Combining GRADE, patient reported outcomes and costs in the NICE Lower Urinary Tract Symptoms (LUTS) Guideline

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Background


- Question: Alpha-blockers (AB) vs combination of AB+5-Alpha-Reductase Inhibitors (Combi)

- Trade-off between efficacy of intervention, side effects profile and costs
Economic perspective

- Cost-effectiveness as well as clinical effectiveness
- To be able to compare interventions across guidelines, we use the same measure of effectiveness:

\[
\text{QALY (Quality-Adjusted Life-Year)} = \text{utility} \times \text{time in state}
\]

Where utility is a quality of life value on a 0 – 1 scale based on public/patients preferences.
Estimating effectiveness in the model (1)

- No utility data in the RCTs included in the clinical review
- Main outcome was mean International Prostate Symptom Score (IPSS) on a scale from 0 (no symptoms) to 35 (worst symptom level)
- No formula converting IPSS to utilities
Estimating effectiveness in the model (2)

- Trueman and colleagues (1999) conducted a survey to collect utilities by symptoms severity in 1115 men in the UK:
  - Moderate LUTS = 0.78
  - No LUTS = 0.91

- If we know the proportion of patients with and without LUTS in both arms we can estimate utility in both arms and QALYs gained:

\[
\text{QALYs per year} = \%_{\text{noLUTS}} \times U_{\text{noLUTS}} + \%_{\text{LUTS}} \times U_{\text{LUTS}}
\]
Pragmatic approach

- We use a modified GRADE approach to evaluate clinical evidence quality

- This includes estimating the Minimally Important Difference (MID) to assess the imprecision of the evidence

- Based on a study on patient reported outcomes (Barry 1995) the Guideline Development Group (GDG) considered the MID for IPSS to be 3 points. The patient representatives and clinical experts thought this represented an important improvement.

- We made the assumption that important improvement = remission; likely overestimation of treatment effectiveness; we tested the important improvement assumption in a sensitivity analysis.
Using the MID to estimate transition probabilities

- From RCTs included in our meta-analysis we estimated the mean IPSS change from baseline to follow-up.

- Assuming a normal distribution around the mean IPSS change, we used the standard deviation (SD) to obtain the proportion of men who had at least a 3 point improvement in the AB arm and Combination arm.

- Assumption:
  - utility of patients with improvement $\geq 3$ point = utility no LUTS;
  - utility of patients with an improvement $<3$ point = utility moderate LUTS.
Proportion of men with symptoms remission

**Mean IPSS change 6 months:**
- **AB:** 6.3 (SD 5.8)
- **Combi:** 6.1 (SD 7.4)

**Mean IPSS change 12 months:**
- **AB:** 7.1 (SD 5.7)
- **Combi:** 7.3 (SD 5.8)
Other model inputs

- Cost of treatment:
  - lifelong treatment if successful;
  - if unsuccessful discontinuation after one year; additional cost of GP visits; some will have surgery (expensive).

- Effectiveness of treatment is stable after one year (from conclusions of our clinical review)

- Incidence of adverse events (AE):
  - AB: 21.4%
  - Combi: 27.0%

- Different adverse events profile in the two arms: dizziness more common in AB arm, sexual side-effects more common in Combi arm. Disutilities and costs.
Results – base case analysis

<table>
<thead>
<tr>
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<th>Mean cost (£)</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-blockers</td>
<td>3,824</td>
<td>12.4347</td>
</tr>
<tr>
<td>Combination</td>
<td>6,411</td>
<td>12.4276</td>
</tr>
</tbody>
</table>

Combination is dominated – fewer QALYs but increased cost.

Combination may be slightly more effective at reducing symptoms in the long term. However, it is less effective in the short-term and is associated with more adverse events.
When the definition of the MID was varied from 0 to 20, the incremental net health benefit of AB was always positive.
Discussion and conclusions

- In the absence of direct evidence we estimated the difference in utilities using the MID calculated for GRADE.
- Approximate method using continuous data to estimate categorical data. Is MID meaningful and does it correlate with utilities?
- Issue if results were sensitive to the definition of important improvement.
- However in this case study the results in terms of cost-effectiveness were not sensitive to this.
- Collaboration between clinical reviewers, health economists and patients’ representatives is helpful in deciding whether changes in health outcomes are large enough to justify the cost.