

Drugs for Overactive Bladder (OAB)

FINAL CONSOLIDATED COMPREHENSIVE RESEARCH PLAN

July 2015

A. Introduction

The objective of the drug class review on drugs for the treatment of overactive bladder is to provide evidence-informed recommendations for the use of these medications through the publicly funded drug program in Ontario. This comprehensive review will include:

- systematic review of the literature,
- reimbursement-based analyses,
- 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 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

- All adult patients with a diagnosis of overactive bladder
- Subgroup analysis: where possible, the review may consider age, gender, socioeconomic status and geographic location (e.g. urban/rural), co-morbid conditions, different formulations

Drugs of interest

Anticholinergics (antimuscarinics)

- Oxybutynin
- Tolterodine
- Trospium
- Darifenacin
- Solifenacin
- Fesoterodine
- Flavoxate

Other

- Beta-3 adrenergic agonist
 - Mirabegron
- Neuromuscular blockers
 - Onabotulinum toxin A

Comparator(s)

- Placebo-controlled trials
- All drugs of interest (as listed above)

Proposal	Research unit	Research question(s)
Patient and Healthcare Professional Perspectives	Qualitative Research Program	<p>What is the perceived effectiveness of overactive bladder therapies?</p> <p>What is the impact of overactive bladder therapies on perceived quality of life?</p> <p>What is the experience of patients using overactive bladder therapies regarding access of these drugs?</p> <p>What is the experience of prescribing these therapies?</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 current evidence for the efficacy and safety of pharmacologic treatments of OAB in adults?</p> <p>Does the efficacy or safety of pharmacologic treatments of OAB in adults vary depending on:</p> <ol style="list-style-type: none"> Sex Age (< 65 v. ≥ 65 yr) Previous pharmacologic treatment (naïve v. experienced) Setting (long-term care v. community)
Environmental Scan and Barriers to Implementation; Local and Historical Context	Formulary Modernization Unit	<p>How are OAB drugs currently being accessed in publicly funded programs across Canada as well as internationally?</p> <p>What is the impact of different reimbursement schemes for OAB drugs on patient access, quality of life and/or utilization and costs?</p> <p>Does sex, gender or socioeconomic status play an important role in any of the analyses described?</p>
Costs and Utilization Trends	Pharmacoepidemiology Unit	<p>To examine national and provincial trends in use of agents for overactive bladder (OAB) across Canada</p> <p>To perform cross provincial comparisons of the trends in utilization of OAB agents in public drug programs</p> <p>To describe characteristics of individuals prescribed publically-funded OAB agents in Ontario</p> <p>To investigate the average duration of OAB agent use among new users of these products in Ontario</p> <p>Review of observational studies that explore the comparative safety and/or adherence of OAB agents</p>
Health Equity	All units	Does sex/gender, age, geographical location (e.g.,

Proposal	Research unit	Research question(s)
		rural vs. urban) or socioeconomic status play an important role in any of the analyses described?
Reimbursement-based Economics	Pharmacoeconomics Program	<p>What is the current evidence for the comparative cost-effectiveness of pharmacologic treatments for overactive bladder (OAB) syndrome?</p> <p>Based on a de novo economic model, what is the comparative cost-effectiveness of pharmacologic treatments for OAB syndrome?</p> <p>What is the budget impact of alternative policies for reimbursing pharmacotherapies for the management of OAB syndrome?</p> <p>Based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing pharmacologic treatments for OAB syndrome?</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 prescription and use of overactive bladder therapies.
- To determine the social acceptability of reimbursement policy recommendations for overactive bladder therapies.

Study Questions:

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

Phase 1: Exploration of factors affecting the dispensing and utilization of drugs used for OAB

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 drugs for OAB review include 1) urologists; 2) primary care physicians (PCPs); 3) urogynecologists, and 4) adult patients who have used drugs for treatment of OAB

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 specialists, 2-3 PCPs, and 20-25 adult patients, which may be sufficient to reach saturation amongst homogenous groups of participants.

