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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Discontinuation of Cholinesterase Inhibitors in Adults with Dementia: Clinical Effectiveness and Guidelines

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Research Questions

1. What is the clinical effectiveness of discontinuing cholinesterase inhibitors in adults who have dementia?
2. What are the evidence-based guidelines for discontinuing cholinesterase inhibitors in adults who have dementia?

Key Findings

One systematic review with meta-analysis and five randomized controlled trials were identified regarding the clinical effectiveness of discontinuing cholinesterase inhibitors in adults who have dementia. Three evidence-based guidelines were identified regarding discontinuing cholinesterase inhibitors in adults who have dementia.

Methods

This report makes use of a literature search strategy developed for a previous CADTH report. For the current report, a limited literature search was conducted by an information specialist on key resources including Medline and PsycINFO via OVID, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were cholinesterase inhibitors, dementia, and discontinuation. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and October 30, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with dementia (e.g., Alzheimer's disease)
Intervention	Discontinuation of cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine)
Comparator	Q1: Continuation of cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., changes in cognitive function, functional status, quality of life, safety) Q2: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

One systematic review with meta-analysis[1] and five randomized controlled trials[2-6] were identified regarding the clinical effectiveness of discontinuing cholinesterase inhibitors in adults who have dementia. Three evidence-based guidelines[7-9] were identified regarding discontinuing cholinesterase inhibitors in adults who have dementia. No relevant health technology assessments or non-randomized studies were identified regarding the clinical effectiveness of discontinuing cholinesterase inhibitors in adults who have dementia.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

One systematic review with meta-analysis[1] and five randomized controlled trials[2-6] were identified regarding the clinical effectiveness of discontinuing cholinesterase inhibitors in adults who have dementia. The authors of the systematic review with meta-analysis[1] included five randomized controlled trials all comparing continued (n = 321) use and discontinued (n = 332) use of cholinesterase inhibitors. Despite lack of differences in adverse events, subjects in discontinuation groups exhibited a significant decrease in cognition and neuropsychiatric symptoms and an increase in dropout rates versus subjects in continuation groups.[1]

Two randomized controlled trials[2,4] investigated the effects of donepezil discontinuation in patients with Alzheimer's disease. Hong et al. randomized 65 patients with extremely severe Alzheimer's disease and taking donepezil or memantine into two groups: discontinuation (n = 35) and continuation (n = 30).[2] After 12 weeks, the discontinuation and continuation group exhibited a 0.5-point decrease and 0.4-point increase in the Baylor Profound Mental State Examination score, respectively.[2] Thus, continuation with donepezil or memantine may be superior to discontinuation with respects to cognition.[2] Howard et al. randomized 295 patients with moderate or severe Alzheimer's disease and taking donepezil into four groups: discontinue donepezil, continue donepezil, discontinue donepezil and start memantine, and continue donepezil and start memantine.[4] During the 52-week trial, subjects in the continued donepezil group exhibited significant functional improvements, and cognitive benefits compared to the other groups.[4]

Additionally, two randomized controlled trials[5,6] investigated the effects of galantamine discontinuation in patients with Alzheimer's disease. In a double-blind randomized controlled trial, Gaudig et al. measured the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale at baseline and 6 weeks.[5] At week 6, the discontinuation and continuation group experienced a mean reduction of 0.7 points and improvement of 1.8 points in this subscale.[5] Continuing galantamine maintains previously achieved cognitive benefits when compared to discontinuing.[5] In another double-blind randomized controlled trial involving patients with mild or moderate Alzheimer's disease, Scarpini et al. investigated the effects of discontinuing galantamine after 12 months of use.[6] Between the discontinuation versus continuation groups, no statistically significant difference was detected for a change in the cognitive subscale of the Alzheimer's Disease Assessment Scale.[6] When compared to the continuation group, galantamine discontinuation subjects

were more likely to drop out prematurely for any reason or lack of efficacy.[6] Scarpini et al concluded that continued galantamine use was effective in delaying cognitive deterioration.[6]

Finally, another double-blind randomized controlled trial[3] investigated the effects of discontinuing cholinesterase inhibitors (donepezil, rivastigmine, or galantamine) in forty long-term care patients with moderate to severe Alzheimer's disease. Between the two groups, no significant differences were identified in rates of adverse events, or clinical worsening on the Clinician's Global Impression of Change scale.[3] Nonetheless, Herrmann et al. suggested using caution when discontinuing cholinesterase inhibitors in patients presenting with hallucinations and delusions.[3]

Summaries of relevant recommendations from three evidence-based guidelines[7-9] are included in Table 2.

