

COST-EFFECTIVENESS OF BOTULINUM TOXIN TYPE A IN THE TREATMENT OF POST-STROKE SPASTICITY

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Objective: Treatment strategies for post-stroke spasticity include oral anti-spastic drugs, surgery, physiotherapy and botulinum toxin type A injection. The objective of this study was to compare the cost-effectiveness and outcomes of oral therapy vs. botulinum toxin type A treatment strategies in patients with flexed wrist/clenched fist spasticity.

Methods: Treatment outcome and resource use data were collected from an expert panel experienced in the treatment of post-stroke spasticity. A decision tree model was developed to analyse the data.

Results: Thirty-five percent of patients receiving oral therapy showed an improvement in pre-treatment functional targets which would warrant continuation of therapy, compared with 73% and 68% of patients treated with botulinum toxin type A first- and second-line therapy, respectively. Botulinum toxin type A treatment was also more cost-effective than oral therapy with the “cost-per-successfully-treated month” being £942, £1387 and £1697 for botulinum toxin type A first-line, botulinum toxin type A second-line and oral therapy, respectively.

Conclusion: In conclusion, botulinum toxin type A is a cost-effective treatment for post-stroke spasticity.

Key words: post-stroke spasticity, cost-effectiveness, clinical efficacy, botulinum toxin type A, Botox, baclofen.

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INTRODUCTION

Stroke is a major burden on healthcare resources. In addition to the initial costs associated with stroke *per se*, approximately 30% of stroke survivors have a disability that requires further hospital resources. This equates to over 28,000 people in the UK each year (1). Post-stroke spasticity is a distressing, disabling condition, which may result in permanent contracture of muscles and soft tissue if untreated, resulting in increased disability and deformity. Treatment regimens for spasticity include physical therapy, oral anti-spastic agents, surgical intervention and injection with botulinum toxin type A (BTX-A). Although a number of recent studies have highlighted the clinical

effectiveness of BTX-A in the treatment of post-stroke spasticity (2–4), few have examined its cost-effectiveness.

Evaluating the cost-effectiveness of treatments for spasticity is challenging. Quantifying and comparing the cost of different treatments is hampered by the variation in intensity and localization of spasticity. Cost comparisons are complicated further by features, such as cognitive impairment, weakness and different patterns and presentations in post-stroke patients (5). Furthermore, treatment strategies for spasticity are often multi-disciplinary, making it difficult to analyse the costs associated with a single treatment (6).

The management of spasticity in the context of rehabilitation following stroke was assessed in the Royal College of Physicians Guidelines on Stroke Management (7). Guidelines on the use of BTX-A in the management of spasticity were subsequently developed by an expert group of clinicians (8). These guidelines were fully endorsed by the British Society of Rehabilitation Medicine and published as *Concise Guidance to Good Practice* by the Clinical Effectiveness and Evaluation Unit of the Royal College of Physicians in July 2002 (9).

To date 2 studies have assessed the economic impact of BTX-A therapy. In 1997, Wallesch et al. (10) reported the results of a decision tree model based on a Delphi panel survey, which included 13 German neurologists. They estimated that the average extent of improvement in spasticity with BTX-A plus physiotherapy was 3 times greater than that for baclofen plus physiotherapy and 10 times greater than for physiotherapy alone. Total direct medical costs associated with the 3 strategies did not differ markedly.

In 2001, Radensky et al. (11) published a study describing management strategies for spasticity following stroke and traumatic brain injury. The authors reported that strategies, which included oral baclofen, were associated with a significant increase in the total cost of treatment for lower limb spasticity. The cost increase appeared to be attributable to an increase in the overall intensity of treatment (i.e. more interventions from medical staff) and to the significant side-effects experienced with baclofen, such as sedation, drowsiness, fatigue and muscle weakness. In contrast, for upper limb spasticity the median cost per case for treatment strategies including BTX-A was less than those without BTX-A. Although the methodology is limited in that it is based on physician opinion and uses 1996 cost data, it indicates that the addition of BTX-A may not increase treatment costs. The objectives of this study were to estimate the treatment outcomes and cost-effectiveness for post-stroke patients with

flexed wrist/clenched fist spasticity, with and without the inclusion of BTX-A.

