Cost-Effectiveness of Botulinum Toxin A Versus Anticholinergic Medications for Idiopathic Urge Incontinence

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Purpose: We assessed the cost-effectiveness of botulinum toxin A injection compared to anticholinergic medications for the treatment of idiopathic urge incontinence.

Materials and Methods: A Markov decision analysis model was developed to compare the costs in 2008 U. S. dollars and effectiveness in quality adjusted life-years of botulinum toxin A injection and anticholinergic medications. The analysis was conducted from a societal perspective with a 2-year time frame using 3-month cycles. The primary outcome was the incremental cost-effectiveness ratio, defined as the difference in cost (botulinum toxin A cost – anticholinergic cost) divided by the difference in effectiveness (botulinum toxin A quality adjusted life-years – anticholinergic quality adjusted life-years).

Results: While the botulinum strategy was more expensive ($4,392 vs $2,563) it was also more effective (1.63 vs 1.50 quality adjusted life-years) compared to the anticholinergic regimen. The calculated incremental cost-effectiveness ratio was $14,377 per quality adjusted life-year, meaning that botulinum toxin A cost $14,377 per quality adjusted life-year gained. A strategy is often considered cost-effective when the incremental cost-effectiveness ratio is less than $50,000 per quality adjusted life-year. Given this definition botulinum toxin A is cost-effective compared to anticholinergics. To determine if there are situations in which anticholinergics would become cost-effective we performed sensitivity analyses. Anticholinergics become cost-effective if compliance exceeds 75% (33% in the base case) and if the botulinum toxin A procedure cost exceeds $3,875 ($1,690 in the base case). For the remainder of the sensitivity analyses botulinum toxin A remained cost-effective.

Conclusions: Botulinum toxin A injection was cost-effective compared to anticholinergic medications for the treatment of refractory urge incontinence. Anticholinergics become cost-effective if patients are highly compliant with medications or if the botulinum procedure costs increase substantially.

Key Words: cost-benefit analysis; botulinum toxins; cholinergic antagonists; urinary incontinence, urge; urinary bladder, overactive

Abbreviations and Acronyms

BoNT-A = botulinum toxin A

E&M = evaluation and management

ICER = incremental cost-effectiveness ratio

QALY = quality adjusted life-year

UTI = urinary tract infection

UUI = urge urinary incontinence

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Overactive bladder, defined as urgency with or without urge incontinence, affects approximately 16% of the United States population. This high prevalence translates into a substantial economic burden with an estimated total annual cost of $12.6 billion. In addition to the financial impact urge incontinence significantly impacts quality of life. Urge incontinence diminishes quality of life through its impact on daily living, physical activity, social

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relationships, sexual function and emotional well-being.

Primary therapy for urge incontinence includes behavioral modification and anticholinergic pharmacotherapy. Although numerous randomized, placebo controlled studies have demonstrated the efficacy of anticholinergic medications, these medications are associated with bothersome side effects such as dry mouth and constipation. These common side effects along with patient perception of inadequate effectiveness often limit compliance, with studies reporting discontinuation rates of up to 80% by 1 year.[1]

Given the limitations of anticholinergics, newer treatments have emerged. One promising therapy is the injection of botulinum toxin into the detrusor muscle. Preliminary studies have shown that botulinum toxin A is highly effective for neurogenic and refractory idiopathic overactive bladder.[2–4] However, as of November 2008 BoNT-A was not yet approved by the Food and Drug Administration for overactive bladder in the United States. It is currently used off-label in many other countries. Botulinum blocks the motor activity of the detrusor muscle by binding to the presynaptic terminals of motor neurons, which inhibits acetylcholine release at the neuromuscular junction. However, this therapeutic effect is limited as the nerve terminals recover function within months.

When considering new therapies, especially potentially costly ones, it is important to assess cost-effectiveness. Although BoNT-A may be more effective, it is likely associated with higher costs. Thus, it is unclear which therapy is more cost-effective. In this study we assessed the cost-effectiveness of botulinum toxin vs anticholinergic medications for the treatment of refractory idiopathic urge incontinence in the United States.

MATERIALS AND METHODS

Decision Model

A Markov decision model was developed to estimate the costs and the effectiveness of anticholinergic medication and botulinum toxin A injection for refractory idiopathic urge incontinence (fig. 1). Our hypothetical study population was women in whom first line therapy with behavioral treatment and 1 anticholinergic medication failed. The analysis was conducted from a societal perspective with a time horizon of 2 years using 3-month cycles.

For the BoNT-A strategy women started with a 200 unit BoNT-A injection. At the end of the 3-month cycle they experienced improvement in incontinence or treatment was considered to have failed. If treatment failed the women could elect to undergo a repeat injection which would occur in the next cycle or enter a state of persistent incontinence. The health states after the initial injection were 1) improved, 2) repeat injection or 3) persistent urge incontinence (fig. 1). Following each injection patients could experience complications such as urinary retention or a urinary tract infection. We assumed that urinary incontinence improved in subjects with retention.

For the anticholinergic medication strategy women started with the 2nd long acting anticholinergic medication, after which conditions improved with or without complications/side effects, or treatment failed. Those in whom the 2nd medication failed could elect a 3rd long acting anticholinergic. After the first cycle they could transition to 1) improved, 2) 3rd medication, 3) improved with 3rd medication or 4) persistent urge incontinence (fig. 1). For those whose condition was improved we also included the probability of continued compliance with medications.

The decision model was constructed and analyzed with TreeAge Pro® Suite 2008 software. One-way sensitivity analyses were used to assess the robustness of the model by varying each parameter through its range of low and high estimates while the probabilities of the other variables were held constant. A Monte Carlo simulation was not performed given the high degree of uncertainty in the distributions of most of the parameter estimates. This study was exempt from institutional review board approval as the research involved the collection of existing data that were publicly available.

Parameter Estimates

Parameter estimates for BoNT-A were derived from an extensive review of the medical literature. A MEDLINE® search was performed in February 2008 using the MeSH® headings “Urinary bladder, overactive,” “Urinary bladder, neurogenic,” “Urinary bladder” or “Urinary incontinence” combined with “Neuromuscular agents,” “Botulinum toxins” or “Neurotoxins.” We limited the search to human subjects and English language, and excluded from the search editorials, letters or comments. Parameter estimates were based on BoNT-A studies that included female subjects with refractory idiopathic detrusor overactivity. For BoNT-A there were 2 randomized placebo controlled trials and most of the base case estimates were based on these 2 trials.[2,3] However, the ranges for the sensitivity analyses were based on studies that included more than 20 subjects with refractory idiopathic detrusor overactivity (see table).

The initial overall failure rate after BoNT-A was 21%.[2] For the remaining 79% with improvement the probability of failure at each 3-month cycle was calculated based on a 50% probability of failure at 9 months.[2] We assumed that 100% of subjects would experience treatment failure at 12 months. Complications after injection included urinary retention and UTI (see table). Although data for repeat injections are limited, several studies suggest similar efficacy in response to initial injections and, thus, the probabilities of failure for the first injection were used for subsequent injections.[5] However, if repeat injection failed subjects transitioned to persistent urge incontinence.

Parameter estimates for anticholinergic medications were primarily abstracted from the Cochrane review comparing anticholinergic drugs to placebo by Nabi et al.[6] The base case probability of improvement at 3 months was 56% and the probability of complications/side effects was 31%. Compliance with medications per cycle was 33% and