Cost-consequence analysis evaluating the use of botulinum neurotoxin-A in patients with detrusor overactivity based on clinical outcomes observed at a single UK centre

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of intra-detrusor injections of botulinum neurotoxin-A (BoNT/A) in patients with overactive bladder (OAB). Patients with urodynamically-proven detrusor overactivity of either neurogenic (NDO) or idiopathic (IDO) origin were considered. The patients received intra-detrusor injections of 200 to 300 units of BoNT/A in 20 to 30 mL saline.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with intractable OAB. Patients were required to have urodynamically-proven phasic or terminal detrusor overactivity. The exclusion criteria were urinary tract infection (excluded through pre-treatment urinalysis), poor bladder compliance in the absence of detrusor overactivity, bladder malignancy, bleeding disorders, anticoagulation therapy, neurotransmission disorders, medication affecting neuromuscular transmission (e.g. aminoglycosides), and pregnancy or planning a family.

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were gathered between September 2002 and April 2005. No dates for the resource use data were reported. The price year was 2003/04.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out on a sample of patients different from that used in the effectiveness analysis.

Study sample
Power calculations were not reported. A sample of 101 patients was enrolled. All patients received BoNT/A injections, thus no external control group was required. In the study sample, there were 38 IDO patients and 63 NDO patients. The mean age of the whole sample was 47 years (Age range: 19 to 80). The proportion of women was 74%.
Study design
This was a within-group comparison study since a single group of patients was considered. The baseline values reflected standard care and were compared with clinical data gathered at the end of the follow-up period. The study was carried out at a single centre, the National Hospital for Neurology and Neurosurgery in London. The patients were evaluated during outpatient consultations that occurred 4 and 16 weeks after therapy. The maximum length of follow-up was 15 months. Overall, 86% of patients attended the 4-week follow-up and 78% of patients attended the 16-week follow-up. Forty-seven patients (47%) were followed up for at least 15 months and 10 patients (10%) were lost to follow-up before the end of the study.

Analysis of effectiveness
The analysis of the clinical study was conducted both on an intention to treat basis (where all patients were included and those with missing data were conservatively assumed to show no improvement) and on a per-protocol basis (including only those patients for whom data were available at the end of the follow-up period. The primary outcome measures were:

the proportion of patients showing a clinical improvement relative to baseline;

time to re-injection;

the duration of clinical improvement;

the percentage change in urgency, frequency and leakage; and

the absolute change in maximum cystometric capacity (MCC) and maximum detrusor pressure on filling (Pdetmax).

A clinical improvement was defined as an improvement of at least 25% in at least two out of five key parameters. Specifically, micturition episodes per 24 hours ("frequency"), number of voids associated with urgency per 24 hours ("urgency"), number of urgency incontinence events per 24 hours ("leakage"), MCC and Pdetmax. Symptoms were recorded on a voiding diary. In addition to the 25% definition of clinical improvement, a secondary analysis considered a 50% definition.

Effectiveness results
The percentage of patients showing an improvement of at least 25% was 82.18% at week 4 and 65.35% at week 16 in the intention to treat population. The corresponding figures in the per protocol population were 98.63% (week 4) and 98.39% (week 16), respectively.

The percentage of patients showing an improvement of at least 50% was 73.27% at week 4 and 53.47% at week 16 in the intention to treat population. The corresponding figures in the per protocol population were 93.42% (week 4) and 83.87% (week 16).

Time to re-injection was 1.628 years (95% confidence interval, CI: 1.461 to 1.796) years.

The duration of clinical improvement was 1.339 years (95% CI: 1.161 to 1.517) using the 25% definition and 1.155 years (95% CI: 0.973 to 1.338) using the 50% definition.

The changes in frequency, urgency and leakage at 4 weeks were as follows:

frequency, 33.2% (95% CI: 28.8 to 37.7);

urgency, 53.2% (95% CI: 45.1 to 61.4); and

leakage, 58.1% (95% CI: 50.1 to 66.2).
The changes in frequency, urgency and leakage at 16 weeks were as follows:

- frequency, 24.5% (95% CI: 20.5 to 28.5);
- urgency, 45.3% (95% CI: 39.1 to 51.4); and
- leakage, 42.4% (95% CI: 34.5 to 50.4).

The increase in MCC was 262 mL (95% CI: 218 to 305) at week 4 and 148 mL (95% CI: 109 to 187) at week 16.

The increase in Pdetmax was 23 cm H2O (95% CI: 17 to 29) at week 4 and 16 cm H2O (95% CI: 10 to 22) at week 16.

**Clinical conclusions**

The effectiveness analysis showed that BoNT/A improved clinical inputs in comparison with standard care (baseline values).