METHODS

The Delphi panel

The effect of treatment and resource use in post-stroke spasticity in patients treated with and without BTX-A were estimated by a Delphi panel. Thirty-three UK clinicians were sent a questionnaire, 45% responded and the Delphi panel included 14 clinicians and 1 physiotherapist.

Participants were asked to define the 3 most useful clinical objectives for treating patients with flexed wrist clenched hand spasticity and these were used to define pre-functional targets. The proportion of patients treated with BTX-A, the proportion of patients treated with oral agents (benzhexol, baclofen or tizanidine) both with and without BTX-A, and the likelihood of improvement in outcome in patients were estimated. In addition, participants were asked to estimate the resources used to treat patients over a 1-year period for each patient group. Resource use included input from neurologists, orthopaedic surgeons, rehabilitation physicians, general practitioners, nurses and physiotherapists. Participants were also asked to estimate the number of days in 1 year a patient would be hospitalized due to their spasticity. The percentage of patients requiring additional resources, i.e. biofeedback, stress management, electrical stimulation and orthotics, was also evaluated.

Feedback and agreement on question responses was obtained at a consensus meeting. A second questionnaire was then completed in which participants estimated the percentage of patients treated successfully or failing to respond to different treatment options. Treatment options included oral therapy, BTX-A therapy and BTX-A therapy as a second-line therapy following failure of oral agents. Surgery was also included as a second-line or third-line treatment. Minimum and maximum values obtained from the Delphi panel results were used for inclusion into the cost-effectiveness model.

Cost-effectiveness modelling

A decision tree model was built to compare 3 treatment options for post-stroke spasticity (oral therapy only, BTX-A therapy only, or second-line BTX-A for patients failing oral therapy) all of which were assumed to include physiotherapy insert (Fig. 1).

The model considered the UK population (58.8 million), with all costs and outcomes based on the estimated number of patients suitable for

treatment. This estimate used age-specific incidence rates to calculate the number of patients experiencing a stroke each year. After accounting for acute mortality (20%), the number of surviving patients with a disability was estimated. Of these patients, 20% were assumed to have upper-limb post-stroke spasticity and of these 38% (approximately 2187 patients) were deemed suitable for treatment.

A period of 1 year was modelled. Treatment success or failure was judged 3 months after initiation of therapy. "Treatment success" was defined as the percentage of patients who had met or had sufficient improvement in pre-treatment functional targets to warrant continuation of therapy. Patients successfully treated at month 3, were assumed to continue therapy until the end of the period modelled, or until death. Those patients who did not achieve sufficient benefit, were assumed to stop therapy at month 3 and were deemed to have used only 3-months' associated resources. Oral therapy followed by BTX-A therapy in treatment failures, was the only scenario in which patients were deemed to receive a second-line therapy; as the need for surgery is small, it was not included in the analysis.

Primary outcomes from the model include the percentage of successfully treated months (STM), cost per successfully treated month (cost/STM) and the total cost to the UK National Health Service (NHS).

Data sources

Demographic data were obtained from the Annual Abstract of Statistics (12), percentage incidence of stroke by age was calculated from data in Ref. 13 and 14, and acute mortality following stroke data was calculated from Ref. 14. The percentage of post-stroke patients with disability was obtained from the agency for healthcare care policy and research (AHCPR) clinical practice guidelines (1). The percentage of patients with clenched fist spasticity and percentage of patients suitable for treatment was estimated based on expert opinion.

