Changing the Landscape of Formulary Modernization: Impact of the Introduction of Generic Products for the Treatment of Overactive Bladder on Reimbursement-Based Economics

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Learning Objectives

• To demonstrate a practical application of economics to formulary modernization

• To highlight the complexities involved in assessing alternative reimbursement strategies
In 2013, the Ontario Drug Policy Research Network (ODPRN) was awarded provincial government funding to conduct research relating to formulary modernization within the OPDP.

This innovative program for drug class reviews incorporates a novel methodological technique called reimbursement-based economics, which focuses on the economic impact of alternative reimbursement strategies rather than individual therapies.

No other conflicts of interest
Overactive bladder (OAB) is a health condition defined by problems in bladder storage causing a sudden urge to urinate, and in some patients, unintentional urine loss (incontinence). It is a common condition among the elderly adult population.

Anticholinergic medications are the treatment of choice for patients with OAB; six anticholinergics are available in Canada and their listing and formulations vary on public drug plans.

Mirabegron is another drug, from a different drug class, that is being increasingly used. It became available in March 2013.
In Ontario, oxybutynin IR is the intended first choice for treatment (listed as general benefit); yet, a small proportion of patients try this drug before other products.

A number of generic products have recently become available.

The aim of this study was to assess the cost-effectiveness of alternative strategies for reimbursing OAB treatments to facilitate drug coverage decision-making in Ontario.
Limited Use

MIRABEGRON 25mg ER Tab

<table>
<thead>
<tr>
<th>Reason For Use Code</th>
<th>Clinical Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>290</td>
<td>For patients with urinary frequency, urgency or urge incontinence who have: Failed to respond to behavioral techniques AND an adequate trial of oxybutynin with gradual dose escalation has shown to be either ineffective or resulted in unacceptable side effects. NOTE: If after a trial of 2 weeks patients continue to experience similar side effects and no greater efficacy than oxybutynin, continued therapy with this more costly agent should be reassessed. Antimuscarinic agents should be used with caution in the elderly due to potentially serious adverse effects (e.g. confusion, psychosis, acute urinary retention, constipation). Antimuscarinic agents should be avoided in older adults with pre-existing cognitive impairment (e.g. dementia) and those who are already using other drugs with significant anticholinergic effects (e.g. tricyclic antidepressants) in order to avoid a high overall anticholinergic drug burden. LU Authorization Period: Indefinite.</td>
</tr>
</tbody>
</table>
Research Questions

RQ1. What is the current evidence for the comparative cost-effectiveness of pharmacologic treatments for OAB syndrome?

RQ2. Based on a de novo economic model, what is the comparative cost-effectiveness of pharmacologic treatments for OAB syndrome?

RQ3. What is the budget impact of alternative policies for reimbursing pharmacotherapies for the management of OAB syndrome?

RQ4. Based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing pharmacologic treatments for OAB syndrome?
• Approaches for reimbursement of anticholinergic medications and mirabegron were identified.
  • Strategies relating to coverage (General Benefit [GB], Limited Use [LU] coverage or enforced step therapy), generic substitution, and generic pricing.

• A systematic review of published economic evaluations was undertaken, focusing on strength and quality of evidence, and applicability to OPDP.

• An applied, policy-oriented economic model was developed to assess the cost-effectiveness of individual therapies.
• Budget expenditures for each reimbursement strategy were forecasted for years 2015-2017, utilizing time-series analyses of OPDP data.

• Using the de novo economic model, cost-effectiveness of alternative reimbursement strategies was assessed.

• ODPRN recommendations to OPDP were based on the economic analysis in combination with a qualitative analysis, systematic review, pharmacoepidemiology report, and environmental scan.
Reimbursement Strategies

• **Initial strategies considered**
  – Status quo (base case): No change to current GB listing for OXYB and LU for currently covered agents
  – Enforced step therapy for all medications
  – GB listing for generic products (oxybutynin IR, tolterodine ER, solifenacin) and LU listing for all other currently covered agents
  – GB listing for oxybutynin IR and solifenacin LU listing for other currently covered agents
  – GB listing for solifenacin and LU listing for all other currently covered agents
  – In addition, all strategies additionally considered coverage of oxybutynin transdermal and gel and tolterodine IR

• **Additional strategy considered**
  – GB listing for solifenacin and enforced step therapy for all other medications covered under LU
Results – Review of the Literature (1)

• 26 economic evaluations identified for inclusion
  – 9 from the UK, 6 from the US, 3 Canadian, 2 Swedish, and 1 each from Germany, Italy, and Spain; 3 studies were conducted across multiple settings
  – 24/26 (92%) funded by industry or had ties to industry

Considerations and limitations relating to the published literature:

• Canadian content
• Sponsorship and industry-affiliated studies
• Utility value derivation
• Discontinuation of therapy
• Adverse events
• Costs of incontinence pads
Results – Review of the Literature (2)

