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Original Article

Systematic review and cost-effectiveness analysis of the treatment of post-stroke spasticity with abobotulinumtoxinA compared to physiotherapy

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A B S T R A C T

Objective: Post-stroke spasticity (PSS) is a common complication in stroke survivors, causing severe burden to patients living with it. The aim of this review was to conduct a cost-effectiveness analysis (CEA) of the treatment of post-stroke spasticity, in adults, with abobotulinumtoxinA compared to the best supportive care, based on results from a systematic literature review. Given that abobotulinumtoxinA (aboBoNT-A) is always accompanied by the best supportive care treatment, the CEA compared aboBoNT-A plus the best supportive care with the best supportive care alone.
Methods: A systematic literature review in EMBASE (including Medline and PubMed), Scopus, and other sources (Google Scholar) was conducted. Articles of all types, providing information on the costs and/or effectiveness measures for the current treatments of PSS in adults were included. The synthesis of information from the review provided the parameters for the design of a cost-effectiveness analysis of the mentioned treatment of interest. The societal perspective was compared to a perspective where only direct costs were observed.
Results: In total, 532 abstracts were screened. Full information was revised from 40 papers and 13 of these were selected as core papers for full data extraction. Data from the core publications formed the basis for the development of a cost-effectiveness model. In all the included papers physiotherapy was the best supportive care treatment (SoC). The cost-effectiveness analysis showed that even in the most conservative scenario, assuming the worst case scenario, the probability of a cost per quality-adjusted life-year (QALY) gained below €40,000, for aboBoNT-A together with physiotherapy is above 0.8, and with certainty below €50,000/QALY when either a direct costs, or a societal perspective was taken. On average, the probabilistic model obtains a negative mean incremental cost-effectiveness ratio of around −15,000 €/QALY.
Conclusion: The cost-effectiveness analyses show that aboBoNT-A together with physiotherapy would be a cost-effective treatment compared with physiotherapy alone, independently of the perspective considered.

Revisión sistemática y coste efectividad del tratamiento con abobotulinumtoxinA Para la espasticidad post-ictus en comparación con fisioterapia

Palabras clave:
Espasticidad post-ictus
abobotulinumtoxinA (aboBoNT-A)
población adulta
Revisión sistemática de la literatura
Análisis de coste-efectividad

R E S U M E N

Antecedentes: La espasticidad post-ictus es una enfermedad común que afecta a los adultos y causa una carga grave a los pacientes que la padecen. El objetivo de la revisión fue realizar un análisis coste-efectividad (ACE) del tratamiento de la espasticidad post-ictus, en adultos, con abobotulinumtoxinA (aboBoNT-A) en comparación con el tratamiento convencional, basado en los resultados de una revisión sistemática de la literatura. Dado que este tratamiento se proporciona siempre al mismo tiempo que el tratamiento convencional, el ACE se realizó del tratamiento aboBoNT-A con el tratamiento convencional, en comparación con recibir únicamente el tratamiento convencional.

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Métodos: Se realizó una revisión sistemática de la literatura en EMBASE (incluyendo Medline y Pubmed), Scopus y otras fuentes (Google Scholar). Se incluyeron artículos de todo tipo que proporcionaran información sobre los costes y/o las medidas de efectividad de los tratamientos actuales del PSS en adultos. La síntesis de la información de la revisión proporcionó los parámetros para el diseño de un análisis coste-efectividad del mencionado tratamiento de interés. Se comparó la perspectiva social con una perspectiva donde solo se observaron los costes directos del tratamiento.

Resultados: Se revisaron un total de 532 resúmenes. Se revisó la información completa de 40 artículos y se seleccionaron 13 artículos para la extracción completa de datos. La información de estos documentos se sintetizó y utilizó para desarrollar un modelo de coste-efectividad. En todos los artículos incluidos se identificó el tratamiento con fisioterapia como el tratamiento convencional principal. El análisis de coste-efectividad mostró que, incluso en el peor escenario posible, asumiendo los costes más elevados, la probabilidad de un coste por año de vida ajustado por calidad (AVAC) ganado por debajo de 40.000 € para el tratamiento con aboBoNT-A y fisioterapia es superior a 0,8 AVACs, y hay certeza de que estará por debajo de 50.000 €/AVAC considerando tanto costes directos como una perspectiva social. El modelo probabilístico obtuvo una ratio coste-efectividad incremental media negativo, que se sitúa entorno a −15.000 €/AVAC.

Conclusión: Los análisis de coste-efectividad muestran que la aboBoNT-A junto con el tratamiento de fisioterapia sería una alternativa coste-efectiva independientemente de la perspectiva considerada.

Lay abstract

After a stroke, patients can often experience muscle and limb stiffness, known as limb spasticity. This may lead to difficulties with movement and personal care, which can affect quality of life.

There are several treatments for limb spasticity. The treatment offered can vary based on the patient's needs. Two treatments are available to relax stiff muscles: botulinum toxin injections and physiotherapy. Other treatments include surgery and oral antispasticity medications including baclofen, pregabaline, tizanidine and benzhexol/trihexyphenidil.

In this Spanish study, the researchers wanted to compare the cost-effectiveness (i.e. the balance between the cost of treatment and how well it works) of two treatments. They compared physiotherapy combined with a specific type of botulinum toxin injection (abobotulinumtoxinA [aboBoNT-A]) versus physiotherapy alone for adults with spasticity after a stroke. To do this, they searched online databases for scientific publications, and they identified 13 core publications that were included in the analysis. Using the information from these publications, the researchers generated a set of probable scenarios, which were put into a simulation model. The model estimated overall costs and effectiveness outcomes, as well as whether the treatment was cost-effective. For accuracy, the researchers also adjusted the costs for inflation to the current year, 2022.

