

PHARMACOLOGIC TREATMENT OF OVERACTIVE BLADDER

FINAL COMPREHENSIVE RESEARCH PLAN

July 2015

Study Team: Systematic Review Unit

Objective

To determine the comparative clinical efficacy and safety of pharmacologic treatments for overactive bladder (OAB) in adults, by use of a systematic review and Bayesian network meta-analysis.

Research Questions

RQ1. What is the current evidence for the efficacy and safety of pharmacologic treatments of OAB in adults?

RQ2. Does the efficacy or safety of pharmacologic treatments of OAB in adults vary depending on:

- a) Sex
- b) Age (< 65 v. ≥ 65 yr or < 75 v. ≥ 75 yr)
- c) Previous treatment experience with muscarinic (naïve v. experienced)

PICO

The population, intervention, comparator, and outcome (PICO) statement, including the study designs of interest is as follows:

Table 1. PICO Criteria

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*.
Intervention	OAB treatments currently available in Canada ^a : <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)[†] • β_3- adrenoceptor agonists: <ul style="list-style-type: none"> - mirabegron (Myrbetique) • Combination therapy (mirabegron + an anticholinergic agent dual therapy)^b
Comparator	<ul style="list-style-type: none"> • Placebo • Neurotoxin: onabotulinumtoxin A (Botox) • OAB treatments listed above

Proposed 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
Proposed outcomes: Safety	<ul style="list-style-type: none"> • Serious adverse events^d • Withdrawals due to adverse events • Dry mouth • Constipation
Study types	<ul style="list-style-type: none"> • Randomized controlled trials^e without limitation on sample size, treatment or follow-up duration
Exclusions	<ul style="list-style-type: none"> • Non-pharmacologic therapies • Other treatments not listed above (e.g., estrogen, tricyclic antidepressants) • Non-randomized or observational studies • Primary studies published only in abstract format • Patients with neurologic conditions or cancer
<p>^aMay include extended- and immediate-release or other Health Canada-approved formulations (e.g., gel, transdermal patch).</p> <p>^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.</p> <p>^cWill be extracted and analyzed as number of events per 24-hr period.</p> <p>^dWill note arrhythmia separately if data reported.</p> <p>^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.</p> <p>* Mixed incontinence is also acceptable and urodynamic measures are not required for diagnosis.</p> <p>† Currently Health-Canada approved but availability is limited in Ontario. High quality systematic reviews may be utilized if they do not include this treatment.</p> <p>^aHealth Canada-approved doses only (Oxybutinin doses can be adjusted by patient so will be accepted up to the recommended daily maximum as stated in the product monographs).</p>	

No language restrictions will be applied; however, articles must be retrievable in full-text format and translatable in the allowed time-frame. Any articles that do not meet this criteria will be noted listed in the appendix of the final reported.

Table 1 contains a proposed list of efficacy and safety outcomes. Analysis of all outcomes may not be possible in the allowed timeframe; outcomes will be prioritized for analysis in consultation with the ODPRN research team, clinical experts, and sufficiency of data.

Methods

The strategy for building and analyzing the evidence base for the efficacy and safety of pharmacologic treatments for OAB in adults consists of two fundamental steps.

- (1) The ideal first step to address the research questions would be a de novo systematic review of the available randomized evidence in the published and grey literature following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews for Interventions (6). 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.

A potentially eligible systematic review will be assessed for quality using AMSTAR (7), and the focus will be on the comprehensiveness of the literature search of the systematic review and thoroughness of the article selection for the inclusion of all eligible articles. Regarding the literature search, the search strategy will need to be available and our experienced information scientist(s) will interrogate the search to provide insight into its comprehensiveness. If the search passes this critical stage, then the quality of the selection of the titles and abstract and then the articles will be investigated. Information on the process (e.g. two independent review authors) and scrutiny of the excluded articles will be used in this assessment, and only if this information is available and meets expectations will the articles from this systematic review be considered in the review process and the PDFs of the articles imported into DistillerSR, an online tool used to create efficiency in the literature screening and data extraction processes.

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 de novo systematic review of the efficacy and safety outcomes prioritized in the PICO. Searches will be conducted in the same manner on bibliographic databases and grey literature with date limitations applied to 1990.

- (2) 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.

*Input from interested stakeholders made available through evidence submission packages to ODPRN will also be considered.

General steps in the systematic review

This protocol was developed using guidance from the PRISMA Statement (1) and follows the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews for Interventions. Our protocol, once approved, will be registered in the PROSPERO database and the protocol will be updated with the assigned registration number (2).