• Independent studies
  – 2 studies: 1 CEA (2006 US) & 1 CUA (2011 Sweden)
    • Broad range of comparators included, except mirabegron
  – Limitations include: poor handling of rates of treatment discontinuation in modeling, disregard for incorporating utility decrements associated with adverse events while on therapy

• Industry-sponsored and industry-affiliated studies
  – 24 studies: 13 CUA, 3 CEA, 4 CEA/CUA, 2 CMA, 1 CCA
  – Sponsor’s product was less costly and more effective in all cases

Need to conduct de novo modeling analysis
De Novo Economic Evaluation

Analytic Framework

- **Model Type**: Multi-state Markov model
  - Model states defined based on number of micturitions per 24 hours (5 categories) and number of incontinence episodes per 24 hours (5 categories)

- **Time horizon**: 12 months (3 months in sensitivity analysis)
  - Cycle length: 1 month

- **Comparators**: Darifenacin, fesoterodine, oxybutynin (IR, ER, transdermal, gel), solifenacin, tolterodine (IR, ER), trospium, mirabegron, and no therapy

- **Efficacy inputs**: companion network meta-analysis and real-world data on compliance and treatment switching

- **Perspective**: Canadian health care payer (societal perspective in sensitivity analysis)

- **Outcome**: Cost per quality-adjusted life year (QALY)

- Robustness of study findings was tested through deterministic and probabilistic sensitivity analyses
### Results – De Novo Economic Evaluation

**Exhibit 1: Findings of the base case analysis**

<table>
<thead>
<tr>
<th>QALYs</th>
<th>Cost</th>
<th>ICUR vs. lowest cost</th>
<th>Sequential ICUR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not dominated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>0.6836</td>
<td>$0.00</td>
<td>$0.00</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>0.6935</td>
<td>$187.78</td>
<td>$19,050</td>
</tr>
<tr>
<td><strong>Dominated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxybutynin IR</td>
<td>0.6889</td>
<td>$145.36</td>
<td>$27,442</td>
</tr>
<tr>
<td>Tolterodine ER</td>
<td>0.6909</td>
<td>$204.09</td>
<td>$27,957</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>0.6927</td>
<td>$464.08</td>
<td>$51,197</td>
</tr>
<tr>
<td>Trospium</td>
<td>0.6920</td>
<td>$442.69</td>
<td>$53,171</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>0.6915</td>
<td>$442.24</td>
<td>$56,168</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>0.6909</td>
<td>$476.93</td>
<td>$65,457</td>
</tr>
<tr>
<td>Oxybutynin ER</td>
<td>0.6934</td>
<td>$645.17</td>
<td>$66,168</td>
</tr>
<tr>
<td>Oxybutynin transdermal</td>
<td>0.6911</td>
<td>$524.62</td>
<td>$70,050</td>
</tr>
<tr>
<td>Oxybutynin gel</td>
<td>0.6911</td>
<td>$553.56</td>
<td>$74,177</td>
</tr>
<tr>
<td>Tolterodine IR</td>
<td>0.6908</td>
<td>$539.74</td>
<td>$75,190</td>
</tr>
</tbody>
</table>

- WTP < $19,050 = no treatment is optimal
- WTP > $19,050 = solifenacin is optimal
Results – De Novo Economic Evaluation

The graph illustrates the probability that a treatment is optimal for different threshold values for a QALY (Quality Adjusted Life Year). The threshold value is plotted on the x-axis and the probability on the y-axis.

- Different treatments are represented by different colored lines:
  - Placebo
  - Tolterodine IR
  - Mirabegron
  - Oxybutynin IR
  - Solifenacin
  - Darifenacin
  - Oxybutynin ER
  - Fesoteridine
  - Oxybutynin transdermal
  - Trospium
  - Oxybutynin gel

The graph shows how the probability of treatment being optimal changes as the threshold value increases.
Results – De Novo Economic Evaluation (2)

- Solifenacin is the optimal therapy for the treatment of OAB
- Oxybutynin IR and tolterodine ER may be a cost effective therapy in patients discontinuing solifenacin
- Mirabegron, trospium, and fesoterodine may be cost effective in patients discontinuing both solifenacin and oxybutynin IR if restricted to specific patient subgroups based on symptom levels
- Darifenacin, oxybutynin ER, transdermal oxybutynin, oxybutynin gel, and tolterodine IR are not cost effective based on a commonly used willingness to pay threshold of $50,000 per QALY gained
Results – BIA (1)

- Expenditure for OAB medications among all patients has increased since 2000.

- With the introduction of generic solifenacin and tolterodine ER at the end of 2015, expenditure is expected to drop to about $6.0 million by 2018 for patients aged less than 65 years and to approximately $30.4 million for patients aged 65 years and older.