Even when the researchers created the most conservative scenario using the highest costs possible, the calculations showed that physiotherapy combined with aboBoNT-A injections could still be a cost-effective treatment compared with physiotherapy alone for patients with limb spasticity after a stroke.

Introduction

Stroke is among the four leading causes of death globally[1] in the general population, with more than 6 million deaths reported in 2017, representing an increase of 16.6% during the last decade.[2] Post-stroke spasticity (PSS) prevalence ranges widely, with estimates ranging between 18% and 42%[3,4] depending on the setting and methods used to calculate it. The condition is associated with markedly impaired quality of life (QoL), causing pain, problems for self-care and performing daily life activities, and reduced mobility among patients.[5] Stroke and post-stroke sequalae, including spasticity, are internationally recognized as an important health problem.[3,5] The exact influence of spasticity on motor impairments and activity limitations in stroke patients is, however, difficult to assess. This might be due to the fact that spasticity can vary from mild to significant neurological impairment, affecting joint mobility in the most severe cases.

Treatment strategies for spasticity are often multidisciplinary, making it difficult to analyze the costs associated with a single treatment. Methods used for measuring costs of PSS treatment are also heterogeneous.

Treatment for PSS include physiotherapy, oral antispastic agents, surgical intervention, and injection with abobotulinumtoxinA (aboBoNT-A).[6] Despite the existence of literature highlighting the clinical effectiveness of the different treatments,[7–10] cost-effectiveness of the different treatments has only been examined in a few studies.[6,11] Recent consensus articles[12] and data from clinical trials[11,13] support the use of aboBoNT-A for focal spastic conditions of the upper and lower limbs in adults with PSS.

AboBoNT-A is administered through injections and the doses may vary depending on the clinician's criteria according to patients' characteristics. It is never given alone, but complements another treatment, which might be physiotherapy, and/or other oral anti-spasticity medication.

The different costs and health outcomes used as measures for each of the treatments, and the heterogeneity of the study findings make it difficult to conduct a cost-effectiveness analysis of the different treatments. While aboBoNT-A and physiotherapy have both unique and common measures of effectiveness in PSS, the effects of physiotherapy on passive function, caregiver burden, or the individual's priority goals for treatment are currently unknown.[14] As a consequence, the comparative value of the effectiveness of aboBoNT-A in combination with physiotherapy compared with physiotherapy alone from a societal perspective remain unknown and underestimated. In addition, the effectiveness measures studied in clinical trials vary among studies and, in some cases, are purely clinical measures. For example, while some studies measure the effectiveness of aboBoNT-A by the Modified Ashworth Scale (MAS; a measure of muscle tone),[7–10,15–17] other studies have used different measures, such as the Perceived function and pain Disability Assessment Scale (DAS),[17] or measures of QoL, such as the 36-item Short-form Survey (SF-36),[14,17] EuroQol-5 dimensions (EQ-5D; a measure of the functional value of a patient),[14,17,18] or the Barthel Index.[16] Because the same study may show results on more than one effectiveness measure, it is often not possible to aggregate results into a single effectiveness score or measurement. Synthesizing information on the costs of the different treatments is difficult because of the heterogeneity of results, due mainly to the different timing of the studies, as well as the different prices in the different healthcare systems within and between countries.

The aim of this review was to conduct a cost-effectiveness analysis of the treatment of post-stroke spasticity, in adults, with aboBoNT-A, administered alongside physiotherapy, compared to the best supportive care, physiotherapy alone, based on results from a systematic literature review.

Methods

Systematic literature review

Search strategy

This systematic review was performed in accordance with the principles of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.[19] The Acronyms standing for Population/Patient Intervention/Exposure Comparison Outcome (PICO/PECO) method was applied to structure the search[20] and keywords were combined using Boolean terms. The framework of this systematic review according to PICO was: people diagnosed from PSS. The intervention was treatment with type A botulinum toxin combined with best supportive care (physical therapy) and comparator was best supportive care alone. The effect of the treatment on costs and/or effectiveness/efficacy of the provided treatment was the main outcome of interest. Additionally, articles comparing patient outcomes for the treatment of interest with patient outcomes without treatment and/or with the best supportive care, as well as those presenting the evolution of direct and/or indirect cost measures over time, were preferred.

The search was conducted in EMBASE (including Medline and PubMed) and Scopus databases. The search strategy is available in the supplementary material. The search results were complemented by materials from other sources (mainly Google scholar), known to be relevant by the researchers, and these were manually retrieved. This step enabled the capture of articles that were not available in the consulted databases.

Inclusion and exclusion criteria

Records were limited to any published academic article or gray literature available in full-text format, in English or Spanish, that provided detailed information on the costs or measures of effectiveness of aboBoNT-A indicated for the treatment of PSS. Studies using this same toxin for other indications (e.g., post-trauma brain damage) were included, but were not considered to be core papers but optional papers. The same principles were applied for studies that included other toxins for the treatment of PSS but which did not disaggregate or provide results for individual toxins on costs and/or effectiveness measures. These publications were available as optional papers for consultation. Studies included both randomized controlled trials (RCTs) and empirical research, which included observational studies data or simulation studies based on RCTs. For studies in which the results were from simulations, the source of the information was verified to be reliable, or the population interviewed to derive the information were verified as providing expert knowledge. Only studies with an adult population were considered. All the exclusion criteria identified are detailed in the PRISMA flow diagram (Fig. S1).

