Canadian Journal of Health Technologies

CADTH

March 2021 Volume 1 Issue 3

CADTH Health Technology Review

Onabotulinum Toxin A (Botox) for Spasticity Associated With Multiple Sclerosis

Rapid Review

CADTH

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ISSN: 2563-6596

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

GRADE	Grading of Recommendations Assessment, Development and Evaluation
MS	multiple sclerosis
SR	systematic review

Key Messages

- Evidence-based clinical practice guidelines recommend the use of *botulinum* toxin (which includes onabotulinum toxin A [Botox]) to treat spasticity caused by multiple sclerosis.
- There is a lack of recent evidence regarding the clinical and cost-effectiveness of Botox as a treatment for spasticity caused by multiple sclerosis; thus, there is a need for well-designed studies on this topic.

Context and Policy Issues

Multiple sclerosis (MS) is a progressive neurodegenerative and autoimmune disease associated with the immune-mediated destruction of myelin (the protective layer of nerves) in the central nervous system.[1-3] The prevalence of MS in Canada (based on survey data from 2010 to 2011) was 290 per 100,000.[2] Multiple sclerosis is the leading cause of disability in young adults; for instance, self-reported data from a survey distributed to Canadian household residents aged 15 or older (i.e., individuals not living in a long-term care institution) reported that 82% were diagnosed between the ages of 20 to 49 (95% confidence interval, 75.9 to 86.5).[1,2] Of note, pediatric MS (onset before 18 years of age) is considered a rare disease; data from 1965 to 2018 of individuals aged 19 and younger reported an overall incidence of 0.05 to 2.85 per 100,000 and an overall prevalence of 0.7 to 26.9 per 100,000.[4] Spasticity affects 40% to 80% of patients with MS and may present differently; however, muscle pain, spasms, weakness, stiffness, and loss of active function and voluntary movement are common manifestations.[5-7] Additionally, spasticity may result in poor body image and low self-esteem potentially causing social isolation.[7] Spasticity impacts a patient's ability and independence to complete daily activities through worsening fatigue and impairing ambulation; thus, reducing one's quality of life and increasing the burden on caregivers and the need for health care resources and utilization.[1,6]

Spasticity management aims to reduce muscle tone to a degree that facilitates active function without eliminating all muscle tone.[1] Pharmacological interventions for spasticity in patients with MS include baclofen (oral or intrathecal administration), tizanidine, dantrolene, and benzodiazepines (e.g., clonazepam and diazepam).[1,3,6] Non-pharmacological interventions include physiotherapy, transcutaneous electrical nerve stimulation, transcranial magnetic stimulation, electromagnetic therapy, and whole body vibration.[1,3]

Botulinum neurotoxins are produced by the *Clostridium botulinum* bacteria and there are various subtypes (A to G) that may have different formulations.[8] Botulinum toxin type A products may be used to treat focal spasticity in patients with MS.[1] To treat spasticity, botulinum toxin type A is administered through intramuscular injections temporarily causing local muscle paresis (i.e., partial paralysis) and may also elicit an analgesic effect lasting for 3 to 4 months.[9] The pharmacological activity of botulinum toxin type A is the inhibition of the pre-synaptic transmission of acetylcholine at the neuromuscular junction.[8,9] There are 3 licensed formulations of botulinum toxin type A available for multiple indications, not exclusive to spasticity, on the North American market: onabotulinum toxin A (Botox), abobotulinum toxin A (Dysport), and incobotulinum toxin A (Xeomin).[9-11] These formulations have different manufacturing processes and vary in pharmacological activity and intracellular targets; therefore, they are not interchangeable.[8,10] This report focuses on onabotulinum toxin A, which will be referred to herein as Botox — its brand name. In Canada, Botox was first

approved by Health Canada in 1999 for the treatment of spasticity in pediatric patients with cerebral palsy.[12]

Treatments to alleviate spasticity in MS have not been well-studied[3]; further, there are limited data on the effectiveness of Botox to treat spasticity and the majority of published data focuses on spasticity due to stroke.[5] Accordingly, there is uncertainty regarding the clinical effectiveness and safety of Botox as a treatment for MS-related spasticity. The purpose of this rapid review is to evaluate recent evidence regarding the clinical effectiveness (including safety), cost-effectiveness, and evidence-based guidelines regarding the use of Botox for the treatment of spasticity associated with MS.

Research Questions

1. What is the clinical effectiveness of onabotulinum toxin A (Botox) in the treatment of spasticity associated with multiple sclerosis?
2. What is the cost-effectiveness of onabotulinum toxin A (Botox) in the treatment of spasticity associated with multiple sclerosis?
3. What are the evidence-based guidelines for the use of onabotulinum toxin A (Botox) in a treatment regimen for spasticity associated with multiple sclerosis?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were onabotulinum toxin A /Botox and multiple sclerosis and/or spasticity. No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents published between January 1, 2016 and January 28, 2021.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2016. Systematic reviews in which

all relevant studies were captured in other more recent or more comprehensive systematic reviews (SRs) were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[13] for SRs and the *Appraisal of Guidelines for Research & Evaluation II* (AGREE) instrument[14] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 515 citations were identified in the literature search. Following the screening of titles and abstracts, 478 citations were excluded and 37 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 35 publications were excluded for various reasons and 5 publications met the inclusion criteria and were included in this report. These comprised 3 SRs and 2 evidence-based guidelines. No relevant economic evaluations were identified. Appendix 1 presents the PRISMA[15] flow chart of the study selection. Additional references of potential interest are provided in Appendix 5.