The specific steps for the systematic review are as follows:

Electronic Search Strategy:

The literature search will be conducted by a professional Information Scientist (MLIS). Literature search strategies for efficacy and safety will be developed using medical subject headings (MeSH) and text words related to the PICO statement. Searches will use validated

filters for RCTs. All studies will be eligible regardless of publication status (i.e., unpublished studies) and year of publication. No language restriction will be applied; however, studies must be retrievable and translatable in the allowed timeframe in order to be considered for inclusion.

Proposed electronic databases are listed below and may be augmented based on feedback from experts and/or the Information Scientist.

- Cochrane CENTRAL
- Medline (indexed, in-process and other non-indexed)
- Embase (via OVID)

A limited grey-literature search will be carried out by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases (following CADTH “Grey Matters Light”).

Eligibility and Study Selection:

Studies will be included if they meet the population, intervention, comparator, and outcome (PICO) criteria. Studies will not be selected based on outcomes. Data will not be extracted from studies that do not report outcomes of interest; such studies will be listed in the final report.

Two independent reviewers will apply the eligibility criteria to each title and abstract identified in the literature search in a standardized manner. Any uncertainties will be resolved by discussion and consensus with a third review author. All studies that meet the selection criteria will be obtained in full-text format, and they will be evaluated against the PICO criteria and a final decision made on inclusion. The reviewers will not be blinded as to the study authors or centre of publication prior to study selection because this can complicate the review process and only weak evidence suggests that this would improve the results.

Data Extraction and Management:

All information will be extracted using a standardized data extraction form, which will be developed, piloted, and modified as necessary.

Abstraction will include:

1. Characteristics of trial participants [mean age \pm standard deviation (or median, range), weight (mean \pm standard deviation (or median, range), proportion female participants (n,%), Duration from symptom onset (yrs, n), previous treatment experience (by type, n), incontinence type at beginning of study (e.g. urge, mixed, none)]
2. Study characteristics (First author, year of publication, study type, setting, country, duration, and other characteristics deemed relevant by clinical experts)
3. Details on each study arm, including but not limited to pharmacological intervention, dose, frequency, route of administration, duration, and co-medication
4. Results of the clinical safety and efficacy outcomes for the overall study population and the *a priori* subgroups identified

Data will be extracted by a single review author and checked for accuracy by an independent second review author. The original, primary publication for each unique study included will be used for data extraction, except where multiple publications for a single RCT are found.

Multiple publications for a unique RCT (e.g. supplemental online appendices, companion publications of specific outcomes or populations from the original study) will be handled by extracting the most recently adjudicated data for each outcome specified *a priori*.

Risk of Bias Assessment:

Cochrane Collaboration's tool for assessing risk of bias will be employed.

Assessment of Heterogeneity:

The results will be assessed for both clinical and methodological diversity. Clinical diversity will be assessed by checking that the participants, interventions, and comparators are not too different from each other such that combining them is not appropriate. Methodological diversity will be assessed by checking that the studies are similar in terms of study design and risk of bias.

Once it has been established that the studies are minimally diverse and that it makes sense to pool them together in a meta-analysis, an assessment of the statistical heterogeneity will be undertaken by examining the forest plot and result of the I^2 statistic (forest plots provide a visual sense of heterogeneity, and the I^2 statistic indicates the presence of statistical heterogeneity). If the effects observed across trials are inconsistent and vary to a large extent (e.g., $I^2 > 50\%$), the results will be explored to assess whether the differences can be explained by some clinical or methodological feature.

Inconsistency that cannot be reduced by pre-specified subgroup or meta-regression analyses will lead to an overall estimate with less confidence when interpreting the inference from the meta-analysis. In this case, a more conservative random-effects model approach will be used so that the uncertainty of the single effect estimate is reflected by wider confidence intervals.

Assessment of Reporting Bias:

Reporting bias will be assessed by use of funnel plots, as well as bias indicators (e.g. Egger, Harbord-Egger), for each outcome.

Data Synthesis:

Data will first be summarized descriptively. A meta-analysis will be undertaken using fixed- or random-effects models when data are available, sufficiently similar, and of sufficient quality. The effect sizes for the identified dichotomous outcomes will be expressed in terms of risk ratio (RR) or odds ratio (OR). In the case of rare events, the Peto OR will be used. For continuous outcomes (e.g., quality of life), the effect size will be expressed in terms of the mean difference (MD) or standardized mean difference (SMD) as appropriate. Pair-wise meta-analyses will be conducted using RevMan.

Subgroup Analysis:

Major outcomes will be assessed in identified subgroups in the specific populations of adults with diagnosed OAB. Subgroups were selected to confirm clinically sound hypotheses and as few subgroups as possible were pre-specified and justified against the criteria proposed by Sun et al.; wherein the greater the number of criteria that are satisfied for each subgroup and outcome, the more plausible is the hypothesized subgroup effect (3, 4).