Data extraction

All the identified references were imported into Zotero, the bibliographic software used for the selection/exclusion of studies. The selection of studies included the exploration of titles and abstracts in a first stage, and full texts in a second stage. The search and selection were carried out in June 2021 by two researchers, independently of each other. Any doubts or disagreements between the two researchers were discussed with a third researcher. The methodology followed for data extraction was reviewed and approved by all authors. There were no cases in which it was necessary to contact any authors of the studies included in this review to request any additional information.

Risk bias and quality assessment

The Parmar et al.[21] check-list for the assessment of bias risk and quality of sources was used as a basis for the assessment of quality and risk of bias of the identified texts. The tool developed by Parmar et al.[21] was considered to have all the relevant questions to make a good quality and bias assessment of both RCTs and observational studies in this review.

For randomized controlled clinical trials, selection bias was assessed by analyzing the adequacy of the sampling methods (power, sample size, blinded design, randomization). Studies that provided information on the potential gains of a treatment relative to other treatments, or to a control group, were considered to be the strongest. In addition, the greater the distance (in years) between the time period analyzed and the time of publication, the greater the risk of time bias. A higher measurement risk in the exposure variable for the types of treatment and self-reported health outcomes, not contrasted by clinical personnel, was considered. In each publication, each domain was scored as 1 for low risk of bias, 2 for moderate risk, and 3 for high risk. The overall rating was computed as follows: 1 (strong) if none of the domains were rated as weak, 2 (moderate) if up to two domains were rated as weak, or 3 (weak) if three or more domains were classified as weak. Only publications of the highest quality (scoring 1 or 2) were included in the final synthesis of results.

Other relevant information on the methodology followed.

The original language of the texts was kept to avoid a possible interpretation bias of the researchers in the data extraction phase.

Cost-effectiveness analysis

Study population and treatments

A model was developed to simulate the cost-effectiveness analysis for the population of adults with PSS being treated with aboBoNT-A and physiotherapy compared with physiotherapy alone or do nothing. AboBoNT-A was the analyzed toxin for the indication of PSS in adults, so patients receiving other botulinum toxins were excluded for the analysis.

Simulation model

A simulation with 1000 observations was conducted in Microsoft Excel 2010. Individuals were assumed to be randomly allocated to either treatment with aboBoNT-A plus physiotherapy, or to the SoC treatment alone, physiotherapy, or do nothing (identified within the reviewed literature as the most common treatments of PSS in adults), with equal probability. Costs and effectiveness were discounted, allowing for two different discount rates (3% and 5%). Costs and effectiveness estimates were updated yearly and up to the present year, 2022. Yearly average exchange rates were used for conversion to original currency to €, when the original currency differed from the €. A time horizon of 10 years was chosen, as it has been suggested by a recent publication for this particular indication and treatment.[22] It was assumed the transition probabilities from the second year onward remain stable.[11] Normal distributions for effectiveness and costs variables were chosen for a baseline analysis. Beta and gamma distributions were also tested to account for uncertainty in our simulation model, as suggested by the literature,[11] but only the more conservative results under the normality assumption are presented (results were more in favor of aboBoNT-A treatment with beta and gamma distributions than with normal distributions, showing lower costs per QALY gained at all the tested scenarios). A normal distribution for costs and effectiveness measures was acceptable in this model given that the probability of death due to PSS is small and that, similar to other common diseases, there will be a small proportion of patients with very high and very low costs of receiving treatment, while most individuals will be concentrated around the average cost.

Costs and effectiveness measures

All medication costs, and not just aboBoNT-A costs, were considered for both groups (aboBoNT-A plus physiotherapy, and physiotherapy alone/do nothing), as well as other medical and nonmedical costs of providing aboBoNT-A treatment to the simulated population. For effectiveness measures, the health outcomes MAS score and QALYs were selected based upon their popularity in the reviewed literature. The primary health outcomes chosen were QALYs. QALYs used were taken from Lazzaro et al. study.[11] MAS results were also taken from the literature and considered as a secondary clinical effectiveness measure for the analyses.[7,18] Only papers that provided results on these outcomes for aboBoNT-A treatment for PSS in adults were included.

Sensitivity analyses

Given the heterogeneity in the costs provided by the literature, a cost-effectiveness analysis model was simulated using the mean, lower, and upper bounds for the estimated costs published. Therefore, a simulation for the most conservative scenario (using the highest costs) and the most optimistic scenario (the lowest costs) was provided. Results using the mean costs were also provided.

Two different cost methods were tested, to compare how results would vary depending on the perspective taken: direct costs only (including only the pharmacological treatment and other medical costs) and societal costs (incorporating any other nonmedical costs). For both methods, three scenarios were allowed: the lowest, mean, and highest cost.

The simulation model also provided cost-effectiveness acceptability curves for each year of the study, as well as the mean for 2, 5, 8, and 10 years, counting from the start of treatment.[23] A graphical representation of the sensitivity analysis is provided in the results, with the presentation of cost-effectiveness acceptability curves (CEACs) and the uncertainty graph, in which the incremental costs per incremental QALY gain are plotted. CEACs show the probability of the aboBoNT-A plus physiotherapy treatment being cost-effective.