Table 1: Selection Criteria

Criteria	Description
Population	Patients with spasticity related to MS
Intervention	Injections of onabotulinum toxin A (i.e., Botox)
Comparator	Q1 and Q2: No treatment, standard care, physical therapy, baclofen (Ozobax), tizanidine (Zanaflex), cyclobenzaprine (e.g., Flexeril), diazepam (Valium), surgery Q3: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., symptoms of spasticity, muscle tightness, quality of life, harms or safety, range of motion) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained, incremental cost-effectiveness ratio) Q3: Recommendations regarding the dose and use of Botox for spasticity related to MS
Study designs	HTAs, SRs, RCTs, non-randomized studies, economic evaluations, and evidence-based guidelines

HTA = health technology assessment; MS = multiple sclerosis; Q = question; RCT = randomized controlled trial; SR = systematic review.

Summary of Study Characteristics

All 3 included SRs had broader inclusion criteria than this review. In all 3 of the SRs, none of the included studies evaluated the comparison of interest for this report (i.e., the clinical effectiveness of Botox for the treatment of MS-related spasticity). Specifically, the SR published in 2018[3] evaluated the effectiveness of botulinum toxin therapy (i.e., the SR may have included various formulations such as Botox) in patients with spasticity due to MS (age criteria were not specified) and included eligible randomized controlled trials (RCTs) published before October 30, 2017.[3] The SR by Baker and Pereira (2016)[7] assessed botulinum toxin type A therapy (i.e., not specific to the Botox formulation) in adult patients with muscle spasticity of any etiology and included eligible RCTs published between 1989 to January 2015.[7] The SR by Phadke et al. (2016)[9] assessed each botulinum toxin type A formulation separately in adult patients with muscle spasticity of various etiologies such as MS, stroke, cerebral palsy, and spinal cord injury and included any study published between 1990 to 2013 (except for SRs).[9] This SR also consisted of a Health Canada dataset, which included information on adverse events from 2009 to 2013 related to Botox treatment for spasticity of multiple etiologies that were not specified.[9] Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Two evidence-based guidelines were included in this review.[6,10] The guideline published in 2020 was developed by an Italian multidisciplinary team of experts in guideline development and MS, patient representatives, and neurophysiologists operating under the Italian Neurological Society, the Associazione Italiana Sclerosi Multipla, and the European Charcot Foundation. A systematic literature search was conducted for each of the 11 pre-specified questions in MEDLINE following PRISMA guidelines. Controlled studies (randomized) with at least 50% of patients with MS that reported spasticity outcome(s) — published in English from January 1, 2007 to August 16, 2017 — were included. Recommendations were developed when there was a consensus of at least 80% for both the existence of efficacy evidence and the rating of the strength of the recommendation. The quality of evidence informing the recommendations was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, with ratings of very low, low, high, or very high.[6] The strength of the recommendations was rated at 3 different levels of no recommendation, weak, and strong but the use of a rating guide was not clearly specified.[6]

The guideline published in 2017 was developed at the University of Wisconsin. The members of the guideline development group were not specified; however, the 2 guideline authors (e.g., names and degrees), who were pharmacists, were identified. The guideline was developed based on literature retrieved through a search of PubMed; however, further search details were not provided (e.g., eligibility criteria, date range, and keywords). Expert opinion and clinical experience were also considered in the guideline development process. Recommendations were developed based on consensus of the development group and all recommendations were reviewed and approved by other stakeholders or committees. The quality of evidence informing the recommendations was rated using GRADE (i.e., as very low, low, moderate, or high).[10] The strength of the recommendations was rated, also using GRADE, as strong or weak/conditional.[10]

Country of Origin

The country where the 2020 guidelines are meant to apply was not directly specified; however, the guideline development group consisted of Italian experts and patient representatives.[6] The

2017 evidence-based guideline was intended for use in the US; namely, within hospitals and clinics affiliated with the University of Wisconsin, which will be collectively referred to herein as University of Wisconsin Health.[10]

Patient Population

The intended users and target population of the 2020 evidence-based guideline were not directly specified; however, the guideline would be useful for clinicians who treat MS spasticity.[6] The 2017 evidence-based guideline was intended for pharmacists, physicians, advanced practice providers, nurses, technical support, and "medication prior authorization (p.4),"[10] and the target population consisted of all adult and pediatric patients treated within University of Wisconsin Health with a disorder for which botulinum toxin therapy may be appropriate.[10]

Interventions and Comparators

Both evidence-based guidelines considered the use of botulinum toxin with no specification of which botulinum toxin sub-type (e.g., A or B) or formulation (e.g., Botox, Dysport, and Xeomin).[6,10] In addition to botulinum toxin, the 2020 evidence-based guideline considered baclofen (oral and intrathecal administration), tizanidine, gabapentin or pregabalin, diazepam or clonazepam, aminopyridines, cannabinoids, peripheral nerve stimulation (e.g., transcutaneous electrical nerve stimulation), magnetic stimulation, and transcranial direct current stimulation for the treatment of spasticity in patients with MS.[6] The 2017 evidence-based guideline considered botulinum toxin injections as part of a documented strengthening and rehabilitation program.[10]

Outcomes

The 2020 evidence-based guideline considered spasticity as measured by the following scales: Tardieu Scale, Ashworth Scale, Modified Ashworth Scale, spasticity visual analogue scale, spasticity Numeric Rating Scale, and MS Spasticity Scale (MSSS-88).[6] The 2017 guideline considered the following major outcomes: sustained relief or reversal of disorders, prevention or delay of surgical or other invasive procedures, and reduced effect of botulinum toxin as a result of antibody formation following prolonged use.[10] Additionally, the 2017 guideline considered the acquisition cost (in US dollars) of a Botox 100-unit vial (i.e., potential financial barriers).[10]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