Table 2: Summary of Relevant Recommendations in Included Guidelines

Recommendations
Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine, 2019[7]

Adults who are already taking a ChEI and/or memantine at the maximum tolerated dose, for a sufficient duration of time:
• *Trial deprescribing involves tapering (e.g., half the dose or step down with available dose formulations) every four weeks to the lowest available dose before completely stopping. Patients need to be periodically monitored and medication(s) need to be re-initiated at the previous minimum effective dose if the patient experiences a noticeable deterioration.[7] (p.7)*
• *For patients with Alzheimer's disease who have been taking a ChEI (donepezil, galantamine, rivastigmine) and/or memantine for more than 12 months, trial deprescribing is recommended if the patient:*
  - *has experienced significant deterioration in cognition and/or function over the last six months (or less)*
  - *has not had any benefit (i.e., improvement, stabilization, or reduced rate of decline) during treatment*
• *- has severe or end-stage dementia, which can be characterized by inability to respond to their environment, dependence in most activities of daily living and/or limited life expectancy.[7] (p.8)*

Dementia: Assessment, Management and Support for People Living with Dementia and their Carers (NICE), 2018[8]
The decision to stop ChEI should not be based solely on disease severity in patients with Alzheimer's disease.[8] (p.21)
Pharmacological Recommendations for the Symptomatic Treatment of Dementia: the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, 2012[9]
Compared to continuing therapy, discontinuing ChEI in patients with moderate or severe Alzheimer's disease may result in cognitive deterioration and functional impairment. ChEI can be discontinued if the patient: • *and/or their substitute decision maker decides to stop after being informed of the risks versus benefits;* • *is non-adherent to their medication therapy;* • *exhibits a rate of deterioration in cognition, function, and/or behaviour greater than before treatment;* • *is intolerant to medication-related adverse events;* • *has comorbidities making continued therapy unacceptably risk or futile (e.g., terminally ill); or* • *experiences disease progression (e.g., Global Deterioration Scale stage 7) making continued therapy not clinically meaningful.[9] (p.3)* *If discontinuation is appropriate, it is recommended to taper the dose before completely stopping the medication(s). During monitoring in the next 1 to 3 months, consider re-initiating the medication(s) if patient deterioration occurs.[9] (p.3)*

ChEI = cholinesterase inhibitor; NICE = National Institute for Health and Care Excellence

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. O'Regan J, Lanctot KL, Mazereeuw G, Herrmann N. Cholinesterase inhibitor discontinuation in patients with Alzheimer's disease: a meta-analysis of randomized controlled trials. *J Clin Psychiatry*. 2015;76(11):e1424-1431.
PubMed: PM26646039

Randomized Controlled Trials

2. Hong YJ, Choi SH, Jeong JH, Park KW, Na HR. Effectiveness of anti-dementia drugs in extremely severe Alzheimer's disease: a 12-week, multicenter, randomized, single-blind study. *J Alzheimers Dis*. 2018;63(3):1035-1044.
PubMed: PM29710726

3. Herrmann N, O'Regan J, Ruthirakuhan M, et al. a randomized placebo-controlled discontinuation study of cholinesterase inhibitors in institutionalized patients with moderate to severe Alzheimer disease. *J Am Med Dir Assoc*. 2016;17(2):142-147.
PubMed: PM26482056

4. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366(10):893-903.
PubMed: PM22397651

5. Gaudig M, Richarz U, Han J, Van Baelen B, Schauble B. Effects of galantamine in Alzheimer's disease: double-blind withdrawal studies evaluating sustained versus interrupted treatment. *Curr Alzheimer Res*. 2011;8(7):771-780.
PubMed: PM21707533

6. Scarpini E, Bruno G, Zappala G, et al. Cessation versus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial. *J Alzheimers Dis*. 2011;26(2):211-220.
PubMed: PM21606568

Non-Randomized Studies

No literature identified.

