

Comprehensive Research Plan:

Cognitive enhancers for the treatment of Alzheimer's disease

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A. Introduction

Cognitive enhancers (namely cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonist) are available in Canada for the treatment of patients with dementia, including Alzheimer's type. There are three cholinesterase inhibitors available in Canada (i.e., donepezil, rivastigmine, galantamine) and one N-methyl-D-aspartate (NMDA) receptor antagonist (i.e., memantine).

The objective of the drug class review on cognitive enhancers for patients with Alzheimer's disease is to provide evidence-informed recommendations for the use of these agents through the publicly funded drug program in Ontario. This comprehensive review will include:

- systematic review of the literature,
- cost-effectiveness and reimbursement-based analyses, and drug utilization studies using administrative claims data from Ontario and across Canada,
- environmental scans of national and international drug policies,
- contextualization of the available evidence and experience from other regions, with consideration given to health equity,
- qualitative analyses of perspectives of patients, pharmacists and prescribers,
- identification of barriers to, and enablers of, successful policy implementation,
- recommendation of potential drug reimbursement models.

B. Research Questions

Patient population and inclusion criteria

- Diagnosis of dementia of the Alzheimer's type
- Subgroup analysis: where possible, the review will consider age, gender, socioeconomic status and geographic location (e.g. urban/rural)

Drugs of interest

- Donepezil, galantamine, rivastigmine, memantine
- all dosage forms

Comparator(s)

- No active comparator drug; placebo-controlled trials will be included
- Comparisons between different cognitive enhancers

Proposal	Research unit	Research question(s)
Patient and Healthcare Professional Perspectives	Qualitative Research Program	<p>What is the perceived effectiveness of cognitive enhancers?</p> <p>What is the impact of cognitive enhancers on perceived quality of life?</p> <p>What is the experience of patients using cognitive enhancers regarding access of these drugs?</p> <p>What is the experience of prescribing these drugs?</p> <p>To what extent are the policy recommendations feasible and acceptable?</p>
Systematic Reviews and Network Meta-Analyses	Systematic Review Unit	<p>What is the comparative safety and efficacy of cognitive enhancers (alone or in combination) versus placebo for patients with Alzheimer's dementia?</p> <p>Which intervention (or combination) is the most effective and safe for patients with Alzheimer's dementia?</p>
Environmental Scan and Barriers to Implementation; Local and Historical Context	Formulary Modernization Unit	<p>How are cognitive enhancers currently being funded in public programs in Canada as well as internationally?</p> <p>What mechanisms are in place to maximize access while minimizing costs? How successful are these mechanisms in achieving a cost-access balance?</p>
Costs and Utilization Trends	Pharmacoepidemiology Unit	<ul style="list-style-type: none"> • To examine national and provincial trends in use of cognitive enhancers across Canada • To perform cross provincial comparisons of the trends in cognitive enhancer utilization • To describe characteristics of elderly patients prescribed publically-funded cognitive enhancers in Ontario • To investigate the patterns of use of cognitive enhancers among elderly patients in Ontario • To summarize any observational studies evaluating the comparative safety and effectiveness of cognitive enhancers
Health Equity	All units	Does sex/gender, age, geographical location (e.g., rural vs. urban) or socioeconomic status play an important role in any of the analyses described?

Proposal	Research unit	Research question(s)
Reimbursement-based Economics	Pharmacoeconomics Program	<p>What is the current evidence for the cost-effectiveness of cognitive enhancers, as compared with placebo, other cognitive enhancers, or best supportive care, for the treatment of Alzheimer’s disease (AD)?</p> <p>Based on a de novo economic model, what is the cost-effectiveness of cognitive enhancers versus placebo, other cognitive enhancers, or best supportive care for the treatment of AD?</p> <p>What is the budget impact of alternative policies for reimbursing cognitive enhancers versus placebo, other cognitive enhancers, or best supportive care for the treatment of AD?</p> <p>Based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing cognitive enhancers versus placebo, other cognitive enhancers, or best supportive care for the treatment of AD?</p>

C. Specific Proposals

The Drug Class Review is comprised of five different reviews, namely the Qualitative Research Unit, Systematic Review Unit, Pharmacoepidemiology Unit, Environment Scan/local and historical context and Pharmacoeconomics Unit. Further information on each of the proposals is can be found on our website: www.odprn.ca

1. Qualitative Review Unit

Objectives:

- To explore factors related to the experience of cognitive enhancer prescription and use
- To determine the social acceptability of reimbursement policy recommendations for cognitive enhancers

Study Questions:

- What is the perceived effectiveness of cognitive enhancers?
- What is the impact of cognitive enhancers on perceived quality of life?
- What is the experience of patients using cognitive enhancers regarding access of these drugs?
- What is the experience of prescribing these drugs?
- To what extent are the policy recommendations feasible and acceptable?

Phase 1: Exploration of factors affecting the dispensing and utilization of drugs within the drug class of interest

Study Design – This phase will use a qualitative framework approach to guide the data collection and analysis processes. One-on-one interviews and accompanying field notes will be the primary and secondary data sources, respectively.