All of the included SRs had a broader scope than this report because they included mixed interventions, mixed populations, or both. The SR published in 2018 searched for and included studies regarding "botulinum toxins" but did not specify which subtypes and formulations were represented.[3] The SR by Baker and Pereira (2016)[7] included adult patients with spasticity of any etiology with the intention of conducting a comprehensive and representative review of botulinum toxin type A as a therapy collectively.[7] The SR by Phadke et al. (2016)[9] also included a mixed population with spasticity of different etiologies.[9] Combining data of various botulinum toxin subtypes and formulations and outcomes of patients with spasticity of various etiologies limits the generalizability of these findings as these have different

pharmacological activity and underlying pathology, respectively. Therefore, these studies did not directly assess the clinical effectiveness and safety of Botox in patients with spasticity related to MS. However, all of the included SRs[3,7,9] had searched multiple databases to retrieve literature. Nevertheless, common limitations included the lack of reporting of a list of excluded studies with the justifications and sources of funding of included studies. Further, it was not specified if reference lists of included studies were reviewed, trial or study registries were searched, and experts were consulted. Moreover, 2 SRs[3,7] only included RCTs; however, an explanation for this inclusion criterion was not provided.

Specific strengths and limitations of the 2018 SR[3] included reporting of the characteristics of included studies (as supplementary material); however, details regarding the study population, intervention and comparator doses, and botulinum toxin type and formulation used were missing. The authors implemented an extensive search date range by searching published literature up until October 30, 2017. Further, 2 authors performed study selection and data extraction, which reduces reviewer bias. However, the inclusion criteria were unclear, particularly regarding the interventions. Included interventions may be deduced from the key terms listed, which were not listed comprehensively, and the results. There may be a risk of reporting bias due to the lack of a specified intervention list; additionally, the authors acknowledged in the discussion that other interventions were considered but not included because of the lack of eligible RCTs. Moreover, the risk of bias and study quality of the included studies were not assessed and considered.

Specific strengths and limitations of the SR by Baker and Pereira (2016)[7] included a lack of reporting of the baseline characteristics of included studies; namely, the spasticity etiologies and botulinum toxin type A formulations used were not provided. The authors used a search date range of 1989 up to January 2015. The authors justified the start year of 1989 as this was when botulinum toxin was approved for clinical use; however, the botulinum toxin product and country this approval refers to were not specified. Regulatory approval is variable for different botulinum toxin products and varies across countries. Nevertheless, the search strategy was transparent as the MeSH terms were detailed in the Appendix together with the number of associated results. Further, it was not specified if multiple authors performed study selection and data extraction independently in duplicate, which poses a risk for reviewer bias. However, it was noted that the quality of the evidence was rated by 1 reviewer using the GRADE approach. Moreover, vague comments pertaining to the risk of bias of included studies were reported in the Appendix (e.g., "problems with randomization and blinding in three out of four studies" and "large sample but wide confidence interval [p.4; Appendix IV])."[7] The type of bias related to the comments, the number of assessors, and if a validated risk of bias tool was used were either not reported or unclear.

Specific strengths and limitations of the SR by Phadke et al. (2016)[9] included reporting of the keywords and MeSH terms used in the search strategy, and the use of 2 authors to perform the study selection and data extraction. However, inclusion criteria regarding eligible patient populations, interventions, and study designs were unclear. Regarding patient populations, the eligibility alluded to "adult subjects" and noted "the etiology of spasticity included in this review was broad and included stroke, MS, spinal cord injury, and cerebral palsy (p.3)."[9] In the results, etiologies beyond these were included such as ataxia and amyotrophic lateral sclerosis; therefore, which spasticity etiologies were or were not eligible was unclear. Regarding interventions, inclusion criteria specified "botulinum toxin type-A;" thus, which botulinum toxin type A formulations were or were not eligible was also unclear. With respect to eligible study designs, it was only specified that "human studies" were eligible and SRs were not; however, further details regarding eligible study designs were not provided and

it was unclear if all study designs other than SRs were eligible. Further, the risk of bias of included studies was not assessed and considered but study quality of included studies was graded using the Oxford Centre for Evidence-Based Medicine (2011) levels. Lastly, all authors reported disclosures: 3 had no financial disclosures, whereas 3 other authors including the first author reported consultant, honoraria, speaker's, and grant fees from Allergan Inc. (manufacturer of Botox) and Merz Pharma (manufacturer of Xeomin). Therefore, these declarations must be considered when evaluating the study conclusions.

Guidelines

Two guidelines were included[6,10] regarding the use of botulinum toxin to treat MS spasticity. Neither guideline specified botulinum toxin subtypes or formulations in the recommendations; therefore, the guidelines were unclear with limited generalizability for use in Canada. In addition to the different manufacturing processes and pharmacological activity of different botulinum toxin products, formularies differ in the accessibility of botulinum toxin products. Namely, the 2017 guideline noted that 4 botulinum toxin products are available in the US but Botox was the only available botulinum toxin type A product at University of Wisconsin Health.[8,10] The different botulinum toxin products are not considered interchangeable and the products that informed the recommendation were not clearly specified; therefore, the links between the supporting evidence and recommendation were unclear.[8,10] Both guidelines were informed by evidence retrieved from systematic database (MEDLINE and PubMed) searches and used the GRADE approach to assess the quality of evidence but provided limited information regarding facilitators or barriers and implementation.

The 2020 guideline[6] was developed by an Italian multidisciplinary group of MS experts with relevant representation (e.g., patient representatives, neurophysiologists, and guideline development experts) and clearly reported the systematic methods used to search for evidence and how the recommendations were formulated. Namely, questions detailing the patients, intervention, comparator, and outcome of interest were devised for each intervention of interest (e.g., "In MS patients with spasticity, is botulinum toxin superior to placebo or other interventions in relieving spasticity symptoms and/or signs (p.2)"[6]) and a MEDLINE search was performed for each question with the inclusion criteria and date range specified, however, keywords searched were not specified. Moreover, the supporting evidence was reported in detail with the health benefits, side effects, and risks considered. Additionally, it was unclear if validated or standard methodology was used to rate the strength of the recommendations. Further, the botulinum toxin recommendation was stated to be based on moderate-quality evidence; however, the methodology noted that quality of evidence was rated from very low, low, high, to very high. Therefore, the rating levels for the quality of evidence were unclear. The target users of the guideline were not specified; given that the guideline was developed by an Italian group, specifying if these guidelines are intended for Italian, European, or global users is important to determine generalizability. Lastly, it was unclear if the guideline had been externally reviewed before publication; nevertheless, these recommendations were published in a peer-reviewed journal with the authors declaring no financial or other conflicts of interest.

