1.28	.20	0.95	2	.62	0.0

Abbreviation: RR = risk ratio.

groups experienced less decline, −1.0 MMSE points. The discontinuation groups experienced a mean increase of 3.8 NPI points relative to the continuation groups.

DISCUSSION

The results of this meta-analysis suggest that ChEI discontinuation may be associated with a statistically significant deterioration in cognition and neuropsychiatric symptoms in AD patients. These changes may also be clinically relevant, as patients continued on ChEIs experienced approximately one-third the rate of cognitive decline observed in untreated AD[23] (−1.0 [ChEI] vs −3.3 [untreated] MMSE points per year), whereas those discontinued from ChEI therapy experienced a rate approaching the natural rate of decline (−2.6 vs −3.3 MMSE points per year). Importantly, worsening cognition is associated with AD progression and functional decline.[24] ChEI discontinuation effects on neuropsychiatric symptoms were similar. An increase of 4 NPI points is thought to indicate a clinically significant worsening of neuropsychiatric symptoms in AD.[25] Patients in the discontinuation groups experienced an estimated average increase of 3.8 NPI points over 1 year relative to those who continued, approaching the threshold for clinically significant worsening of neuropsychiatric symptoms. Worsening of neuropsychiatric symptoms has been associated with greater impairment in activities of daily living, decreased quality of life, earlier institutionalization, increased cost of care, and greater caregiver depression.[26,27]

The worsening of cognition and of neuropsychiatric symptoms observed after ChEI discontinuation across the included studies are important factors for clinicians to consider when deciding whether or not to discontinue ChEI therapy. Nevertheless, the decision to discontinue therapy should remain highly individualized, and other factors such as side effects, current cognitive and functional status, and caregiver preference should be taken into account in addition to the potential for cognitive and neuropsychiatric deterioration.[28]

The significant cognitive decline observed in the ChEI discontinuation group might be explained as a loss of therapeutic benefit upon removal of the ChEI. Cholinergic neuronal degeneration and loss of cholinergic neurotransmission are thought to be contributing factors to the cognitive deficits associated with AD.[29] ChEIs work by inhibiting the acetylcholinesterase enzyme, thereby preventing the breakdown of acetylcholine and enhancing acetylcholine neurotransmission. Cessation of the ChEI may therefore lead to an increase in acetylcholinesterase activity, causing reductions in acetylcholine levels. As a result, the therapeutic benefit of the medication may be lost, revealing the underlying degree of cognitive impairment. In line with this hypothesis would be the suggestion that ChEIs demonstrate therapeutic benefits in mild to moderate and severe AD patients despite prolonged use.

Conversely, the cognitive effects of ChEI discontinuation observed by this meta-analysis may also be explained by a ChEI withdrawal effect in the discontinued group. It has

been postulated that prolonged administration of ChEIs may cause drug tolerance, characterized by up-regulation of acetylcholinesterase and down-regulation of acetylcholine receptors within the central nervous system (CNS).[30–32] Upon ChEI discontinuation, the CNS may be unable to rapidly compensate for the reduced synaptic levels of acetylcholine, leading to the emergence of withdrawal symptoms.[31] Case reports have described delirium, confusion, cognitive decline, increased anxiety, and agitation in patients 5 to 6 days following ChEI discontinuation.[32,33] Although cognitive decline is expected in AD, in all of the studies included in this meta-analysis the discontinuation group maintained poorer cognitive performance at each follow-up time point compared to those continued on ChEIs. In the study by Holmes et al,[14] it was speculated that the reemergence of neuropsychiatric symptoms upon donepezil cessation was not caused by a withdrawal effect, as symptoms in 10 placebo arm dropout patients were still persisting upon termination (average period of 30.5 days after randomization). Furthermore, the lack of significant heterogeneity in each outcome suggested that differences in tapering from ChEIs (rate of withdrawal) in the discontinuation groups did not have a substantial effect on changes in cognition or neuropsychiatric symptoms in the included studies. If patients were experiencing a true withdrawal syndrome, similar to those described in case reports, we might expect to observe an acute increase in the rate of cognitive deterioration followed by a return to the level of cognitive functioning that is typical of that AD stage (ie, the level observed in the group continued on ChEIs). Accordingly, our findings suggest that the decline observed following cessation might be caused by a loss of therapeutic efficacy rather than a withdrawal effect.

Neuropsychiatric symptoms may be influenced by cholinergic deficits.[26] It is therefore conceivable that patients who discontinue ChEI use may experience greater neuropsychiatric symptoms due to reductions in acetylcholine levels following ChEI cessation. However, an open-label study[34] examining ChEI discontinuation in 44 institutionalized patients with AD was unable to detect any differences between the ChEI discontinuation group and the control group with respect to neuropsychiatric symptoms as measured by the NPI, but did observe significant decreases in neuropsychiatric symptoms in the discontinuation group. Although this study was excluded from this meta-analysis due to its design (nonrandomized, nonblinded), these conflicting findings highlight the need for more RCT data to confirm the effects of ChEI discontinuation on neuropsychiatric symptoms.