Planned subgroups include:

- a) Sex
- b) Age (< v. ≥ 65 yr, < v. ≥ 75 yr)
- c) Previous treatment experience (naive v. experienced)

Sensitivity Analysis:

Sensitivity analysis will be conducted based on aspects of the PICO statement and study methodology to examine the robustness of the results to the risk of bias and the influence of other variables. In particular, the results of studies at low risk of bias will be compared to those from studies at higher risk of bias; if the results differ substantively, the conclusions of the review will be based on analyses of studies at low risk of bias only.

Bayesian Network Meta-Analysis Methods

Bayesian network meta-analyses will be conducted using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) (5). The use of a Bayesian network meta-analysis offers several advantages, including:

1. Comparison of treatments that have not been compared directly
2. Comparison of all active- and placebo-controlled evidence

Summary effect estimates against a common comparator (e.g., placebo) as well as to each other will be presented. We will also construct graphical aids to assist in decision making.

We will conduct a Bayesian network meta-analysis using a model that accommodates complex interventions (6). The advantage of using the approach by Welton et al. (6) is that the proposed models (e.g., additive) may allow us to estimate treatment effects for comparisons that may not have been compared directly.

Both fixed- and random-effects network meta-analyses will be conducted. Model fit for Bayesian analyses will be based on the deviance information criterion and comparison of residual deviance to number of unconstrained data points (7-9). Selection of the final model will depend on the outcome of interest and the availability of data. Heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols will be carefully assessed. To further investigate heterogeneity, subgroup analyses and meta-regressions (8, 9) will be conducted to explore the effect of various characteristics including, but not limited to, the variables considered for the subgroup and sensitivity analyses. We will also perform analyses including removal of studies from the network of therapies that were not scored as being of high quality. We will formally (9) and informally assess consistency between direct and indirect evidence by comparing direct estimates obtained from pair-wise meta-analysis with estimates from the Bayesian network meta-analysis (10). Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic will be assessed to ensure model convergence. At least two chains will be fit in WinBUGS for each analysis, each employing at least 40,000 iterations, with a burn-in of at least 20,000 iterations (5, 8).

Deliverables

We will provide a written report detailing methods adopted, results, discussion and key outcome highlights. The report will comprise of an executive summary followed by a detailed technical report.

Timelines

On acceptance of this proposal, work will commence. The systematic review, meta-analysis, and Bayesian network meta-analysis will be completed in approximately 12 weeks to 16 weeks. Any reanalyses and a revised final report will be available 4 weeks after receipt of stakeholder reviews.

References

1. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-34.
2. Booth A, Clarke M, Dooley G, Gherzi D, Moher D, Petticrew M, et al. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Syst Rev*.1(1):2.
3. Sun X, Briel M, Busse JW, You JJ, Akl EA, Mejza F, et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. *BMJ*.344:e1553.
4. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ*.340:c117.
5. Spiegelhalter D, Thomas A, Best N, Lunn D. WinBUGS User Manual. Version 1.42003 [cited 2011 June 1]. Available from: <http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/manual114.pdf>.
6. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. *Am J Epidemiol*. 2009;169(9):1158-65.
7. Dias S, Sutton A, Welton N, Ades A, Golfinopoulos V, Kyrgiou M, et al. NICE DSU Technical Support Document 1: Introduction to evidence synthesis for decision making.May 2011 [cited 2012 June 13]:[1-24 pp.]. Available from: <http://www.nicedsu.org.uk/TSD6%20Software.final.08.05.12.pdf>.
8. Dias S, Sutton A, Welton N, Ades A, Golfinopoulos V, Kyrgiou M, et al. NICE DSU Technical Support Document 2: Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials.May 2011 [cited 2012 June 13]:[1-96 pp.]. Available from: <http://www.nicedsu.org.uk/TSD6%20Software.final.08.05.12.pdf>.
9. Dias S, Sutton A, Welton N, Ades A, Golfinopoulos V, Kyrgiou M, et al. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials.May 2011 [cited 2012 June 13]:[1-39 pp.]. Available from: <http://www.nicedsu.org.uk/TSD6%20Software.final.08.05.12.pdf>.
10. Dias S, Sutton A, Welton N, Ades A, Golfinopoulos V, Kyrgiou M, et al. NICE DSU Technical Support Document 3: Heterogeneity: Subgroups, meta-regression, bias and bias-adjustmentMay 2011 [cited 2012 June 13]:[1-24 pp.]. Available from: <http://www.nicedsu.org.uk/TSD6%20Software.final.08.05.12.pdf>.