The 2017 guideline[10] was intended for clinicians such as pharmacists, nurses, and physicians to treat patients at University of Wisconsin Health. It was unclear if systematic methods were used to search for evidence as the only search detail provided was the use of PubMed; eligibility criteria, search dates, and keywords searched were not reported. Therefore, the reproducibility of the search was limited. The methodology used to formulate the recommendations was not clearly described, and the link between the recommendations and supporting evidence was not clear as the supporting evidence was not described (only cited).

Additionally, it was noted that expert opinion and clinical experience were also considered but it was unclear if this information was obtained in an objective manner, especially as the membership of the development group, besides 2 guideline authors, and their potential competing interests or conflict of interests were not reported. Accordingly, it was unclear if the development group was representative of all relevant professional groups; however, the review individuals were reported and consisted of various clinicians (medical doctors practicing in various specialties such as neurology, orthopedics/rehabilitation, anesthesiology, and others; pharmacists; and physiotherapists). The review committee had reasonable representation; however, patient representation could have provided an additional relevant perspective. There were other indications that evidence-based guideline development methods were used; in particular, authors used GRADE to rate the quality of the evidence and the strength of the recommendations, and the authors considered cost-effectiveness (e.g., the high cost of botulinum toxin products available at the University of Wisconsin Health formulary were noted), patient preferences, and the balance of benefits or harms in their recommendation development. However, details on these considerations were not provided (only briefly mentioned in a schematic in the Appendix). Moreover, it was noted that pharmacists, nursing staff, and prescribers would be educated about the guideline through electronic distribution, which facilitates the implementation of the guideline. Lastly, it was unclear if the guideline had been externally reviewed before its publication.

Summary of Findings

Appendix 4 presents the main study findings and authors' conclusions.

Clinical Effectiveness of Botox for Spasticity Related to MS

No relevant evidence was identified regarding the clinical effectiveness of Botox for the treatment of spasticity related to MS; therefore, no summary regarding the clinical effectiveness can be provided.

Cost-Effectiveness of Botox for Spasticity Related to MS

No relevant evidence was identified regarding the cost-effectiveness of Botox for the treatment of spasticity related to MS; therefore, no summary regarding the cost-effectiveness can be provided.

Guidelines

The 2020 evidence-based guideline recommends the use of botulinum toxin for MS-related spasticity (strong recommendation based on moderate-quality evidence).[6] The 2017 evidence-based guideline recommends the use of botulinum toxin for MS-related spasticity, alongside other etiologies associated with spasticity in the upper and lower limbs (strong recommendation based on high-quality evidence).[10]

Limitations

Overall, this report is limited in the quantity and quality of relevant evidence regarding the clinical and cost-effectiveness and use of Botox as a treatment for MS-related spasticity. The 3 included SRs and 2 evidence-based guidelines consisted of mixed populations of combined spasticity etiologies, mixed interventions of combined botulinum toxin subtypes or formulations, or mixed populations and mixed interventions. No included studies directly assessed the clinical effectiveness of Botox for the treatment of spasticity associated with MS in individuals of any age. The 2020 evidence-based guideline did not specify age criteria

for the intended population and the 2017 guideline is intended for both adult and pediatric patients; however, the inclusion of pediatric patients in the supporting evidence is unclear.

Both included guidelines were developed by groups outside of Canada; accordingly, it is uncertain whether the recommendations are generalizable to Canada. Namely, the 2017[10] guideline is intended for use at the University of Wisconsin and may be specific to the US context. The target users of the 2020 guideline[6] were not specified and, given that the guideline was developed by an Italian group, it was unclear if these were intended for Italian, European, or global users. There are differences in clinical practice between countries and provinces due to clinician-specific practice and resource constraints such as formulary access. Thus, geographical considerations and the clinical practice needs of the intended patient population may have influenced the inclusion of evidence used to develop the 2020 guideline.

Conclusions and Implications for Decision- or Policy-Making

This report comprised 3 SRs,[3,7,9] which collectively contained no relevant primary studies regarding the clinical effectiveness of Botox for the treatment of spasticity associated with MS, and 2 evidence-based guidelines[6,10] regarding the use of botulinum toxin for the treatment of spasticity associated with MS. Both evidence-based guidelines recommend the use of botulinum toxin (with no specification to a type or formulation) to treat MS spasticity.[6,10] Further, no relevant economic evaluations regarding the cost-effectiveness of Botox for the treatment of spasticity associated with MS were identified.

This review was limited by the lack of evidence specific to the use of Botox for the treatment of spasticity associated with MS. The included SRs[3,7,9] combined results across studies that examined different types of spasticity and different botulinum toxin products; however, the pathophysiology of spasticity varies by etiology and different botulinum toxin products have different pharmacotherapeutic effects. Indirect evidence from the 2018 SR[3] suggested the superior efficacy of botulinum toxin (which may have included Botox — included botulinum toxin products were not specified) over placebo, tizanidine, and baclofen and favourable safety (comparable to placebo) in patients with MS-related spasticity. Indirect evidence from the SR by Baker and Pereira (2016)[7] suggested that there was inconclusive evidence related to the effect of botulinum toxin type A therapy on quality of life across various spasticity etiologies including MS. Further, the SR by Phadke et al. (2016)[9] suggested that botulinum toxin type A injections may result in muscle weakness in the injected and non-injected (opposite) limbs as reported in 2 cases of Botox treatment for MS-related spasticity in the lower limb. However, given that all 3 SRs pooled evidence across various types of spasticity and botulinum toxin products, it was not possible to directly evaluate the effect of Botox on spasticity associated with MS. Botox has regulatory approval in Canada[12] for various indications; however, its use in the treatment of MS-related spasticity is considered off-label.[16]

Overall, there is a need for well-designed clinical and cost-effectiveness studies and clinical practice guidelines that are specific to the use of Botox in the treatment of spasticity associated with MS.