Costs

The drug costs used in the resource analysis were obtained from the British National Formulary, eMIMs (June 2002) and from Allergan Ltd. The weighted annual cost of BTX-A therapy (£806.08) was a weighted average cost which took into account the cost per vial (£128.93), number of vials per treatment (2) and frequency of treatment (Allergan: data on file). Resource use costs are presented in Table I. Patients were assumed to receive 6 sessions of biofeedback, 6 sessions of stress management, 4 sessions of electrical stimulation and 3 sessions of orthotics per annum.

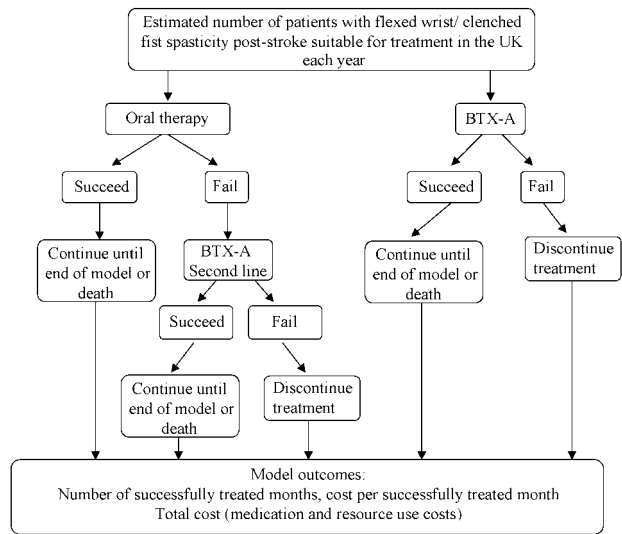


Fig. 1. Diagram of the flow through the model. BTX-A = botulinum toxin type A.

Table I. Resource costs for treating post-stroke spasticity

| Resource | Unit costs (£) |
|---|---|
| Neurologist | 54.50/30 minutes of patient contact ¹ |
| Orthopaedic surgeon | 55.50/30 minutes of patient contact ¹ |
| Rehabilitation physician | 54.50/30 minutes of patient contact ¹ |
| Nurse | 19.50/30 minutes of patient contact ^{1*} |
| Physiotherapist | 19.50/30 minutes of patient contact ^{1*} |
| General practitioner | 18 per consultation ¹ |
| Hospitalization | 152/day ¹ |
| Surgery | 1272/surgery ² |
| Biofeedback | 42/hour ¹ |
| Stress management (based on therapy given by a clinical psychologist) | 64/hour ¹ |
| Electrical stimulation | 42/hour ¹ |
| Orthotics | 150/fitting ³ |

* Average cost of staff nurse, district nurse and practice nurse.
¹ From Netten & Curtis (15). ² From Department of Health Reference costs 2002 (16). ³ From NHS Purchasing and Supply Agency Orthotics pathfinder event (17).

RESULTS

The Delphi panel

The panel was asked to identify up to 3 of the most useful clinical objectives for treating patients. The outcomes highlighted most frequently were improved hygiene, function and appearance. These outcomes were included as pre-functional targets.

The mean proportion of patients receiving BTX-A injection was 38% (25%) (mean (SD); range 0–70%). The mean proportion of patients receiving anticholinergics (benzhexol) was 5% (9%) (range 0–40%) and the mean proportion of patients receiving muscle relaxants (baclofen and tizanidine) was 70% (33%) (range 0–100%).

Thirty-five percent of patients receiving oral therapy reported treatment success (95% confidence interval (CI) 24%–46%) compared with 73% (95% CI 68%–78%) for BTX-A first-line therapy and 68% (95% CI 60%–76%) for BTX-A second-line therapy (Table II).

Physicians were asked to estimate the range of improvement in meeting treatment targets. With or without BTX-A relatively few patients fully meet treatment expectations (12% of patients treated with BTX-A compared with 6% without BTX-A). However, 58% of patients treated with BTX-A achieve at least 75% of the treatment target compared with only 7% of patients without BTX-A (Table III). Ten percent of patients treated with oral therapy achieved at least 50% of their treatment goal compared with 76% of patients receiving BTX-A.