Results

Synthesis of information from the systematic literature review

Our search strategy (in titles and abstracts), after excluding duplicates, identified 532 potential studies from EMBASE (n = 421), Scopus (n = 111), and other sources (n = 14); in total, 20 articles were manually retrieved based on knowledge of the study and of its relevance. We excluded 508 abstracts and selected 24 for full-text review. Finally, 13 articles were selected as the core papers for the synthesis of information extraction. Information was also extracted in full from the remaining 11 publications, although they were considered optional for the purpose of a cost-effectiveness modeling. All the extracted information and reasons for exclusion are available in the supplementary material.

A PRISMA flow chart depicting the study selection process, including the reasons for exclusion in the exploration and eligibility phases, is presented in Fig. S1 in the supplementary material. Reference lists of the main research reports and previously published systematic reviews that had a focus on aboBoNT-A were screened to identify additional studies.

Tables S1 and S2 in the supplementary material present the main results of the core articles (n = 13) in relation to the cost and effectiveness measures (or cost-effectiveness/utility in the case of a study of this type).

Among the reviewed and extracted core papers (n = 13), four were effectiveness studies,[9,10,16,17] three evaluated efficacy measures[7,15,16] (two also assessed safety), and six assessed costs (one studied annual-costs projections,[23] two conducted a budget-impact analysis,[24,26] and three were cost-effectiveness or cost-utility studies[6,11,25]).

Data extraction tables, and a detailed assessment of the risk of bias and study quality are also available in the supplementary material.

With respect to costs, the majority of the included articles compared the cost of aboBoNT-A with the cost of physiotherapy or rehabilitation therapies. However, there were a few papers in which the SoC was other toxins for the same indication.[23,24] In some of the studies patients were taking concomitant medications whether they were in the aboBoNT-A (plus physiotherapy) treatment group or in the physiotherapy alone group. Therefore, all medication costs had to be extracted as well when measuring the PSS SoC direct costs. There were three articles that did not consider the nonmedical costs of providing treatment to patients[12,23,24] but considered direct costs only. Three papers considered nonmedical costs, thus offering a societal perspective in their costs analysis[11,25,26]; in two of these three papers, nonmedical costs were significantly greater than the direct costs.[11,25] There was a marked difference in the SoC treatment costs when considering a direct cost versus a societal cost perspective.

As shown in table S2, the EQ-5D and the SF-36 were the instruments used most frequently to assess QoL. The efficacy measure used most frequently in the literature to study efficacy of aboBoNT-A in patients with PSS was the MAS (with seven papers using it as a primary efficacy outcome measure). Other efficacy measures identified that also appeared frequently in the selected literature were the Physician Global Assessment and the Tardieu Scale.

Synthesis of costs and effectiveness outcomes

Information on costs was extracted; mean costs were calculated when sufficient information was available in the reviewed source. Overall, six core papers included information on costs.[6,11,23–26]

Table 1 shows the synthesis and explanation of the cost information used in the cost-effectiveness model. High heterogeneity among studies was observed, not only in the cost and cost-savings results obtained, but also in the type of costs considered in the studies, with some papers considering only medical (direct) costs and not including other costs. Given that the publication by de Andrés-Nogales et al.[23] considered other type A botulinum toxins as comparators, in contrast to the remaining included papers that did not include other toxins as comparators, the comparator suggested for that paper was a 'do nothing' alternative. The rates to update costs are provided, and the summary was calculated after updating all costs.

Table 2 shows the synthesis of the effectiveness results extracted from the selected core papers, and the most relevant effectiveness measures identified and selected for the cost-effectiveness analysis (MAS and QALYs). Only Lazzaro et al.[11] provided valid information regarding QALYs gained with aboBoNT-A compared with physiotherapy. Given that the publications by Rosales et al.[10,16] and Shaw et al.[17] only provide incremental MAS values, it was suggested to compute the mean based on results from papers that provided specific MAS values for both aboBoNT-A and SoC treatments.

The most common aboBoNT-A regime was to use 500 or 1000 Units injections, although a dose depending on patients' severity or to response of the treatment at the first visit was frequently observed as well. Regimes and doses recommended in each study are shown in Tables S1 and S2 in the supplementary tables.

Simulation model: assumptions and parameters

Table 3 presents the parameters used for the cost-effectiveness analysis and their sources.

Cost-effectiveness deterministic results

Mean costs and effectiveness results for the three scenarios (mean, lowest and highest costs) are summarized in Table 4.

The analysis showed that aboBoNT-A treatment, provided with physiotherapy, was highly cost-effective. In the scenario in which the mean costs were considered, the incremental cost-effectiveness ratio

Table 1
Synthesis of treatments' costs (information from the reviewed literature) used in the cost-effectiveness model.

Reference and comparator for cost-effectiveness analysis	AboBoNT-A & PT costs, €			SoC costs, €			Years of analysis	2022 update rate[a,b]
	AboBoNT-A cost	Other medical cost (*)	Other nonmedical costs	SoC direct healthcare cost	SoC other medical cost	SoC nonmedical costs		
(Abogunrin et al., 2015)[26] SMR and PT	2066.55	27,278.46	39.06	1148.08	31,642.83	38.58	2015	1.05
(de Andrés Nogales et al., 2014),[23] Do nothing	1180.72	NC	NC	NC	NC	NC	2013	1.06
(Neusser et al., 2019)[24] SMR and PT	3208.68	454.89	NC	184.18	617.03	NC	2013–2017	1.04
(Lazzaro et al., 2020)[11] SMR and PT	1080.21	2716.41	7683.00	0	896.33	5036.81	2018	1.03
(Shackley et al., 2012)[25] SMR and PT	154	341	1675	0	340	1456	2007	1.2
(Ward et al., 2005)[6] SMR, ES, and PT	417.96	7270.01	NC	9641.97	NC	NC	2005	1.26
Updated cost (in 2022),[c] mean (SD)	1430.42 (1156.14)	7862.58 (10,997.97)	3320.82 (4097.61)	3386.48 (5865.50)	9748.76 (14,659.24)	2325.21 (2621.93)	–	–