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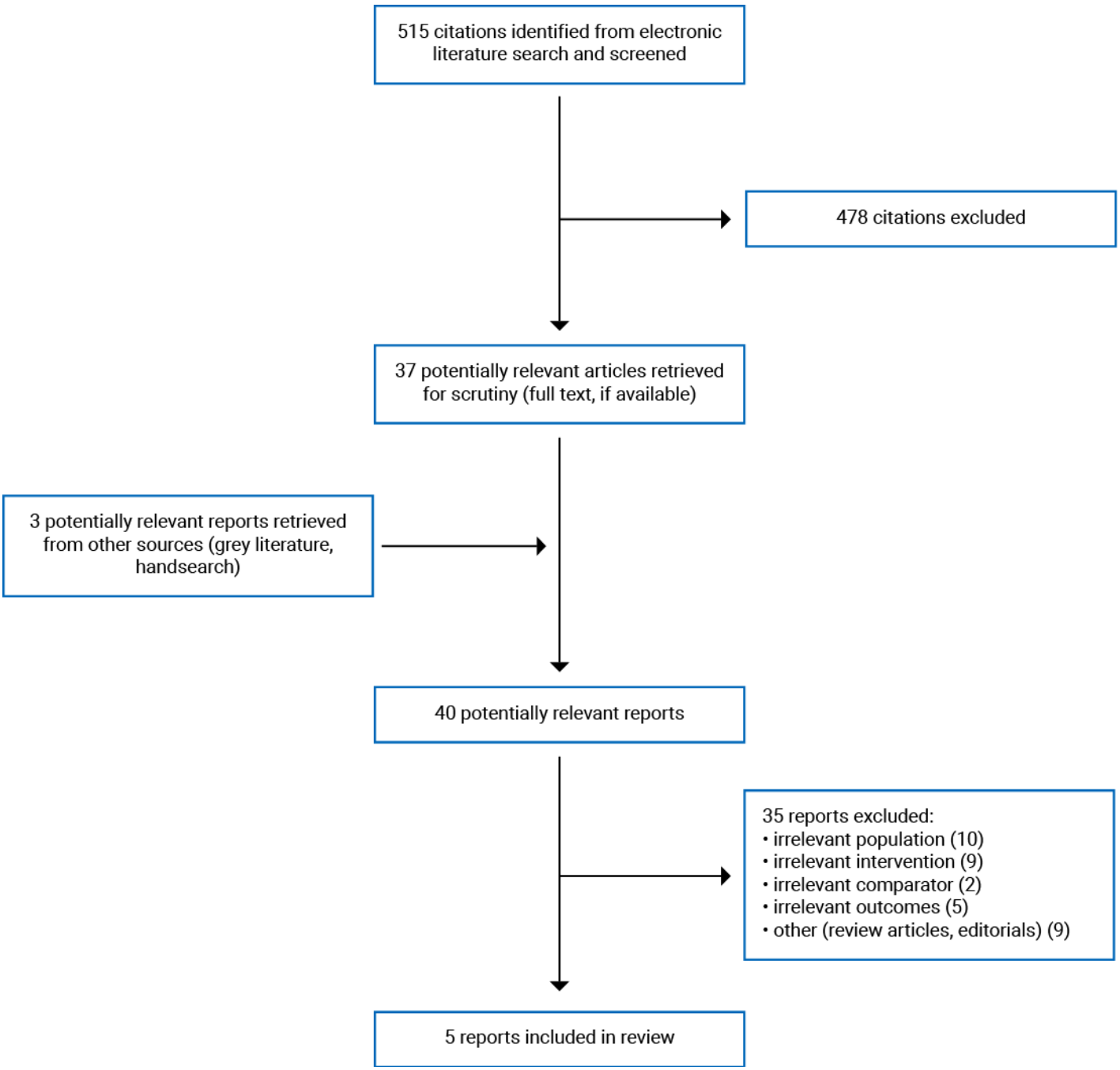
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Fu et al. (2018)[3] **China** **Funding:** Project of Precision Medicine for Neurologic Disorders in Jilin Province	**Study Design:** Systematic review of RCTs **Total Number of Primary Studies Included:** 23 **Number of Relevant Primary Studies:** None	Patients with spasticity caused by MS Age criteria were not specified (e.g., age of eligibility)	**Interventions (based on searched key terms):** Botulinum toxins,[a] cannabinoids, baclofen, tizanidine, dantrolene, and transcutaneous electric nerve stimulation **Comparator (based on the results):** Placebo	**Eligible Clinical Outcomes:** • Spasticity scale scores (Ashworth Scale or Modified Ashworth Scale) as mean change and standard deviation • Number of patients with significant improvement • Severe and mild adverse effects **Follow-up**: NR
Baker and Pereira (2016)[7] **UK** **Funding:** Australian National Health and Medical Research Council (NHMRC) — early career fellowship	**Study Design:** Systematic review of RCTs **Total Number of Primary Studies included:** 25 **Number of Relevant Primary Studies:** None	Adult patients with muscle spasticity of any pathological origin — including patients with MS	**Eligible Intervention:** BoNT-A (single dose) **Relevant Intervention:** BoNT-A (possibly including Botox but this was unclear) **Eligible Comparator:** Placebo (saline injections)	**Eligible Clinical Outcomes:** • Barthel Index for Activities of Daily Living • Action Research Arm Test • Active Range of Movement • Gait analysis, speed, and distance • GAS (with active-based goals) • FIM • FAT • Modified Rankin Scale • Nine-Hole Peg Test • Quality of life (assessed by any validated measure) **Follow-up**: NR