In the majority of patients (81%) BTX-A had a duration of effect of at least 16 weeks. The number of BTX-A treatments required ranged from 1.6 to 4.3 treatments per year and the average annual cost of medication only was £806.08.

The use of oral medication was less in patients treated with BTX-A. The use of benzhexol was 4.4% in patients treated with oral therapy only compared with 1.3% in patients treated with BTX-A. Similarly the use of baclofen was 45.6% and 16.9% and the use of tizanidine was 1.7% and 0 in patients treated with oral therapy only and with oral therapy and BTX-A, respectively.

The use of electrical stimulation and stress management was less in patients treated with BTX-A. The percentage of patients using electrical stimulation was 7% and 17% in patients treated with and without BTX-A, respectively. Similarly, 8% of patients treated with BTX-A compared with 14% of patients treated without BTX-A received stress management. Biofeedback

Table II. Mean success rate for treatment of post-stroke spasticity

| Treatment | Success rate (%) | | | |
|------------------------------|------------------|------|------|---------|
| | Mean | Min. | Max. | 95% CI* |
| Oral therapy | 35 | 10 | 80 | 24–46 |
| BTX-A as first-line therapy | 73 | 55 | 85 | 68–78 |
| BTX-A as second-line therapy | 68 | 40 | 85 | 60–76 |

* 95% confidence interval. BTX-A = botulinum toxin type-A.

Table III. Range of improvement (%) in pre-treatment functional targets in post-stroke spasticity patients

| | Without BTX-A | With BTX-A |
|--------------------------|---------------|------------|
| Exceeds expectations | 0 | 0 |
| Fully meets expectations | 6 | 12 |
| Reaches 75% of target | 1 | 46 |
| Reaches 50% of target | 3 | 18 |
| Reaches 25% of target | 24 | 16 |
| No improvement | 66 | 7 |

BTX-A = botulinum toxin type A.

therapy was used by 3% and 2% of patients treated with and without BTX-A, respectively. Orthotic devices were used by 50% of BTX-A-treated patients compared with 45% of patients treated without BTX-A.

Resource use was estimated with and without BTX-A treatment (Table IV). Based on results from the Delphi panel the average number of physiotherapy contacts per patient per year was 99 and 60 for patients receiving oral therapy and BTX-A therapy, respectively.

There was broad agreement that nursing time would be less in patients treated with BTX-A. Based on the results from the Delphi panel the average number of nursing contacts per patient per year was 125 and 41 for patients receiving oral therapy and BTX-A therapy, respectively. Whilst in the patient group considered, hospitalization may be either for the management of the underlying condition or for respite care, the average number of hospital days was 15 and 16.5 (range 2–45) with and without BTX-A, respectively.

Cost-effectiveness modelling

The percentage of STM per annum was 35% (128 days out of 365) for oral therapy only compared with 73% (266 days out of 365) for BTX-A first-line and 68% (248 days out of 365) for BTX-A second-line. The cost/STM was £942 for BTX-A as first-line treatment, £1387 for BTX-A as second-line treatment and £1697 for oral therapy alone.

The number of nurse hours was considerably less in patients receiving first-line BTX-A therapy compared with those receiving oral therapy (Table V). The total number of nursing hours required for patients using oral therapy was 303,653 compared with 243,701 and 412,409 for patients using BTX-A as first-line

Table IV. Units of resource utilization per patient used in the treatment of flexed wrist/clenched fist post-stroke spasticity

| Resource | Without BTX-A | With BTX-A |
|--------------------------|-------------------|-------------------|
| Neurologist | 1.9 contacts/year | 2.1 contacts/year |
| Orthopaedic surgeon | 1.1 contacts/year | 0.7 contacts/year |
| Rehabilitation physician | 4.6 contacts/year | 4.0 contacts/year |
| Nurse | 5.7 hours/week | 3.0 hours/week |
| Physiotherapist | 3.2 hours/week | 2.7 hours/week |
| General practitioner | 4.9 contacts/year | 2.4 contacts/year |
| Hospitalization | 16.5 days/year | 15 days/year |

BTX-A = botulinum toxin type A.