In terms of safety and tolerability, this study found that patients randomized to ChEI discontinuation were more likely to drop out for any reason in comparison to those who continued on ChEI therapy. However, there were no differences in the number of adverse events or deaths experienced between those who continued and discontinued ChEIs. It is important to note, however, that there are conflicting case reports describing the alleviation of side effects upon ChEI cessation.[35,36] Those reports were not included in this meta-analysis because of lack of randomization and blinding. In discontinuation studies, all patients, caregivers, and treating physicians are aware of the potential to receive a placebo. As such, any perceived deterioration may lead to trial dropout, as the patient can easily begin using a ChEI on an open-label basis. Accordingly, the statistically significant increase in dropout from the discontinuation arms of the included studies, unrelated to adverse events, indicates that ChEI discontinuation likely resulted in clinically significant changes in function.

The lack of heterogeneity for each outcome indicates that the effect of ChEI discontinuation was consistent across studies. This is surprising considering the variation between study designs. For instance, of the 5 included studies, 3 examined the effects of donepezil discontinuation,[14,15,22] while the others studied galantamine cessation.[20,21] Additionally, the studies all varied in duration of follow-up. One study looked at patients for 6 weeks[21]; 2 studies, for 3 months[14,22]; and the other 2 studies followed patients for 12 and 24 months, respectively.[15,20] The populations were also different with respect to AD severity, as 4 studies included patients with mild to moderate AD, and the other examined moderate to severe AD. Finally, the studies varied significantly in terms of the duration of ChEI treatment prior to randomization: 3 studies randomized after only 3 months of acute treatment, 1 after 12 months,[20] and another with varying degrees of treatment but an average of 33 months. While we did not find associations between study characteristics and discontinuation effects in meta-regression, those findings were limited by the small number of included studies.

Interestingly, of the 3 studies[14,15,20] that followed patients for longer than 6 weeks, all observed the greatest rate of cognitive decline in the 6 weeks following discontinuation regardless of the length of previous ChEI use. As such, the majority of the statistical difference in outcomes may be accounted for during the first 6 weeks of discontinuation, limiting the heterogeneity between the studies. This can potentially provide clinicians with an important clinical guideline: when discontinuing a ChEI, patients should be monitored closely for 6 weeks for significant declines in cognition or worsening of neuropsychiatric symptoms.

This is the first meta-analysis of RCTs assessing the discontinuation of ChEIs in AD patients. Limitations include the small number of studies included and the inability to perform subanalyses for individual ChEIs. For example, we could not determine the effect of rivastigmine discontinuation on measures of cognition or neuropsychiatric symptoms, as rivastigmine was not examined in any study. The included studies were also limited by relatively small sample sizes and large variability, which led to wide confidence intervals for each study and a relatively small number of patients in our meta-analysis of study outcomes. Additional studies are needed to confirm these findings. The included studies were restricted to community dwelling patients, limiting the generalizability of these findings to that population. Thus, we are unable to determine the effects of ChEI discontinuation

in institutionalized AD patients, a population in which the balance between cognitive efficacy and adverse events may be different. For 2 of the included studies,[20,22] MMSE scores were calculated from ADAS-cog scores[13] and are therefore an approximation. However, the calculated effect sizes and tests of statistical significance were consistent with findings in both of those studies.

CONCLUSIONS

This meta-analysis indicates that discontinuation of ChEI use after variable lengths of treatment duration is associated with a worsening of cognition and neuropsychiatric symptoms. As such, the decision to discontinue AD patients from ChEI therapy after long-term use should remain highly individualized. Clinicians considering ChEI discontinuation should be particularly cognizant of the risk for cognitive and neuropsychiatric decline within the first 6 weeks following discontinuation and should monitor patients closely during this timeframe. It may be advantageous to initiate a slower tapering regimen to minimize these effects. More double-blind RCTs of ChEI discontinuation after long-term use are required to better elucidate the effects of ChEI discontinuation and help clarify discontinuation guidelines.

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Drug names: donepezil (Aricept and others), galantamine (Razadyne and others), memantine (Namenda), rivastigmine (Exelon and others).