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Phadke et al. (2016)[9] **Canada** **Funding:** NR	**Study Design:** Systematic review of any study design except for systematic reviews **Total Number of Primary Studies:** 29 **Number of Relevant Primary Studies:** None	Adult (> 18 years of age) patients with spasticity of various etiologies including MS, stroke, cerebral palsy, and spinal cord injury	**Interventions:** BoNT-A (including Botox)	**Clinical Outcomes:** • AE type • Number and proportion of patients experiencing an AE • Maximum dose • Location of injection • Guidance technique **Follow up**: NR

AE = adverse event; BoNT-A = botulinum toxin type A; FAT = Frenchay Arm Test; FIM = Functional Independence Measure; GAS = Goal Attainment Scale; MS = multiple sclerosis; NA = not applicable; NR = not reported; RCT = randomized controlled trial.

[a]The botulinum toxin products (type and formulation) that were considered were not reported; the data may include Botox, which is relevant to this report.

Table 3: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Italian consensus on treatment of spasticity in MS (2020)[6]						
Intended users: NR **Target population:** patients with MS-related spasticity	Interventions for MS-related spasticity **Pharmacological:** • BoNT • Baclofen (oral and intrathecal administration) • Cannabinoids • Tizanidine • Gabapentin/ pregabalin • Diazepam/ clonazepam • Aminopyridines **Non-pharmacological:** • Peripheral stimulation (e.g., TENS) • Magnetic stimulation • TDCS	**Clinical Outcomes:** Spasticity assessed by clinicians and patient-reported outcomes	• Systematic literature search was conducted for each of the 11 pre-specified PICO questions in MEDLINE following PRISMA guidelines • Studies from January 1, 2007 to August 16, 2017 were included • Relevant literature published before 2007 was obtained from 2 high-quality SRs • Studies were reviewed for inclusion by 2 independent reviewers	Quality of evidence for each outcome was assessed using the GRADE approach Quality ratings ranged from very low, low, high, to very high. Study design, indirectness, inconsistency, imprecision, and risk of bias were considered	• Summary of findings tables organized evidence for each outcome of each PICO question based on ratings of evidence quality and served the basis for developing recommendations • Recommendations were developed by consensus among patients and experts who read the included studies and reviewed the GRADE assessments • For each of the 11 PICO questions, guideline developers were asked to respond "yes" or "no" when asked if there was evidence for the efficacy of the specific intervention of each question • Agreement was reached when at least 80% of votes represented the same response (yes or no) • For the recommendations, consensus on the strength rating required at least 80% of votes to represent the same response • Recommendations were rated as no, weak, and strong (the methodology and the use of a validated or published tool were not specified) • The 3 guideline development panels (assessment, interventional, and methodological) were involved in the final consensus	NR

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Botulinum Toxin – Adult/Pediatric – Ambulatory Clinical Practice Guideline (2017)[10]						
Intended users: pharmacists, physicians, advanced practice providers, nurses, technical support, and "medication prior authorization (p.4)" **Target population:** adult and pediatric patients treated at UW Health with a disorder for which BoNT may be appropriate	BoNT — in some contexts as a second- or third-line therapy	• Sustained relief or reversal of disorders • Prevention or delay of surgical or other invasive procedures • Reduced effect of BoNT due to antibody formation following prolonged use	• PubMed was searched by the guideline author(s) and working group members to collect evidence • Expert opinion and clinical experience were sought and considered as evidence	GRADE methodology was used to assess the quality of evidence with ratings from very low, low, moderate, to high	• Recommendations were internally developed or adopted from external sources • Consensus among the working group members was required for the development of a recommendation • Working group members discussed the evidence from the literature and expert experience • Strength of recommendations was rated using GRADE (strong vs. weak/ conditional)	All recommend-ations were reviewed and approved by other stakeholders or committees

BoNT = botulinum toxin; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MEDLINE = Medical Literature Analysis and Retrieval System Online; MS = multiple sclerosis; NR = not reported; PICO = population, intervention, comparison, outcome; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SR = systematic review; TDCS = transcranial direct current stimulation; TENS = transcutaneous electrical nerve stimulation; UW = University of Wisconsin; vs. = versus.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[13]

Strengths	Limitations
Fu et al. (2018)[3]	
• Multiple databases were searched (2) and an extensive search date range allowed for a comprehensive search. • Literature search was conducted within 24 months of completing the review. • Two authors performed study selection and data extraction independently and a third investigator settled disagreements. • Authors reported the funding source for the published systematic review.	• No explicit statement was made indicating that the review methods were established before the conduct of the review. • Only some of the keywords used in the search strategy were reported. • Inclusion criteria were unclear particularly regarding the interventions. The included interventions may be deduced from the key terms listed (not a complete list) and results. • Only RCTs were included; however, an explanation was not provided. • It was not specified if reference lists of included studies were reviewed, trial or study registries were searched, and experts were consulted. • Baseline characteristics of included studies were reported in supplementary material; however, details regarding the study population, intervention and comparator doses, and type and formulation of botulinum toxin used were not reported. • Risk of bias and study quality of included studies were not assessed and considered. • Sources of funding of included studies were not reported. • A list of excluded studies with their justifications was not provided.
Baker and Pereira (2016)[7]	
• Multiple databases were searched (5) and search date range was reported. • MeSH terms used in the search strategy were detailed in the Appendix with the number of associated results. • Literature search was conducted within 24 months of completing the review. • Inclusion and exclusion criteria were clearly stated. • One reviewer rated the quality of evidence among the included studies using the GRADE approach. • Authors reported the funding source for the published systematic review.	• No explicit statement was made indicating that the review methods were established before the conduct of the review. • Only RCTs were included; however, an explanation was not provided. • It was not specified if reference lists of included studies were reviewed, trial or study registries were searched, and experts were consulted. • It was not specified how many authors performed study selection and data extraction. • Included studies were not described in detail (i.e., baseline characteristics of included studies were not reported). • Vague comments pertaining to the risk of bias of included studies were reported in the Appendix (e.g., "problems with randomization and blinding in three out of four studies" and "large sample but wide confidence interval (p.4; Appendix IV))".[7] The type of bias related to the comments, the number of assessors, and if a validated risk of bias tool was used were either not reported or unclear. • Sources of funding of included studies were not reported.