**Measure of benefits used in the economic analysis**

Three summary benefit measures were used in the economic analysis: duration of clinical improvement, response at 4 weeks (initial response) and response at 16 weeks. These were derived directly from the effectiveness analysis:

**Direct costs**

The analysis of costs was conducted from the perspective of the NHS. The categories of costs included were pre-operation, intra-operation and post-operation. Pre-operation included consultant, cystometry or urodynamics, and urinalysis. Intra-operation included BoNT/A, saline, needle, saline irrigation, theatre cost and antibiotic prophylaxis. Post-operation included specialist registrar, specialist urology nurse and urinalysis. The unit costs were presented separately from the quantities of resources used. The costs came from NHS reference prices and Personal and Social Services Research Unit. The resource use data were presumably based on the opinions of the study investigators. Discounting was not relevant as the costs were incurred during a short timeframe. The costs were based on 2003/04 prices.

**Statistical analysis of costs**

Statistical analyses of the costs were not carried out.

**Indirect Costs**

The indirect costs were not included.

**Currency**

UK pounds sterling (£).

**Sensitivity analysis**

Univariate sensitivity analyses were performed to assess the robustness of base-case cost-effectiveness ratios to variations in BoNT/A injection time and the costs of urodynamics and urinalysis. The authors appear to have defined the ranges of values used.

**Estimated benefits used in the economic analysis**

See the 'Effectiveness Results' section.
Cost results
The cost of administering one set of intra-detrusor BoNT/A injections was 826 (745.33 for the typical IDO patient and 874.62 for the typical NDO patient).

Synthesis of costs and benefits
Incremental cost-effectiveness ratios were calculated to combine the costs with each measure of benefit associated with BoNT/A in comparison with standard care.

The cost per treated year (cost per time to re-injection) was 507 (386 for the typical IDO patient and 609 for the typical NDO patient).

The cost per improved patient per year was 617 (480 for the typical IDO patient and 745 for the typical NDO patient) when using the 25% definition, and 715 (510 for the typical IDO patient and 928 for the typical NDO patient) when using the 50% definition.

The cost per initial response was 1,005 (944 for the typical IDO patient and 1,040 for the typical NDO patient) when using the 25% definition, and 1,127 (1,089 for the typical IDO patient and 1,148 for the typical NDO patient) when using the 50% definition.

The cost per sustained response was 1,264 (1,416 for the typical IDO patient and 1,198 for the typical NDO patient) when using the 25% definition, and 1,545 (1,770 for the typical IDO patient and 1,450 for the typical NDO patient) when using the 50% definition.

The sensitivity analysis showed that the cost-effectiveness ratios increased by 14 to 16% when the injection time was doubled, and decreased by 15 to 17% when excluding the costs of urodynamics and urinalysis.

Authors’ conclusions
Intra-detrusor botulinum neurotoxin-A (BoNT/A) injection was an effective treatment for patients with urodynamically-proven detrusor overactivity of either neurogenic (NDO) or idiopathic (IDO) origin, with 82% of patients showing a clinical improvement of 25% or more at week 4. BoNT/A was likely to be a cost-effective intervention from the perspective of the UK National Health Service (NHS).

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear as it reflected the conventional care for patients with OAB. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was obtained from a single group of patients, thus it appears that a within-group comparison study has been used. In effect, baseline values of clinical outcomes were used to represent patient conditions associated with standard care. A control group was therefore not required, thus reducing the potential impact of confounding factors. However, this observational and open-label design can result in selection bias and observer bias. Further, time-dependent confounding variables such as variations in medical practice, evolution of subjects, or variability in the severity of illness, could not be controlled due to the design of the study, and this might represent a limitation of the analysis. The patients were enrolled at a single institution, so the effectiveness results might not be generalisable to other patient groups. No justification for the size of the sample was provided and power calculations were not performed. These issues limit the internal validity of the study.

Validity of estimate of measure of benefit
The summary benefit measures were specific to the disease considered in the study. They are not comparable with the benefits of other health care interventions. The authors made a preliminary calculation of the quality-adjusted life-years
(QALYs), owing to the lack of published data on utility weights associated with the disease considered in the analysis.

**Validity of estimate of costs**
The cost analysis was carried out in accordance with the perspective adopted in the study. A breakdown of the cost items was provided, as were extensive details of the unit costs and quantities of resources used. This enhances the possibility of replicating the analysis in other settings. The sources of the costs were clearly reported, but information on the source of resource consumption was less clear. The price year was reported, which will permit reflation exercises in different time periods. Statistical analyses of the costs were not performed but alternative cost estimates were used in the sensitivity analyses.

**Other issues**
The authors did not make extensive comparisons of their findings with those from other studies. The issue of the generalisability of the study results was addressed, in that the authors stated that the analysis was carried out at a single institution. Caution will thus be required if extrapolating the conclusions of the analysis to other patients and centres. Also, some sensitivity analyses were performed. The study referred to patients with OAB and this was reflected in the authors’ conclusions.

**Implications of the study**
The study results support the use of BoNT/A for the treatment of OAB. The authors pointed out that more research is required to calculate the cost-effectiveness of BoNT/A in terms of the cost/QALY in comparison to other treatment options, such as neuromodulation and surgery.

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**Other publications of related interest**


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