aboBoNT-A, abobotulinumtoxinA; ES, electrical stimulation; NC, not considered in the paper; PT, physiotherapy; SD, standard deviation; SMR, skeletal muscle relaxant; SoC, standard of care/best supportive care.
(*) Includes the cost of PT and other concomitant medications.
[a] Updated to 2022 according to inflation tool (https://www.inflationtool.com/euro), for the Eurozone.
[b] The paper provided[11] the cost for a 2-year period, so the actual estimate was divided by two to get the yearly cost.
[c] Estimates of aboBoNT-A costs are the mean of two values provided.

(ICER) was within the acceptable threshold. This was especially relevant when a societal perspective was assumed because the ICER was negative, indicating dominance of aboBoNT-A plus physiotherapy with respect to the SoC treatment (physiotherapy alone). When a direct cost perspective was assumed, the mean ICER was below €30,000, suggesting it could be a cost-effective option. When the lowest cost scenario was assumed, the ICER was small (below €2000 per QALY gained), independent of the perspective of either being direct or societal costs. Finally, when the highest costs were selected in the model, the ICER direct cost was approximately −€25,000 per QALY gained.

Using MAS as a clinical effectiveness measure to calculate ICER, although there was no rule to discriminate between alternatives, the analysis showed that a one-point reduction in MAS score would result in a cost savings of between €5400 and €6900, based on mean costs and depending on the study perspective.

Cost-effectiveness probabilistic results and sensitivity analysis

The mean costs scenario

When the mean costs scenario was analyzed, the mean direct costs per patient per year of treatment with aboBoNT-A plus physiotherapy were €7982.56, which was lower than the mean cost for SoC estimated at €9748.76. Societal costs for aboBoNT-A and SoC were estimated to be €9642.98 and €11,143.88 per patient and year, respectively.

Acceptability curves were generated for the mean costs' scenario for each of the years of the time horizon considered, as well as for the mean of the 10 years (Fig. S2-up in the supplementary material).

Using direct costs as the costs measurement method (Fig. S2-A), the results showed that in the simulation analysis, aboBoNT-A treatment had a high likelihood of being within the cost-effectiveness threshold and could therefore be considered to be cost-effective in this scenario, in which the mean of costs and effectiveness was presumed.

Table 2
Summary of aboBoNT-A effectiveness based on papers that included the MAS and QALYs.

Reference	QALYs AboBoNT-A Mean (SD)	QALYs SoC Mean (SD)	MAS AboBoNT-A Mean (SD)	MAS SoC Mean (SD)
(Lazzaro et al., 2020)[11]	0.81 (0.081)[a]	0.575 (0.07)		
(Marque et al., 2019)[8], (Gracies et al., 2015)[18]			3.9 (0.5)[b]	3.9 (0.4)[b]
			2.7 (1)[c]	3.7 (0.7)[c]
(Gracies et al., 2017)[15]			3.75 (0.5)[b]	3.9 (0.5)[b]
			3.15 (0.9)[b]	3.4 (0.8)[b]
			3.35 (0.8)[d]	3.5 (0.7)[d]
(McCrory et al., 2009)[9]			7.1 (1.2)[b]	3.9 (1.1)[b]
			5.3 (1.7)[e]	6.5 (1.3)[e]
			5.3 (1.7)[f]	6.6 (1.3)[f]

aboBoNT-A, abobotulinumtoxinA; MAS, Modified Ashworth Scale; QALY, quality-adjusted life-year; SD, standard deviation; SoC, standard of care/best supportive care.
[a] The paper provided the effectiveness gained for a 2-year period, so the actual estimate was divided by two to get the yearly QALYs gained. In addition, the SD for QALYs gained was not provided, so a coefficient of variation of 10% of the estimate was used instead.
[b] MAS at baseline.
[c] MAS at 4 weeks.
[d] MAS at 12 weeks.
[e] MAS at 8 weeks.
[f] MAS at 20 weeks.

Table 3
Model parameters and sources.

Parameter	Mean (calculated SD)	Min. (calculated SD); max. (calculated SD)	Source
Transition probabilities between health states			
Pr(survive at year 1)	0.937	NA	[11]
Pr(death due to stroke at year 1)	0.054	NA	
Pr(death due to other causes at year 1)	0.009	NA	
Pr(survive at year 2)	0.957	NA	
Pr(death due to stroke at year 2)	0.033	NA	
Pr(death due to other causes at year 2)	0.01	NA	
Costs, €			
Total aboBoNT-A costs per patient per year	9642.98 (10,209.87)	1251.56 (0.125); 28,681.44 (2868.144)[a]	Mean costs and calculated SD,based on results from selected articles
AboBoNT-A cost per patient per year	1430.42 (1156.14)	184.80 (NP); 3337.03 (NP)	Mean calculated based on mean costs from articles[6,11,23–25]
AboBoNT-A Other Medical Costs	7862.58 (10,997.97)	409.20 (NP); 26,472.50 (NP)	Mean calculated based on mean costs from articles[6,23–25]
aboBoNT-A Other nonmedical costs	3320.85 (4097.61)	39.06 (NP); 7913.41 (NP)	Mean calculated based on mean costs from articles[11,24,25]
SoC costs per patient per year	11,143.89 (13,762.24)	833.26 (83.326); 12,148.88 (1214.888)[a]	Mean costs and calculated SD,based on results from selected articles
SoC Direct healthcare costs	3386.48 (5865.50)	0 (NP); 12,148.88 (NP)	Mean calculated based on mean costs from all articles
SoC Other medical costs	8799.47 (16,285.03)	408.00 (NP); 33.224.97 (NP)	Mean calculated based on mean costs from all articles
SoC Other nonmedical costs	2325.21 (2621.92)	40.51 (NP); 5187.91 (NP)	Mean calculated based on mean costs from articles[11,24,25]
Effectiveness			
QALYs gained per year with aboBoNT-A + rehabilitation	0.81 (0.081)[a,b]	Not provided	[11]
QALYs gained per year with rehabilitation	0.575 (0.07)[b]	Not provided	[11]
MAS with aboBoNT-A	4.12 (0.942)	2.7 (1); 7.1 (1.2)	Mean and calculated SD, based on results from selected articles
MAS with rehabilitation	4.59 (0.786)	3.4 (0.8); 6.6 (1.3)	Mean and calculated SD, based on results from selected articles