Table V. Nurse and physiotherapy resources associated with treating post-stroke spasticity

| | Treatment paradigm | | | Change relative to oral therapy | |
|-------------------------|--------------------|------------|------------|---------------------------------|------------|
| | Oral | BTX 1 line | BTX 2 line | BTX 1 line | BTX 2 line |
| Nurses | | | | | |
| Hours | 303,653 | 243,701 | 412,409 | -59,952 | +108,756 |
| Cost (£) | 5,925,447 | 4,751,761 | 8,141,140 | -1,173,686 | +2,215,693 |
| WTEs | 181 | 145 | 246 | -36 | +65 |
| Physiotherapists | | | | | |
| Hours | 170,472 | 219,331 | 268,352 | +48,859 | +97,880 |
| Cost (£) | 3,326,567 | 4,276,585 | 5,320,690 | +950,018 | +1,994,123 |
| WTEs | 101 | 129 | 160 | +28 | +59 |

WTEs = whole time equivalents; BTX = botulinum toxin.

and second-line therapy. This equates to cost savings of £1,173,686 for first-line BTX-A therapy.

In contrast, the number of physiotherapist hours was higher with BTX-A use (Table V). Treatment with BTX-A resulted in an additional 48,859 and 97,880 physiotherapist hours (above that for oral therapy) for BTX-A as first-line and second-line treatment, respectively. This equates to an additional cost of £950,018 and £1,994,123 for first-line and second-line BTX-A treatment, respectively.

The total NHS cost for oral therapy was estimated at approximately £13.6 million per annum compared with £16.0 million and £21.1 million for BTX-A as first- and second-line therapy, respectively (Table VI).

The baseline scenario did not include the cost of surgery. However, the results of the Delphi panel suggest that approximately 64% of all treatment failures (oral therapy and BTX-A) will undergo corrective surgery. Using the anticipated success rates for surgery reported in the Delphi panel (43% and 64% for surgery following oral therapy and BTX-A, respectively) the inclusion of surgery increases the overall success rate to 46% for oral therapy plus surgery and 77% for BTX-A plus surgery. These results suggest that even when BTX-A therapy is considered alone, it is more effective than oral therapy plus surgery (efficacy of BTX-A therapy alone 73% vs. 46% for oral

therapy plus surgery). The cost/STM for patients receiving surgery following oral therapy and BTX-A therapy was £1733 and £1125, respectively.

The baseline scenario was based on the “mean” rate of efficacy reported by Delphi panel members for both oral and BTX-A therapies. However, the estimates provided varied considerably from between 24% and 46% for oral therapy and 68% to 78% for BTX-A. A further analysis was therefore conducted to determine the impact of such variation on the cost-effectiveness of BTX-A vs. oral therapy. The analysis showed that, within the range of efficacy reported, BTX-A remained more cost-effective than oral therapy (Table VII).

DISCUSSION

In this study, cost-effectiveness was calculated based on the number of successfully treated months per year and the cost of providing treatment. Successfully treated months were defined as months in which patients received sufficient benefit to warrant continuation of therapy. This definition revealed an interesting paradigm.

Clinicians estimated that 35% of patients treated with oral medication received sufficient benefit to warrant continuation of therapy and yet they conceded that only 10% of patients would