Strengths	Limitations
Phadke et al. (2016)[9]	
• Multiple databases were searched (4) and keywords and MeSH terms used in the search strategy were reported. • Authors did not include systematic reviews but reviewed the reference lists of identified systematic reviews to identify relevant articles. • Two authors performed study selection; they had to mutually agree to include or exclude articles. • The diagnoses of included patients and the BoNT-A formulation and maximum dose administered were reported for the included studies. • Authors graded the quality of the included studies with the Oxford Centre for Evidence-Based Medicine (2011) levels.	• No explicit statement was made indicating that the review methods were established before the conduct of the review. • Inclusion criteria were unclear; particularly, for patient populations, interventions, and study designs. • No explanation was made for the selection of eligible study designs. • It was not specified if reference lists of included studies were reviewed, trial or study registries were searched, and experts were consulted. • It was unclear if 2 authors performed data extraction. • A list of excluded studies with their justifications was not provided. • Details of the included studies were not provided such as study design, age of patients, disease duration, all outcomes (not just those relevant to the review), all comparators and interventions with all the doses (range) administered. • Risk of bias of included studies was not assessed and considered. • Sources of funding of included studies were not reported. • One author was a grant recipient from Merz Pharma (manufacturer of Xeomin); 1 reported consultant and honoraria or speaker's fees from Allergan Inc. (manufacturer of Botox) and consultant, honoraria or speaker's fees, and grants from Merz Pharma; and 1 reported consultant and honoraria fees from Allergan Inc. and consultant, honoraria, and grants from Merz Pharma. The remaining authors did not have anything to disclose.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; BoNT-A = botulinum toxin type A; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; MeSH = Medical Subject Headings; RCT = randomized controlled trial.

Table 5: Strengths and Limitations of Guidelines Using AGREE II[14]

Item	Italian consensus on treatment of spasticity in MS, 2020[6]	*Botulinum Toxin – Adult/pediatric – Ambulatory Clinical Practice Guideline* (2017)[10]
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Unclear; the subtypes and formulations of BoNT were not specified
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Unclear
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
4. The guideline development group includes individuals from all relevant professional groups.	Yes; Italian group of experts in guideline development and MS, patient representatives, and neurophysiologists	Unclear; only guideline authors were reported (2 pharmacists, 1 with a MBA); composite members of the "guideline workgroup" were not reported
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Unclear; appendix noted patient preferences were considered but details not provided
6. The target users of the guideline are clearly defined.	Unclear; it was not specified but presumably it would be clinicians who treat patients with MS-related spasticity	Yes
7. Systematic methods were used to search for evidence.	Yes	Unclear; search of PubMed specified but the eligibility criteria, search dates, and keywords were not specified
8. The criteria for selecting the evidence are clearly described.	Unclear; inclusion criteria were reported in a table but few details were noted, particularly for the study design and outcomes, which were stated with the following text: "Comparative study (e.g. randomized, controlled) and Spasticity outcome(s) (p.3; Table 3)"[6]	No
9. The strengths and limitations of the body of evidence are clearly described.	Yes; limitations provided for some supporting evidence	No
10. The methods for formulating the recommendations are clearly described.	Yes	Unclear
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Unclear; appendix noted the balance of benefits or harms were considered but details not provided

Item	Italian consensus on treatment of spasticity in MS, 2020[6]	*Botulinum Toxin – Adult/pediatric – Ambulatory Clinical Practice Guideline* (2017)[10]
12. There is an explicit link between the recommendations and the supporting evidence.	Unclear; supporting evidence was reported and detailed in supplementary files but the actual recommendation was brief and could have incorporated more of the supporting evidence	No
13. The guideline has been externally reviewed by experts before its publication.	Unclear; authors noted the assessment, interventional, and methodological panels were involved in the final consensus but it was unclear if this constituted a review for validation before publication Nevertheless, recommendations were published in a peer-reviewed journal	Unclear; recommendations were reviewed and approved by other stakeholders or committees but it was not clear if these bodies were external
14. A procedure for updating the guideline is provided.	No	No
15. The recommendations are specific and unambiguous.	Unclear; BoNT formulation (and type) was not specified for treatment	Unclear; BoNT formulation (and type) was not specified and dosing was provided for onaBoNT-A (Botox) but the etiology of spasticity it applied to was not specified
16. The different options for management of the condition or health issue are clearly presented.	Yes	No
17. Key recommendations are easily identifiable.	Yes	Yes
18. The guideline describes facilitators and barriers to its application.	No	Yes; financial barriers were noted due to the high cost of BoNT and the appendix noted that cost-effectiveness was considered but details were not provided
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No	Unclear; only standard dosing of onaBoNT-A (Botox) was noted without reference to the relevant spasticity etiologies
20. The potential resource implications of applying the recommendations have been considered.	No	Yes; UW Health acquisition cost was reported for onaBoNT-A (Botox) and rimaBoNT-B
21. The guideline presents monitoring and/or auditing criteria.	No	Yes
22. The views of the funding body have not influenced the content of the guideline.	NA; no funding body reported	NA; no funding body reported