All costs extracted from the literature were updated to the year 2022.
aboBoNT-A, abobotulinumtoxinA; MAS, Modified Ashworth Scale; max., maximum; min., minimum; NA, Not Appliccable; NP, Not Provided; Pr, probability; QALY, quality-adjust life-year; SD, standard deviation; Soc, standard of care/best supportive care.
[a] Mean calculated. A 10% coefficient of variation was used as SD.
[b] SD is the mean of SD of 2 years.

Specifically, the cost per QALYs gained was lower than €30,000 with a probability higher than 0.9. Using the societal costs (Fig. S2-B) as the cost's measurement method, the results were almost identical.

Assuming uncertainty, observations were also plotted to understand the possible range of QALYs gained for each level of cost increase. Fig. S2 also represents results under uncertainty using either the direct costs (A) or the societal costs method (B). For both perspectives, direct costs or societal costs, half of the observations in the uncertainty plot were found in the upper-right side of the graph, indicating incremental costs and incremental QALYs for about half of the patients taking aboBoNT-A. In addition, for the majority of the patients, the cost increase would remain below €20,000, for all possible values of the incremental QALYs. As an example, for a cost increase of €5000 the amount of QALYs gained varied between 0 and 0.4.

The lowest costs scenario

The lowest costs scenario, using the direct costs, assumed mean direct costs per patient per year of €594 for aboBoNT-A plus physiotherapy and €408 for SoC treatment (physiotherapy alone), and mean societal costs per patient per year of €1251.56 and €833.25 for aboBoNT-A and SoC treatment, respectively. Accounting for direct costs or societal costs, the results showed certainty of aboBoNT-A plus physiotherapy being cost-effective, independently of the method used. Acceptability curves are omitted because, for all observations, the cost per QALY gained was lower than €1000. Fig. S3 in the supplementary material demonstrates the above as well as showing that, for most observations, the result would be an incremental cost for the QALY gain.

The highest costs scenario

In accordance with this scenario, direct costs per patient per year were estimated at €28,642.38 for aboBoNT-A plus physiotherapy and €34,430.45 for SoC treatment. Similar costs were observed when considering the societal perspective, specifically €28,861.44 and €34,470.96, respectively, for aboBoNT-A plus physiotherapy and SoC treatment.

Acceptability curves were generated for the highest cost' scenario for each of the years of the time horizon considered (Fig. S4-up in the supplementary material), as well as for the mean of the 10 years.

Using direct costs as the costs measurement method (Fig. S4-A), the results showed that aboBoNT-A plus physiotherapy treatment, according to the simulation analysis, had a high likelihood of being within the cost-effectiveness threshold, and could therefore be considered to be cost-effective in this scenario in which the highest costs were presumed. Specifically, the cost per QALYs gained was with certainty lower than €40,000, and the probability of the cost per QALY gained for aboBoNT-A plus physiotherapy of being less than €30,000 is above 0.8 QALYs. Results were very similar when the societal perspective was assumed (Fig. S4-B). It is noteworthy that, based on the scenario of highest costs presumed, the cost per QALY gained with aboBoNT-A would be over €10,000 for all individuals.

Assuming uncertainty, observations were also plotted to understand the possible range of QALYs gained for each level of cost increase; Fig. S4

Table 4
Mean costs and effectiveness results, per patient, and year[a].

Scenario: mean costs	Direct costs, €	Societal costs, €	QALYs	MAS[b]
Mean aboBoNT-A	10,254.61	11,025.88	0.733	4.120
Mean SoC	13,530.80	13,606.88	0.523	4.593
Incremental	−3276.19	−2580.99	0.210	−0.473
ICER (direct costs perspective)			*−15,600.904*	*6926.40*
ICER (societal costs perspective)			*−12,290.428*	*5456.64*
Scenario: lowest costs				
Mean aboBoNT-A	526.53	1111.74	0.735	4.120
Mean SoC	363.56	740.60	0.523	4.593
Incremental	162.97	371.14	0.212	−0.473
ICER (direct costs)			*768.73*	*−344.54*
ICER (societal costs)			*1750.66*	*−784.65*
Scenario: highest costs				
Mean aboBoNT-A	25,346.17	25,428.6	0.736	4.12
Mean SoC	30,624.88	30,644.38	0.526	4.59
Incremental	−5278.71	−5215.78	0.209	−0.473
ICER (direct costs)			*−25,256.98*	*11,160.06*
ICER (societal costs)			*−24,867.79*	*11,027.02*

aboBoNT-A, abobotulinumtoxinA; ICER, incremental cost-effectiveness ratio; MAS, Modified Ashworth Scale; QALY, quality-adjusted life-year; SoC, standard of care/best supportive care; SD, standard deviation.