Guidelines and Recommendations

7. Reeve E, Farrell B, Thompson W, et al. Evidence-based clinical practice guideline for deprescribing cholinesterase inhibitors and memantine. Sydney (AU): University of Sydney: 2019; https://cdpc.sydney.edu.au/wp-content/uploads/2019/06/deprescribing-guideline.pdf. Accessed 2019 Nov 11.
See: Recommendations (p.7)

8. National Institute for Health Care and Excellence. Dementia: assessment, management and support for people living with dementia and their carers. *(NICE guideline NG97).* 2018: https://www.nice.org.uk/guidance/ng97. Accessed 2019 Nov 11.
See: *Section 1.5 Pharmacological management of Alzheimer's disease (p.21)*

9. Herrmann N, Lanctot KL, Hogan DB. Pharmacological recommendations for the symptomatic treatment of dementia: the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012. *Alzheimers Res Ther*. 2013;5(Suppl 1):S5.
PubMed: PM24565367
See: Table 1. Summary of approved recommendations (p.3)

Appendix — Further Information

Previous CADTH Reports

10. Discontinuance of cholinesterase inhibitors in adults with dementia: clinical effectiveness and evidence-based guidelines. *(CADTH Rapid response report).* Ottawa (ON): CADTH; 2010: https://www.cadth.ca/discontinuance-cholinesterase-inhibitors-adults-dementia-clinical-effectiveness-and-evidence-based. Accessed 2019 Nov 11.

Systematic Reviews and Meta-analyses

Unclear Methodology

11. Renn BN, Asghar-Ali AA, Thielke S, et al. A systematic review of practice guidelines and recommendations for discontinuation of cholinesterase inhibitors in dementia. *Am J Geriatr Psychiatry*. 2018;26(2):134-147. PubMed: PM29167065

Unclear Comparator

12. Ehret MJ, Chamberlin KW. Current practices in the treatment of Alzheimer disease: where is the evidence after the phase III trials? *Clin Ther*. 2015;37(8):1604-1616. PubMed: PM26122885

Randomized Controlled Trials – Alternative Outcome

13. Howard R, McShane R, Lindesay J, et al. Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analyses. *Lancet Neurol*. 2015;14(12):1171-1181. PubMed: PM26515660

14. Hager K, Baseman AS, Nye JS, et al. Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer's disease. *Neuropsychiatr Dis Treat*. 2014;10:391-401. PubMed: PM24591834

Non-Randomized Studies – No Comparator

15. Droogsma E, van Asselt D, Diekhuis M, Veeger N, van der Hooft C, De Deyn PP. Initial cognitive response to cholinesterase inhibitors and subsequent long-term course in patients with mild Alzheimer's disease. *Int Psychogeriatr*. 2015;27(8):1323-1333. PubMed: PM25779465

Clinical Practice Guidelines

16. Badrakalimuthu R. Cholinesterase inhibitors guideline. Southampton (GB): NHS Southern Health; 2019: http://www.southernhealth.nhs.uk/EasysiteWeb/getresource.axd?AssetID=42413&type=full&servicetype=Inline. Accessed 2019 Nov 11.

17. O'Brien JT, Holmes C, Jones M, et al. Clinical practice with anti-dementia drugs: a revised (third) consensus statement from the British Association for Psychopharmacology. *J Psychopharmacol*. 2017;31(2):147-168. PubMed: PM28103749

18. Berkshire Healthcare NHS. Acetylcholinesterase inhibitors; 2012: https://dementiapartnerships.com/wp-content/uploads/sites/2/nhs-berkshire-acetylcholinesterase-inhibitors.pdf. Accessed 2019 Nov 11.

Review Articles

19. Glynn-Servedio BE, Ranola TS. AChE inhibitors and NMDA receptor antagonists in advanced Alzheimer's disease. *Consult Pharm*. 2017;32(9):511-518. PubMed: PM28855009

20. Deardorff WJ, Grossberg GT. Pharmacotherapeutic strategies in the treatment of severe Alzheimer's disease. *Expert Opin Pharmacother*. 2016;17(13):1789-1800. PubMed: PM27450461

Additional References

21. Consultant Pharmacy Services, Primary Health Tasmania, PHN Tasmania. A guide to deprescribing - cholinesterase inhibitors; 2016: http://www.cpsedu.com.au/uploads/Documents/Deprescribing%202016%20Version/7.%20CHOLINESTERASE%20INHIBITORS%20V3.pdf. Accessed 2019 Nov 11.

22. Deardorff WJ, Feen E, Grossberg GT. the use of cholinesterase inhibitors across all stages of Alzheimer's disease. *Drugs Aging*. 2015;32(7):537-547. PubMed: PM26033268