Study Population – Identified stakeholders for the atypical antipsychotics drug class review include 1) patients over the age of 65 with dementia and/or their family members; 2) primary care physicians (PCPs) and long-term care (LTC) physicians; 3) nursing and support staff; 4) geriatricians; 5) health navigators including discharge planners and community care access centres (CCAC) staff; 6) pharmacists.

Methods – A purposive sampling approach using a convenience sample will be used in order to elicit the specific perceptions and opinions of those who will be involved in or affected by drug policy decisions. Clinicians will be recruited through circles of contact, professional networks and snowball recruitment. Publicly available contact information will also be searched to develop contact lists. An ODPRN member or study coordinator will make contact with clinicians by phone, e-mail or fax. Patients will be recruited through circles of contact. A patient recruitment flyer will also be sent to participating clinicians who agree to distribute the flyer to patients. Patient networks will be used to send recruitment notices by e-mail. General calls for recruitment of all eligible groups will be placed in professional newsletters, e-blasts and social media (Twitter, Facebook).

We will aim to recruit 6 to 8 participants from each identified stakeholder group and 20-25 patients, which may be sufficient to reach saturation amongst homogenous groups of participants. Note that for the cognitive enhancers review, we will be approaching the same participants involved in the atypical antipsychotics review to participate again in interviews. To reduce burden on these participants, the interviews will be shorter in length than those conducted for the previous drug class reviews.

Outcomes:

- Experiences of the disease condition and of taking cognitive enhancers
- Experiences accessing cognitive enhancers
- Experiences treating patients with and dispensing cognitive enhancers
- Perceived safety and effectiveness of cognitive enhancers
- Perceived barriers to access and health equity issues
- Any unanticipated issues related to cognitive enhancers

Phase 2: Assessment of the social acceptability of recommended policy actions related to the drug class of interest

Study Design – RAND Appropriateness Method and Survey

Study Population – Representatives of the general public; stakeholder groups (i.e. among the 6 groups described in Phase 1 above); patient advocacy groups; topic-specific interest groups; and industry

Methods – Members of the general public will be recruited to participate in a meeting/webinar to rate or prioritize a series of questions, discuss these questions, then re-rate and prioritize them. An online survey will also be distributed to assess aspects of social acceptability, including affordability, accessibility, and appropriateness. Survey analysis will include descriptive statistics (e.g., mean, standard deviation, median) and thematic content analysis for open-ended questions.

Outcomes -The primary outcome of interest is the feasibility and acceptability of draft recommendations

2. Systematic Review Unit

Study Questions:

- What is the comparative safety and efficacy of cognitive enhancers (alone or in combination) versus placebo for patients with Alzheimer’s dementia?
- Which intervention (or combination) is the most effective and safe for patients with Alzheimer’s dementia?

PICO (Population, interventions, comparator, outcomes)

Population	Patients with Alzheimer’s dementia (AD). Time permitting, a sub-group analysis by severity of AD may be conducted.
Interventions	Cognitive enhancers (donepezil, rivastigmine, galantamine, and memantine)

Comparator	Eligible comparators are: donepezil, rivastigmine, galantamine, and memantine in any combination, no treatment, placebo, and best supportive care. Concomitant Alzheimer’s disease medications will be included if all treatment arms receive the same interventions.
Outcomes: Efficacy	Potential efficacy outcomes: <ol style="list-style-type: none"> 1. Cognition –Mini-Mental State Examination [MMSE], Alzheimer’s Disease Assessment Scale-cognition subscale [ADAS-cog] 2. Function – Alzheimer’s Disease Cooperative Study activities of daily living inventory [ADCS-ADL] 3. Behaviour–Neuropsychiatric Inventory [NPI] 4. Global Status–Clinician’s Interview-Based Impression of Change plus Caregiver Input [CIBIC-plus] 5. Mortality
Outcomes: Safety	Potential safety outcomes include: nausea, diarrhea, vomiting, serious adverse events, headaches, falls, bradycardia
Included Study Designs	RCTs and non-randomized studies

Notes: Efficacy and safety outcome lists may be truncated if we identify many studies for inclusion, as this is a rapid review. We will not perform a meta-analysis (or network meta-analysis) on all of these outcomes and will work with all stakeholders to select the two most important efficacy outcomes and safety outcomes with sufficient data to conduct network meta-analysis. Prior to conducting network meta-analysis, we will ensure that all factors are considered as this analysis only is valid when homogenous studies and patient populations are included.

Methods

Information sources and literature search

The previous systematic review by Tricco et al. will be updated by conducting a comprehensive literature searches by an experienced librarian in consultation with the team. We will search the MEDLINE, EMBASE, and Cochrane Library electronic databases from September 2011 until January 2015. Literature saturation will be ensured by searching the reference lists of included studies and reference lists of relevant reviews.

Study selection

Two reviewers will screen citations for inclusion, independently (Level 1 screening). They will then independently review the full-text of potentially relevant articles to determine inclusion using the same inclusion and exclusion criteria (Level 2 screening). Conflicts will be resolved by discussion or the involvement of a third reviewer.