Table VI. Total National Health Service costs associated with oral therapy and botulinum toxin type A (BTX-A) therapy in the treatment of post-stroke spasticity

| Resource | Cost associated with | | |
|--------------------------|----------------------|----------------------|-----------------------|
| | Oral therapy (£) | BTX-A first-line (£) | BTX-A second-line (£) |
| Neurologist | 106,160 | 178,777 | 189,521 |
| Orthopaedic surgeon | 62,589 | 60,686 | 90,886 |
| Rehabilitation physician | 257,018 | 340,527 | 451,801 |
| Nurse | 5,925,447 | 4,751,761 | 8,141,140 |
| Physiotherapist | 3,326,567 | 4,276,585 | 5,320,690 |
| General practitioner | 90,422 | 67,481 | 121,888 |
| Other* | 1,193,332 | 1,511,754 | 1,898,246 |
| Hospitalization | 2,571,200 | 3,561,478 | 4,231,877 |
| Total resource cost | 13,532,735 | 14,749,049 | 20,410,049 |
| Prescription costs | 62,440 | 1,278,137 | 658,420 |
| Total cost | 13,595,175 | 16,027,186 | 21,068,469 |

* Other costs include orthotics, biofeedback, stress management and electrical stimulation.

Table VII. Sensitivity analyses for oral therapy and botulinum toxin type A (BTX-A) first-line therapy

| | Efficacy of BTX-A | | | Efficacy of oral therapy | | |
|-------------------------|-------------------|----------------|----------------|--------------------------|----------------|----------------|
| | Baseline 73% | Minimum 68% | Maximum 78% | Baseline 35% | Minimum 24% | Maximum 46% |
| No of STM | 17,025 | 15,587 | 17,880 | 8,163 | 5,501 | 10,544 |
| Cost per STM (£) | 942 | 965 | 921 | 1,697 | 2,061 | 1,459 |
| Total resource cost (£) | 14,749,049 | 13,841,013 | 15,152,129 | 13,532,735 | 11,284,838 | 15,317,319 |
| Total drug cost (£) | 1,278,137 | 1,199,448 | 1,313,068 | 62,440 | 52,068 | 70,674 |
| Total cost (£) | 16,027,186 | 15,040,461 | 16,465,196 | 13,595,175 | 11,336,906 | 15,387,993 |

STM = successfully treated months.

achieve 50% or more of their pre-treatment targets. Compare this with BTX-A, where 73% of patients were seen to receive sufficient benefit to continue therapy and yet 76% were thought to achieve 50% or more of their pre-treatment targets. This suggests that the definition of “successfully treated” was more rigorously applied to BTX-A patients than to oral therapy patients. If this is the case, then the number of successfully treated months for orally treated patients may have been overestimated. Furthermore, it suggests that clinicians will maintain patients on oral therapy even when little progress is being made towards a clinical target.

Treatment success will also affect the total cost of a therapy option. The total cost of BTX-A first-line is higher than that for oral therapy, not only because the cost of the drug is higher but also because more patients will remain on it. The cost of second-line BTX-A therapy is higher still, as patients first incur the costs associated with oral therapy and then those associated with BTX-A. Some of the costs associated with oral therapy were not included in this analysis, for example, the cost of treating gastrointestinal upset, liver toxicity and dry mouth were omitted. Loss of quality of life resulting from drowsiness, sedation and generalized muscle weakness (other side-effects of oral therapy) were also not addressed.

Estimating the physiotherapy and nursing time required to treat this patient group is challenging. Further investigation is required to quantify physiotherapy and nursing utilization, as they are likely to be major drivers of treatment cost and cost-effectiveness. This analysis also estimated the number of patients suitable for treatment with BTX-A. Further research is required to validate this figure.

A possible limitation of the current study is that the data is derived from a Delphi panel. Delphi has been used extensively in healthcare applications and has been used to assist in the development of clinical guidelines (18). However, outcomes are based solely on expert opinion and as such may be subject to bias and inaccuracy.

This study demonstrates that BTX-A is a cost-effective and clinically efficacious treatment for post-stroke spasticity. However, further data collection and analysis is required to quantify accurately the major cost drivers. A prospective study is currently under way to investigate the clinical and cost-effectiveness of BTX-A in post-stroke spasticity. A comprehensive, computer-based spasticity management and outcomes

registry will be formed which will link together patient information, pre-treatment defined goals and post-treatment validated outcomes.

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