

ODPRN Comprehensive Research Plan:
Testosterone Replacement Therapies (TRT)

June 6, 2014

A. Introduction

Testosterone replacement therapies (TRT) are available in Canada for the treatment of adult males for conditions associated with a deficiency or absence of endogenous testosterone (hypogonadism). There are currently three dosage forms marketed in Canada:

- Oral: testosterone undecanoate (Andriol, generics)
- Long-acting injectable: testosterone cypionate (Depo-Testosterone), testosterone enanthate (Delatestryl)
- Topical products: Androderm, Testim, AndroGel, Axiron

The objective of the testosterone drug class review is to provide evidence-informed recommendations for the use of testosterone replacement therapies 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

- Male patients (all age groups) with diagnosis of hypogonadism
- Subgroup analysis: where possible, the review will consider age, gender, socioeconomic status and geographic location (e.g. urban/rural)

Drugs of interest

- Oral: testosterone undecanoate (Andriol, generics)
- Long-acting injectable: testosterone cypionate (Depo-Testosterone), testosterone enanthate (Delatestryl)
- Topical products: Androderm, Testim, AndroGel, Axiron

Comparator(s)

- No active comparator drug; placebo-controlled trials will be included
- Comparisons between different testosterone products

Proposal	Research unit	Research question(s)
Patient and Healthcare Professional Perspectives	Qualitative Research Program	<p>What is the perceived effectiveness of testosterone replacement therapy (TRT)?</p> <p>What is the impact of TRT on quality of life?</p> <p>What is the experience of patients using TRT regarding access of these drugs?</p> <p>What is the experience of prescribing/dispensing 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 current evidence for the efficacy and safety of testosterone replacement therapy in adult men with androgen deficiency?</p> <p>Does the efficacy or safety of testosterone replacement therapy vary based on age, duration, dose or comorbidity?</p>
Environmental Scan and Barriers to Implementation; Local and Historical Context	Formulary Modernization Unit	<p>How are testosterone replacement therapies 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	<p>To examine national and provincial trends of testosterone use and costs among public drug plan beneficiaries over the past 5 years</p> <p>To perform cross-provincial comparisons of the characteristics of testosterone use among a population of public drug plan beneficiaries</p> <p>To characterize users of testosterone products in Ontario</p> <p>To describe current patterns of testosterone adherence in Ontario</p>
Health Equity	All units	<p>Does sex/gender, age, geographical location (e.g., rural vs. urban) or socioeconomic status play an important role in any of the analyses described?</p>
Reimbursement-based Economics	Pharmacoeconomics Program	<p>What is the current evidence for the cost-effectiveness of testosterone replacement therapy in all clinical areas where it is indicated?</p> <p>What is the economic impact of alternative policies for reimbursing testosterone replacement therapies?</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 provided below.

1. Qualitative Review Unit

Objectives:

- To explore factors related to the experience of testosterone replacement therapy (TRT) prescription, dispensing and use for various conditions.
- To determine the social acceptability of reimbursement policy recommendations for TRT.

Study Questions:

- What is the perceived effectiveness of TRT?
- What is the impact of TRT on quality of life?
- What is the experience of patients using TRT regarding access of these drugs?
- What is the experience of prescribing/dispensing 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 include primary care physicians (PCPs), endocrinologists, urologists, pharmacists, and patients (patient caregivers may be considered). Inclusion criteria are: clinicians (PCPs, respirologists, pharmacists) who have prescribed or dispensed TRTs; and patients who have current or prior experience using TRT for any indication.

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.

Outcomes:

- Experiences of the disease condition and of taking TRT
- Experiences accessing TRT through Ontario Drug Benefit
- Experiences accessing TRT through other means

- Experiences treating and dispensing TRT to patients
- Perceived safety and effectiveness of TRT
- Perceived barriers to access and health equity issues
- Any unanticipated issues related to TRT

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 (PCPs, endocrinologists, urologists, pharmacists, patients), 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 testosterone replacement therapy in adult men with androgen deficiency?