- Numerous alternative reimbursement strategies considered
  - LU/GB/Step therapy

- Step therapy may be cost saving
  - Also may not!
## Results – BIA (2)

<table>
<thead>
<tr>
<th>REIMBURSEMENT STRATEGY</th>
<th>TOTAL</th>
<th>Net Budget Impact</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status quo (base case): No change to current GB listing for OXYB and LU for currently covered agents</td>
<td>$30,367,530</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Enforced step therapy for ACh medications (no increase in overall time on all OAB agents)</td>
<td>$20,893,125</td>
<td>-$9,474,405</td>
<td>↓31%</td>
</tr>
<tr>
<td>Enforced step therapy for Ach medications (no change in time on individual OAB therapy)</td>
<td>$32,446,435</td>
<td>$2,078,905</td>
<td>↑7%</td>
</tr>
<tr>
<td>GB listing for generic products (OXYB, TOLT ER, SOLF) and LU listing for all other currently covered agents</td>
<td>$32,085,429</td>
<td>$1,717,899</td>
<td>↑6%</td>
</tr>
<tr>
<td>GB listing for OXYB AND SOLF and LU listing for other currently covered agents</td>
<td>$30,723,833</td>
<td>$356,303</td>
<td>↑1%</td>
</tr>
<tr>
<td>GB listing for SOLF and LU listing for all other currently covered agents</td>
<td>$31,047,162</td>
<td>$679,632</td>
<td>↑2%</td>
</tr>
</tbody>
</table>

1. In this scenario, the total time on OAB medications is the same (based on rates obtained from OPDP data).
2. In this scenario, the total time on other (non-oxybutynin IR) OAB medications is the same, but there is also additional time added for oxybutynin IR.
Reimbursement-based Economic Evaluation

Analytic Framework

- Used data from both BIA and de novo economic model to estimate costs and QALYs associated with alternate reimbursement strategies

- Considered same strategies as BIA

- Given results of the de novo modelling, one further strategy was considered:
  - Move solifenacin to GB and enforce step therapy with either solifenacin or oxybutynin ER
## Results – Reimbursement Based Economic Evaluation

<table>
<thead>
<tr>
<th>QALYs</th>
<th>Cost</th>
<th>ICUR vs. GB Listing of Solifenacin</th>
<th>Sequential ICUR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not dominated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GB Listing for Solifenacin</td>
<td>0.17258</td>
<td>$41.06</td>
<td></td>
</tr>
<tr>
<td>GB Listing for Solifenacin and Enforcement of Step Therapy</td>
<td>0.17298</td>
<td>$45.72 $11,793</td>
<td>$11,793</td>
</tr>
<tr>
<td>Enforcement of Step Therapy (Oxybutinin IR only)</td>
<td>0.17298</td>
<td>$47.21 $15,543</td>
<td>$7,684,670</td>
</tr>
<tr>
<td><strong>Dominated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GB listing for Solifenacin and Tolterodine IR</td>
<td>0.17259</td>
<td>$41.85 $169,092</td>
<td>Subject to extended dominance</td>
</tr>
<tr>
<td>Status Quo</td>
<td>0.17257</td>
<td>$41.07 Dominated</td>
<td>Subject to dominance</td>
</tr>
</tbody>
</table>

- WTP < $11,793 = Strategy 5 is optimal
- WTP > $19,050 and < $7,684,670 = Strategy 4 is optimal
- WTP > $7,684,670 = Strategy 3 is optimal
Conclusions (1)

Review of available cost-effectiveness studies suggests that there are few independent analyses

- Most studies have industry affiliations – all of which favour the manufacturer’s therapy

De novo modeling suggests that solifenacin, on the basis of cost effectiveness, is the optimal therapy for the treatment of OAB

Some therapies may be cost-effective as second-line treatments, while darifenacin, oxybutynin (ER, transdermal, gel), and tolterodine IR are not cost effective at a WTP of $50,000 per QALY gained.
Enforced step therapy may lead to increased expenditures. However, may not be feasible.

Increased use of mirabegron is unlikely to significantly increase overall OAB medication expenditure.

Based on the reimbursement-based economic evaluation, a strategy where solifenacin and oxybutynin IR were considered as first line therapies with the enforcement of step therapy is optimal.

If step therapy not feasible, listing solifenacin as GB would be optimal.
ODPRN RECOMMENDATION

**Oxybutynin IR, telterodine ER or solifenacin as General Benefit, all other OAB medications Limited Use**

- Oxybutynin IR, tolterodine ER and solifenacin listed as General Benefit
- All other currently listed products (darifenacin, fesoterodine, tolterodine IR, trospium, mirabegron) listed as Limited Use
  - Criteria for use include intolerance or failure to respond to oxybutynin IR OR tolterodine ER OR solifenacin

- Recommendation leads to improved access to anticholinergic medications
- Not necessarily optimal in terms of budget impact, patient outcomes or cost effectiveness
- Other factors impact decision making.
QUESTIONS?