Item	Italian consensus on treatment of spasticity in MS, 2020[6]	*Botulinum Toxin – Adult/pediatric – Ambulatory Clinical Practice Guideline* (2017)[10]
23. Competing interests of guideline development group members have been recorded and addressed.	Yes; the authors declared no financial or other conflicts of interest	No

AGREE II = Appraisal of Guidelines for Research & Evaluation II; BoNT = botulinum toxin; MBA = Master of Business Administration; MS = multiple sclerosis; NA = not applicable; ona-BoNT-A = onabotulinumtoxin A; rima-BoNT-B = rimabotulinumtoxin B; UW = University of Wisconsin.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Italian consensus on treatment of spasticity in MS (2020)[6]	
Question related to recommendation: "In MS patients with spasticity, is botulinum toxin superior to placebo or other interventions in relieving spasticity symptoms and/or signs (p.4)?"[6] **Recommendation:** "There was a consensus to recommend the use of botulinum toxin to treat spasticity in MS (p.4)"[6] **Supporting evidence:** Recommendation was based on clinical and safety evidence from 1 study without study quality assessment and 4 trials that were assessed for study quality using GRADE (2 were randomized single-blind trials and 2 were randomized double-blind, placebo-controlled trials of which 1 had a crossover design). Of note, the botulinum toxin product investigated in the supporting evidence was not clearly reported and may not be specific to Botox. The supporting evidence demonstrated significant reduction (compared to placebo) in spasticity with aboBoNT-A (Dysport) therapy through clinical scales such as the MAS and VAS (outcomes of scales not reported). Further, supporting safety evidence demonstrated that "muscle weakness is the obvious adverse effect of the botulinum toxin treatment. (p.4; Supplementary Appendix 2)."[6] Other adverse effects reported at high doses included nausea, constipation, and fatigue.	The quality of evidence was ranked as moderate and the strength of the recommendation was rated as strong.
Botulinum Toxin – Adult/Pediatric – Ambulatory Clinical Practice Guideline (2017)[10]	
Treatment of upper and lower extremity spasticity: **Recommendation:** "BoNT should be offered to treat spasticity resulting from a stroke, traumatic or non-traumatic spinal cord injury, multiple sclerosis or other demyelinating disease of the central nervous system, traumatic brain injury or other central process with BoNT injections as a component of a documented rehabilitation and strengthening program (p.7)."[10] **Supporting evidence:** Recommendation was based on 17 publications; however, details were not provided. The publications covered a variety of spasticity etiologies (e.g., stroke, spinal cord injury, head injury, and traumatic brain injury) and BoNT subtypes and BoNT-A formulations (e.g., BoNT-B and aboBoNT-A). **Dosing for Botox:** **Recommendation:** Usual or starting doses of Botox for spasticity (cause not specified) and non-cervical dystonia in adult and pediatric patients: "0.5 – 20 units/kg with a maximum dose of 400 – 600 units; initiate therapy at the lower end of the dose range (p.11)."[10] **Supporting evidence:** Recommendation was based on 3 publications; however, details were not provided. One publication was an injection manual for BoNT; thus, it may not be specific to Botox. The other 2 publications cited evidence regarding pediatric patients, with 1 specific to children with cerebral palsy.	**Treatment of upper and lower extremity spasticity:** The quality of evidence was ranked as high and the strength of the recommendation was rated as strong. **Dosing for Botox:** The quality of evidence and strength of recommendation were not reported.

aboBoNT-A = abobotulinum toxin A; BoNT = botulinum toxin; BoNT-A = botulinum toxin type A; BoNT-B = botulinum toxin type B; MAS = Modified Ashworth Scale; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MS = multiple sclerosis; VAS = visual analogue scale.

Appendix 5: References of Potential Interest

Review Article

1. Dressler D, Bhidayasiri R, Bohlega S, et al. Botulinum toxin therapy for treatment of spasticity in multiple sclerosis: review and recommendations of the IAB-Interdisciplinary Working Group for Movement Disorders task force. *J Neurol*. 2017 Jan;264(1):112-120. Medline

Mixed Population — Various Spasticity Etiologies

2. Wein T, Jog M, Bhogal M, et al. Long-term safety and dosing of onabotulinumtoxinA: a prospective, observational study. *Can J Neurol Sci*. 2019 11;46(6):742-752. Medline
3. Jog M, Wein T, Bhogal M, et al. Real-world, long-term quality of life following therapeutic onabotulinumtoxinA treatment. *Can J Neurol Sci*. 2016 Sep;43(5):687-696. Medline
4. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016 May 10;86(19):1818-1826. Medline

Mixed Intervention — Various Botulinum Toxin Subtypes or Formulations

5. Ertzgaard P, Anhammer M, Forsmark A. Regional disparities in botulinum toxin A (BoNT-A) therapy for spasticity in Sweden: budgetary consequences of closing the estimated treatment gap. *Acta Neurol Scand*. 2017 Mar;135(3):366-372. Medline

No Comparator

6. Esquenazi A, Bavikatte G, Bandari DS, et al. Long-term observational results from the ASPIRE study: onabotulinumtoxinA treatment for adult lower limb spasticity. *PM R*. 2020 Nov 05. Medline
7. Francisco GE, Bandari DS, Bavikatte G, et al. High clinician- and patient-reported satisfaction with individualized onabotulinumtoxinA treatment for spasticity across several etiologies from the ASPIRE study. *Toxicon X*. 2020 Sep;7:100040. Medline

Systematic Review Published Prior to 2016

8. Nalysnyk L, et al. OnabotulinumtoxinA muscle injection patterns in adult spasticity: a systematic literature review; *BMC Neurol*. 2013;13:118. Medline