Outcomes:

- Experiences of living with overactive bladder
- Experiences accessing overactive bladder therapies
- Experiences treating patients with overactive bladder therapies
- Perceived safety and effectiveness of overactive bladder therapies
- Perceived barriers to access and health equity issues

- Any unanticipated issues related to overactive bladder therapies

Phase 2: Assessment of the social acceptability of recommended policy actions related to drugs for treatment of OAB

Study Design – RAND Appropriateness Method and Survey

Study Population – Representatives of the general public; stakeholder groups (i.e. among the 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 current evidence for the efficacy and safety of pharmacologic treatments of OAB in adults?
- Does the efficacy or safety of pharmacologic treatments of OAB in adults vary depending on:
 - a) Sex
 - b) Age (< 65 v. ≥ 65 yr)
 - c) Previous pharmacologic treatment (naïve v. experienced)
 - d) Setting (long-term care v. community)

PICO (Population, interventions, comparator, outcomes)

Population	Adults (aged 18 years or older) with overactive bladder as diagnosed by a health care professional and having symptoms of urgency, frequency, nocturia, or urgency incontinence
Interventions	<p>OAB treatments currently available in Canada^a:</p> <ul style="list-style-type: none"> • Anticholinergic (antimuscarinic) agents^a <ul style="list-style-type: none"> - oxybutynin (generics, Ditropan XL, Oxytrol, Gelnique) - tolterodine (Detrol, Detrol LA) - darifenacin (Enablex) - solifenacin (Vesicare) - trospium (Trosec) - fesoterodine (Toviaz) - flavoxate (Urispas)[†] • β₃- adrenoceptor agonists: <ul style="list-style-type: none"> - mirabegron (Myrbetique) <ul style="list-style-type: none"> ○ Combination therapy (mirabegron + an anticholinergic agent dual therapy)^b
Comparator	<ul style="list-style-type: none"> • Placebo

	<ul style="list-style-type: none"> • Neurotoxin: onabotulinumtoxin A (Botox) • OAB treatments listed above
Outcomes: Efficacy	<ul style="list-style-type: none"> • Urinary frequency^c and change in daily number of micturitions • International Continence Society (ICS)-defined urgency episode reduction • Incontinence^c • Disease-specific health-related quality of life • Nocturia^c
Outcomes: Safety	<ul style="list-style-type: none"> • Serious adverse events^d • Withdrawals due to adverse events • Dry mouth • Constipation
Included Study Designs	<ul style="list-style-type: none"> • Randomized controlled trials^e without limitation on sample size, treatment or follow-up duration

^aMay include extended- and immediate-release or other Health Canada-approved formulations (e.g., gel, transdermal patch).

^bMust be combination of mirabegron and another anticholinergic drug in Health-Canada approved doses and formulations. Combinations will only be considered if a de novo systematic review is conducted.

^cWill be extracted and analyzed as number of events per 24-hr period.

^dWill note arrhythmia separately if data reported.

^eCross-over trials will be eligible for inclusion. Data from such trials will be included in the analyses provided that data for the first period is reported separately and by treatment group.

Note: Efficacy and safety outcome lists may be truncated if we identify many studies for inclusion, as this is a rapid review. We will work with all stakeholders to select the most important efficacy and safety outcomes with sufficient data to conduct network meta-analysis.

Methods

Search Strategy

A literature search will be conducted by a professional Information Scientist (IS). Literature search strategies will be developed using medical subject headings (MeSH) and text words related to the population, interventions and comparators specified in the PICO statement. In order to meet the rigorous timelines of the review process, we propose to search broadly for a comprehensive, well-conducted, recent (within 5 years) evidence synthesis that meets the PICO requirements. If we are able to update an existing high-quality systematic review of the available randomized evidence, we will build onto the studies included in the existing review. A new literature search will capture studies published from the date of the last literature search to present.

Studies published from 2000 onwards will be eligible for inclusion based on the introduction of the definition of OAB in 2000. Articles identified from an existing systematic review will be subjected de novo to standard systematic review processes, namely: data abstraction by two independent review authors (or extraction by one reviewer with checking by a second) and quality assessment. These methods and procedures will be identical to those followed for the articles identified in the updated literature search, and the information on the articles from these two sources will be combined in generating the table of characteristics (with design elements and PICO elements), the risk of bias tables (at the article and review level) and the

analysis datasets for pair-wise meta-analysis and network meta-analysis.

NOTE: If we do not locate an evidence synthesis that meets our requirements, we will conduct a rapid systematic review of the efficacy and safety outcomes prioritized in the PICO. The rapid systematic review will provide a summary of the best available evidence published in the previous five years, including systematic reviews and meta-analyses and randomized controlled trials. Searches will be conducted in the same manner on bibliographic databases and grey literature with only date limitations applied.