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Cholinesterase Inhibitor Discontinuation in Patients With Alzheimer's Disease: A Meta-Analysis of Randomized Controlled Trials

Author(s): Jordana O'Regan, MSc; Krista L. Lanctôt, PhD; Graham Mazereeuw, PhD; and Nathan Herrmann, MD, FRCPC

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List of Supplementary Material for the article

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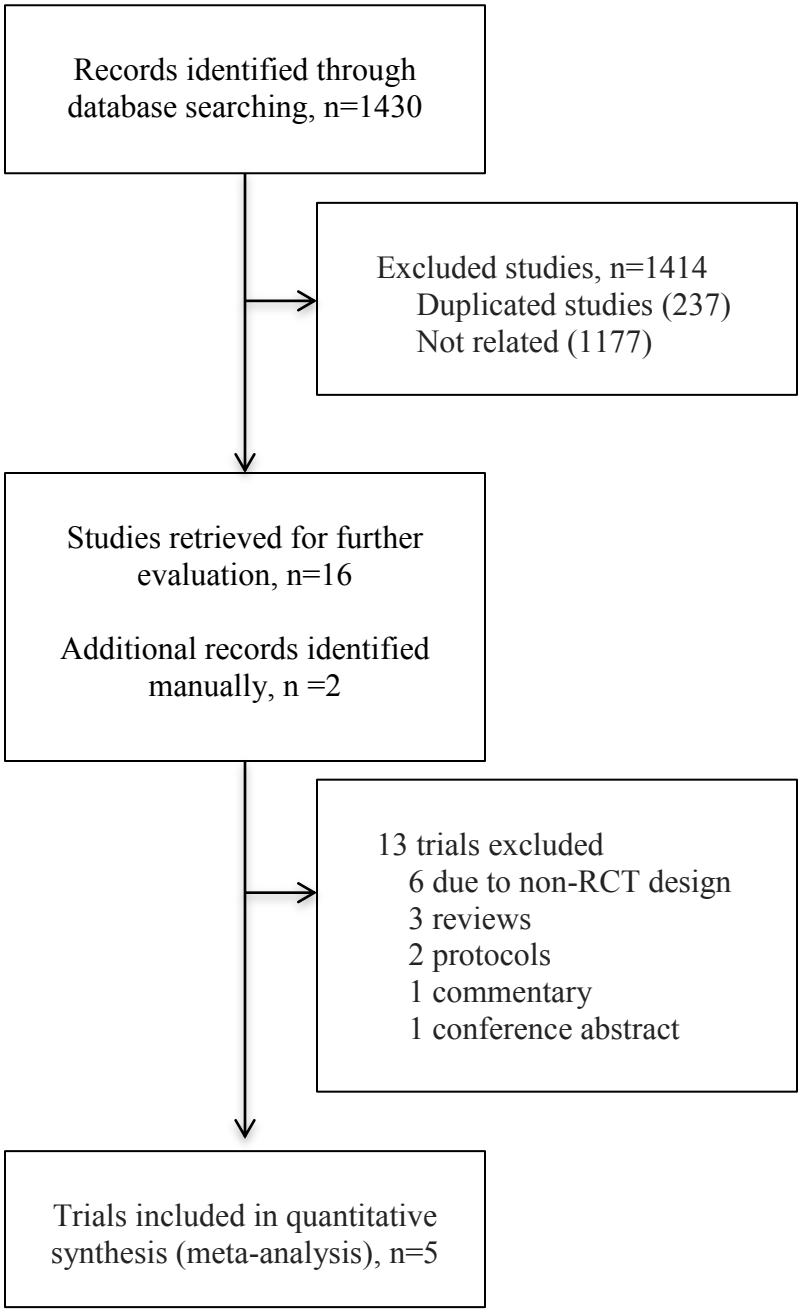
This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary files



Supplementary eFigure 1: PRISMA flow diagram

Supplementary files

Supplementary eTable 1: Study quality indicators and risk of bias items

	General risk of bias items									Reporting quality				
	All patients met AD criteria*	Random sequence generation	Unbiased participant selection	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Similarly aged groups	Similar gender proportion	Similar in other characteristics	Demographics reported	Concomitant medications reported	Medical co-morbidities reported	Tapering/discontinuation protocol reported	Likelihood of high overall quality
Gaudig, 2011	+	+	+	+	?	?	+	+	+	+	?	-	+	+
Holmes, 2004	+	+	-	+	+	+	+	+	+	+	+	-	+	+
Howard, 2012	+	+	+	+	+	+	+	+	+	+	?	-	+	+
Johannsen, 2006	+	+	-	+	?	?	+	+	+	+	+	-	-	+
Scarpini, 2011	+	+	-	+	?	?	+	?	?	+	+	?	-	+

+ Yes; - No; ? uncertain

* DSM-IV and/or NINCDS-ADRDA criteria

Risk of bias was assessed using study quality items from the Newcastle Ottawa scale[11] and the Cochrane Collaboration's risk of bias assessment tool[12], addressing key methodological criteria relevant to included studies. Overall methodological quality was assessed based on a composite of individual indicators.