[a] Results from simulation model for the different scenarios for a time horizon of 10 years and a 5% discount rate, and normal distribution for costs and effectiveness measures assumed. Because of the use of random distributions results these means (for costs and QALYs) are not stable, and change every time a parameter is modified. However, the mean and SD of the distribution are given and, thus, remain stable.

[b] There is no threshold to interpret ICER using MAS for decision-making, but one could interpret a positive ICER using MAS as the cost decrease for a reduction of one point in the MAS score.

also represents results under uncertainty using either the direct costs or the societal costs method. For most patients, the treatment incremental costs per QALY gain places them in the lower-right quadrant, indicating that the treatment is producing savings to the system compared with the SoC treatment. Additionally, the cost increase would remain below €20,000 for all patients for all possible values of the incremental QALYs. Results were similar, independent of the perspective selected.

Discussion

The literature review helped, first, to identify the effect of treating PSS identified various efficacy measures of relevance, demonstrating how these could be used for measuring improvements for these patients (for example, in motor function).[27] Secondly, it provided the necessary information to conduct a cost-effectiveness analysis, based on results from RCTs and studies with real world data of adult patients being treated for PSS with aboBoNT-A. Despite the heterogeneity of recommended doses and starting date of the treatment, the literature shows common patterns, with most patients being treated with 500 or 1000 Units of aboBoNT-A, a periodicity of 4 weeks between study visits, and the eligibility of participants into a study being at least 6 months after the stroke,[9] although this could sometimes be before week 12 since the stroke episode.[10]

A published review of the safety and efficacy of high doses of aboBoNT-A for this indication[28] concluded that there are no data to support the injection of high doses (1500 to 2000 Units) in clinical practice, except for selected patients. However, none of the papers reviewed in the current analysis included a cost-effectiveness analysis of aboBoNT-A to support such a conclusion.

Current data support that in the treatment of PSS, aboBoNT-A is associated with a high and greater number of QALYs than rehabilitation alone.[11] Although criticism has been leveled at QALYs suggesting that they do not capture all the value of health for individuals, thereby bringing into question their use in evaluating the effectiveness of new health technologies,[29] QALYS remain the preferred QoL measure used in economic evaluation studies for health technology assessment agencies and the National Institute for Health and Care Excellence.

To date, cost-effectiveness of treatments for this population are based on observational studies and with a small number of patients and high heterogeneity in the treatment recommendations, similar to findings in a recent systematic review.[32] The main contribution of this study to the available literature is that the systematic review conducted combined data from all completed relevant studies and synthetized it to develop a probabilistic model.

The search strategy for the presented literature review captured publications from a variety of countries (the list includes Australia, Austria, Belgium, Czech Republic France, Germany, Hong Kong, Hungary, Italy, Malaysia, the Netherlands, the Philippines, Poland, Russia, Singapore, Slovakia, Spain, Switzerland, Thailand, Turkey, the United Kingdom and the United States) and, thus, various healthcare systems were represented in our analyses; the results can therefore be used to evaluate the effectiveness of aboBoNT-A in adults with PSS in different countries or in a set of countries depending on the aim of the research. Note that this could also serve the purpose of sensitivity analyses, in which the researcher can filter the parameters of the model and compare how results vary depending on the selected outcomes because mean values will change depending on the parameter selection.

The costs used in this analysis were the result of a synthesis of costs (mean and standard errors, when provided) extracted from a set of selected papers by their relevance and quality of the data. Different methodologies were detected in the literature for measurement of costs of treating patients with PSS with aboBoNT-A. According to a simple budget-impact analysis,[29] for example, prescribing rehabilitation and aboBoNT-A costs the Italian national health service €5.39 million more than rehabilitation treatment alone, over a 2-year period. Another budget-impact analysis study[24] conducted in the UK estimated a total mean cost for aboBoNT-A of £19,800 per patient per year; this study included not only medication costs (of approximately £1500 per patient and year), but also the associated costs of other medical (physiotherapy treatment and other concomitant medications) and nonmedical resources used. The study concluded that there will be cost savings compared with best supportive care without aboBoNT-A of £4029 per patient per year (or £6.283 million in total over a 5-year period). The study by Shackley et al.[25] included medication and other healthcare and medical costs, concluding that the total mean cost per participant treated with aboBoNT-A plus an additional therapy would be approximately €2000 (mostly owing to other healthcare and social services costs rather than medication costs), with a small difference (cost increase) compared with the comparator cost (therapy alone) of €374 per patient and year. The most complete study in terms of the resources used that was considered in our review is the paper of Lazzaro et al[11] This paper considered not just direct costs (medication and other medical and healthcare resources) but also incorporated out-of-pocket expenses, and loss of productivity and informal care costs. The authors estimated that the total mean cost of providing aboBoNT-A treatment, besides physiotherapy, would be over €20,000, and the cost increase per patient per year compared with usual care would be greater than €11,000. A larger proportion of the costs was due to out-of-pocket expenses, and a nonnegligible part of them was owing to the value of loss of productivity and informal care. These results illustrate the high heterogeneity in medication costs of aboBoNT-A among countries, even though the time horizon was not that different across studies. One important observation was that when resources other than medication costs are used, irrespective of whether these are direct or indirect, the costs of treating patients with aboBoNT-A increases significantly. Excluding these costs would, thus, result in an underestimation of the costs of treating patients with PSS with aboBoNT-A.