A Bayesian network meta-analysis of randomized evidence will be conducted for each outcome specified a priori. The methods and procedures to be followed are those developed by the Canadian Collaboration for Drug Safety, Effectiveness and Network Meta-Analysis (ccNMA), funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institute of Health Research.

3. Pharmacoepidemiology Unit

Analysis 1 – National and provincial trends in overactive bladder agents utilization

Study question: Cross-sectional analysis with quarterly time intervals

Short description of analysis: We will examine trends in use of drugs for overactive bladder between October 2009 and March 2015.

Analysis 2 – Cross-provincial comparisons of the trends in overactive bladder agent utilization in public drug programs

Study question: Cross-sectional analysis with quarterly time intervals

Short description of analysis: We will examine changes in drugs for overactive bladder prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI and British Columbia between January 2000 and June 2015

Analysis 3 – Characteristics of individuals prescribed publically-funded overactive bladder agents in Ontario

Study question: To characterize patients prescribed overactive bladder agents in Ontario

Short description of analysis: We will look at descriptive characteristics (April 2012-March 2014), including age, gender, socioeconomic status, proportion of patients residing in LTC, prescriber of initial prescription (specialist or general practitioner), number of physician office visits within the last 1 year, comorbidities, past medication use (psychotropics, alpha blockers, 5-alpha reductase inhibitors)

Analysis 4 – Duration of OAB agent utilization among new users of these products in Ontario

Study questions: To investigate the average duration of OAB agent use among new users of these products in Ontario

Short description of analysis: We will include all publically-funded beneficiaries over the age of 66 years who newly initiate an OAB agent over the study period (January 2011-December 2014).

Analysis 5 – Summary of observational literature related to the comparative safety and adherence of overactive bladder agents

Study questions: To review and summarize observational studies that explore the comparative safety and/or adherence of OAB agents

Short description of analysis: We will conduct a rapid review of observational literature.

4. Pharmacoeconomic Unit

Research Questions

- What is the current evidence for the comparative cost-effectiveness of pharmacologic treatments for overactive bladder (OAB) syndrome?
- Based on a de novo economic model, what is the comparative cost-effectiveness of pharmacologic treatments for OAB syndrome?
- What is the budget impact of alternative policies for reimbursing pharmacotherapies for the management of OAB syndrome?
- Based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing pharmacologic treatments for OAB syndrome?

Methods

1. Systematic Review of Published Economic Evaluations

We will conduct a review of the available literature on the cost-effectiveness of pharmacotherapy options for the treatment of OAB. Selected comparators will include anticholinergic medications, mirabegron, botulinum toxin type A and combination therapy (anticholinergic + mirabegron), as compared to each other or placebo

2. De novo Economic Evaluation

We will develop a de novo economic model to assess the cost-effectiveness of alternative pharmacotherapies for the treatment of OAB.

3. Reimbursement Based Budget Impact Analysis

We will develop a model which will identify the budget impact analysis that will facilitate the reimbursement decision-making process. Emphasis will be placed on identifying the budget impact of alternative approaches to the current reimbursement status of pharmacologic treatments for patients with OAB.

4. Reimbursement Based Economic Evaluation

We will use data from the de novo economic model to allow identification of the optimal reimbursement criteria through considering cost-effectiveness as criteria with a focus on reimbursement strategies not just interventions.

5. Environmental Scan

Research Questions

1. ***To summarize the pharmacy benefit programs for drugs for the treatment of OAB 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:

- Anticholinergics (oxybutynin, tolterodine, trospium, darifenacin, solifenacin, fesoterodine, flavoxate)
- Others (beta-3 adrenergic agonist: mirabegron; neuromuscular blockers: onabotulinum toxin A)

2. ***To determine the impact of different reimbursement schemes for drugs for treatment of OAB 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

Outcome(s) of interest: Indirect/direct measurements of clinical outcomes, patient satisfaction, quality of life, utilization and/or costs, functionality at work, days of productivity at work

3. To summarize the guidelines for use of drug treatment for OAB

Method: Literature review

Intervention: Guidelines/recommendations for the use pharmacotherapy for OAB