We will abstract data on study characteristics (e.g., study design, year of conduct [if not reported, we will use the year of publication], sample size, setting [e.g., hospital, community, multi-center, single center], country of study conduct [if not reported, we will use the country of origin of the first author], duration of treatment, duration of follow-up, intervention and comparator dosage, monotherapy, combination therapy), participant characteristics (e.g., number of patients, age mean and standard deviation, AD severity, how AD was diagnosed, baseline cognition, co-morbidities) Finally, we will abstract the outcome results (e.g. cognition, function, behaviour, global status, mortality, harms, and withdrawal) for the longest duration of follow-up only. We will appraise the included RCTs using the Cochrane Risk of Bias Tool.

Synthesis of included studies

We will first describe our results, reporting study characteristics, patient characteristics, risk of bias results, and frequencies of outcomes across the included studies. Subsequently, we will conduct meta-analysis, and Bayesian network meta-analysis, if deemed appropriate. Network meta-analysis will be conducted to derive the combined outcome effect size between each 2 comparisons, as well as rank the safety among all available interventions.

3. Pharmacoepidemiology Unit

Analysis 1 – National and provincial trends in cognitive enhancer drug use

Study question: To examine national and provincial trends of cognitive enhancers over the past 5 years

Short description of analysis: We will examine trends in cognitive enhancer use between 2009 and September 2014.

Analysis 2 – Cross-provincial changes in prescribing of cognitive enhancers in public drug programs

Study question: to examine cross-provincial changes in prescribing of cognitive enhancers in specific jurisdictions across Canada

Short description of analysis: We will examine changes in cognitive enhancer prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI and British Columbia between January 2000 and December 2013.

Analysis 3 – Characteristics of elderly patients prescribed cognitive enhancers in Ontario

Study question: To characterize elderly patients prescribed cognitive enhancers in Ontario

Short description of analysis: We will look at descriptive characteristics (January 2012-December 2013), including age, gender, socioeconomic status, proportion of patients with diagnosed dementia, concomitant psychotropic use, hospitalizations and emergency room visits, various comorbidity measures, long-term care or community dwelling

Analysis 4 – Investigate the adherence and patterns of use for newly initiated cognitive enhancer medications among elderly patients in Ontario

Study questions: To describe patterns of use for elderly patients newly initiated on cognitive enhancers

Short description of analysis: We will look at all publically-funded beneficiaries of Ontario age 66 and older who initiated cognitive enhancers over the study period.

4. Pharmacoeconomic Unit

Research Questions

- What is the current evidence for the cost-effectiveness of cognitive enhancers, as compared with placebo, other cognitive enhancers, or best supportive care, for the treatment of Alzheimer’s disease (AD)?
- Based on a de novo economic model, what is the cost-effectiveness of cognitive enhancers versus placebo, other cognitive enhancers, or best supportive care for the treatment of AD?
- What is the budget impact of alternative policies for reimbursing cognitive enhancers versus placebo, other cognitive enhancers, or best supportive care for the treatment of AD?
- Based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing cognitive enhancers versus placebo, other cognitive enhancers, or best supportive care for the treatment of AD?

Methods

RQ1 Systematic Review of Published Economic Evaluations

We will conduct a review of the available literature on the cost-effectiveness of cognitive enhancers, as compared with placebo, other cognitive enhancers, or best supportive care for the pharmacologic treatment of Alzheimer’s disease (AD).

RQ2 De Novo Economic Model

We will develop a new economic model assessing the cost-effectiveness of cognitive enhancers versus placebo, supportive care, and other cognitive enhancers for the treatment of patients with AD.

RQ3 Reimbursement Based Economic Assessment

We will develop a model which will identify the budget impact of alternative policies for the pharmacologic treatment of AD. Analysis will identify the change in the forecasted drug budget for the next three years associated with different reimbursement policies and will be discussed in conjunction with any impact on clinical effectiveness.

RG4 Reimbursement Based Economic Evaluation

We will use the results from the de novo economic model to identify the cost-effectiveness of the alternative policies relating to pharmacotherapies in the treatment of AD, as identified in RQ3.

5. Environmental Scan

Research Questions

1. To summarize the pharmacy benefit programs for cognitive enhancers (including cholinesterase inhibitors and memantine) in Ontario, across Canada and in select international jurisdictions

Method: summary of available information available through the Internet; interviews with individuals at the government agencies responsible for the public drug plan

Interventions:

- Cholinesterase inhibitors (i.e., donepezil, galantamine, rivastigmine)
- N-methyl-D-aspartate (NMDA) receptor antagonist (i.e., memantine)

2. To determine the impact of different drug reimbursement schemes for cognitive enhancers (e.g., restricted access) on patient access, quality of life and/or utilization and costs

Method: Literature review

Intervention: various drug reimbursement schemes, including general benefits, step therapy, special authorization

3. To summarize the guidelines for management of patients with Alzheimer's disease, in particular the use of cognitive enhancers in this patient population

Method: Literature review

Intervention: Guidelines/recommendations for the use of cognitive enhancers in patients with Alzheimer's disease