Does the efficacy or safety of testosterone replacement therapy vary based on:

- Age
- Duration
- Dose
- Comorbidity

PICO (Population, interventions, comparator, outcomes)

Population	Adult men with androgen deficiency
Interventions	Testosterone replacement therapies currently available in Canada
Comparator	Placebo, all intervention comparisons
Outcomes: Efficacy	Achievement of normal serum testosterone levels, symptom improvement, quality of life
Outcomes: Safety	Cardiovascular death, myocardial infarction, stroke, erythrocytosis, serious adverse events, newly diagnosed disease (diabetes, heart disease, prostate cancer), skin or site reactions

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

For efficacy, RQ1 and RQ2 will be answered by a de novo systematic review of randomized clinical trials (RCT) and a meta- and network meta-analyses of key efficacy outcomes will be conducted.

For safety, RQ1 and RQ2 will be answered using a stepped approach. First, we will search for a well-conducted, recent evidence synthesis that meets the PICO. Then, if a recent review is available, we conduct a new literature search for primary studies back to the date of the last database search. If no review is located that meets our requirements, a de novo systematic review and meta-analysis of evidence from RCTs and high quality comparative non-randomized studies will be conducted. Bayesian network meta-analysis will also be considered for key safety outcomes.

3. Pharmacoepidemiology Unit

Analysis 1 – National and provincial trends in testosterone use

Study question: To examine national and provincial trends of testosterone use and costs among public drug plan beneficiaries over the past 5 years

Short description of analysis: We will examine trends in testosterone replacement therapies between 2009 and February 2014.

Analysis 1a – Cross-provincial changes in prescribing of testosterone in public drug programs

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

Short description of analysis: We will examine changes in testosterone prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI and British Columbia between January 2000 and December 2012

Analysis 2 - Cross-provincial comparisons of characteristics of testosterone use in public drug programs

Study question: To perform cross-provincial comparisons of the characteristics of testosterone use among a population of public drug plan beneficiaries (January 2012 to December 2012)

Short description of analysis: Using National Prescription Drug Utilization Information System Database (NPDUIS), we will look at various outcomes for each province including number and rate of testosterone users, number and rate of testosterone prescriptions dispensed, and age at time of first prescription.

Analysis 3 – Characteristics of testosterone users in the Ontario Public Drug Program

Study question: To characterize users of testosterone products in Ontario

Short description of analysis: We will look at descriptive characteristics (January-December 2012), including age, gender, socioeconomic status, number of hospitalizations and emergency room visits, various comorbidity measures (e.g., diabetes, cardiovascular diseases), stratified by age and formulation of testosterone.

Analysis 4 – Patterns of Testosterone Adherence in Ontario

Study questions: To describe current patterns of testosterone adherence in Ontario

Short description of analysis: We will look at all publically-funded beneficiaries of Ontario age 66 and older who initiated testosterone therapy over the study period. The analysis will include for patients dispensed more than 1 prescription the median duration of therapy and number of different testosterone products.

4. Pharmacoeconomic Unit

Research Questions

- What is the current evidence for the cost-effectiveness of testosterone replacement therapy in all clinical areas where it is indicated?
- What is the economic impact of alternative policies for reimbursing testosterone replacement therapies?

Methods

RQ1 Systematic Review of Published Economic Evaluations

We will conduct a review of the available literature on the cost-effectiveness of testosterone replacement therapy in all clinical areas where it is indicated.

RQ2 Reimbursement Based Economic Assessment

We will develop a model which will identify the optimal policy relating to reimbursing testosterone replacement therapies. 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.

5. Environmental Scan

Research Questions

To summarize the pharmacy benefit programs for TRT 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:* Testosterone replacement therapies:
 - Oral: testosterone undecanoate (Andriol)
 - Injectable: testosterone cypionate (Depo-testosterone), testosterone enanthate (Delatestryl)
 - Topical: Androderm, Testim, Androgel, Axiron

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

Method: Literature review

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

To summarize the guidelines for management of hypogonadism, in particular the role of testosterone replacement therapies

Method: Literature review

Intervention: Guidelines/recommendations for the management of patients with hypogonadism