The heterogeneity found on treatment starting date recommendations might have an influence on costs estimates. The more recent the study, the earlier the starting times of treatment of PSS with aboBoNT-A. It is possible that an earlier start of treatment with aboBoNT-A might have positive effects for patients in terms of better outcomes.

Our proposed analysis considered all observed costs, standardized them (updating costs to 2022 using average exchange rates for the year), and synthetize them according to three different scenarios: the mean cost, the lowest cost, and the highest cost of the treatment. The comparison of the different scenarios is presented as a sensitivity analysis. Other scenarios could also be tested to complement the sensitivity analysis. One could filter by starting time of treatment, to compare how the analysis would vary when the model considers only studies where patients received early treatment after the stroke, or alternatively, when late treatment applies. Another possibility would be to filter by doses and periodicity of the treatment recommended.

Similarly, literature measuring the effectiveness of aboBoNT-A shows heterogeneity in the cost-effectiveness measures utilized. The MAS appeared to be one of the most utilized scales for the measurement of muscular tone change and impairment.[8,9,16–19] However, there is high heterogeneity in the results observed in different studies. Furthermore, some studies used MAS[17] as a secondary efficacy measure rather than as a primary outcome measure. EQ-5D is another instrument commonly used to measure QoL in patients treated with aboBoNT-A[7,15,17,18,25]; this instrument is a generic QoL instrument generally well-accepted for its use in cost-effectiveness analysis. For aboBoNT-A, however, EQ-5D was sometimes used a secondary effectiveness measure, probably because the main objective and primary outcome of the paper was to assess treatment safety, and the results of the EQ-5D assessment were not presented in the paper.[7,18] The QALY (an outcome measure that expresses the duration and QoL) is the main pillar of cost-effectiveness analyses.[30] The QALY combines changes in morbidity (quality) and mortality (amount) in a single indicator.[31] One study investigated the QALYs of rehabilitation and aboBoNT-A versus rehabilitation in Italy over a 2-year period, and combined this with cost estimates to perform a cost utility analysis.[11] This study demonstrated that combined rehabilitation and aboBoNT-A outperformed rehabilitation therapy in terms of the estimated amount of QALYs gained (1.620 vs 1.150), and it was the study we used as reference for our QALYs parameters in our simulation model. For the MAS measure, the mean of all studies was used.

The cost-effectiveness results in the aboBoNT-A treatment had a very high probability of being cost-effective in two of the three scenarios, when considering uncertainty in costs. The cost per QALY gained in the mean scenario ranged between €20,000 and €30,000 with a probability of 0.8–0.9. This differed from the findings by Lazzaro et al.,[11] which demonstrated higher costs associated with aboBoNT-A plus physiotherapy than physiotherapy alone.

The present study has several strengths and limitations. The main strength of the simulation tool is that it uses information from a systematic literature review and it can therefore be readily updated with additional parameters if new relevant research is published. Limitations included heterogeneity in the methodology and reporting of the included papers, include the treatment recommendations of doses and starting date of treatment, the time horizon studied, the country of analysis, and the measures or methods used to quantify outcomes. Researchers who might want to use the results of our study should take account of these issues.

The fact that this is a simulation exercise based on parameters obtained from literature is a limitation of the study. However, some papers did not provide all the required information, such as standard deviations of means. In these cases, a 10% coefficient of variation was used instead, similar to a previous study.[11] Not all the papers accounted for the same type of costs and some studied different years. The analysis had to find a way to standardize all the information; this could have some minor implications in the final results. In terms of model assumptions, normality in the distributions for costs and effectiveness measures was assumed. Although other distributions, such as beta or gamma distributions, were tested, normality for this exercise simplified calculations and interpretations of the results.

The simulation model presented allows results to be estimated based on different perspectives, accounting for direct costs versus societal costs, and presents results in different scenarios depending on the magnitude of costs and their relationship with the QALYs gained. The results show a high probability that aboBoNT-A could be cost-effective even when it is evaluated at the most conservative scenario of highest costs. Sensitivity analyses confirm the robustness of this result in all the three scenarios. In the most conservative scenario, in which the highest costs are presumed, the probability of aboBoNT-A being cost-effective will be lower than in the lowest cost and mean scenarios. However, even in this case, there is certainty of a cost per QALY gained below €50,000, and the sensitivity analysis showed how, compared with the SoC treatment, aboBoNT-A would be within the most cost-effective option for the majority of patients, and even a dominant choice for a large proportion of them.

Authorship declaration

All authors have substantially contributed to this work either through the conception and design of the work, or through the collection, analysis, and interpretation of the data.

María Fernández is responsible for the conception of the work. María Errea Rodríguez, Juan del Llano, and Roberto Nuño-Solinís are responsible of the design of the analysis, choice of methods, analysis and interpretation of the data.

All the authors have contributed to the article writing, reviewed and approved the final version for publication.

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Conflicts of interest

María Errea Rodríguez, independent researcher, declares she has received funding from Ipsen for developing the CEA modeling, interpretation of the results and contribution in writing the article. Juan del Llano and Roberto Nuño-Solinís, declare they have received funding for their work on this project from Ipsen via the Gaspar Casal Foundation. María Fernandez declares that she worked at Ipsen while the study was conducted but her contribution has not influenced the study results.

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Appendix A. Supplementary data

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