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Is Botulinum toxin A an effective treatment for treating children who have lower limb spasticity from cerebral palsy?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

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In

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Department of Physician Assistant Studies
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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not botulinum toxin A is an effective treatment for children who have lower limb spasticity from cerebral palsy.

STUDY DESIGN: The study by Carraro et al was a randomized double-blind clinical trial done in 2015.⁶The study done by Kim et al was a randomized, double-blind controlled clinical trial done in 2010.⁷ The study by Py et al was a clinical trial done in 2005-2006.⁸

DATA SOURCES: Data sources obtained for this review were articles published in peer-reviewed journals found using PubMed Database.

OUTCOMES MEASURED: The outcome measured the effectiveness of Botox and Botox verse Xeomin and Neuronox, as well as the improvement of Gross Motor function with the use of Botox and Neuronox.

RESULTS: The study Carraro et al showed that incobotulinum toxin A (Xeomin) was just as effective for the treatment of spasticity from cerebral palsy, as onabotulinum toxin A (Botox).⁶The study by Kim et al, showed the Neuronox was just as effective as Botox.⁷Lastly, the study by Py et al, provided clear evidence that onabotulinum toxin A (Botox), was an effective treatment of spastic gait in cerebral palsy in the first place.⁸

CONCLUSIONS: The results of the studies showed at Xeomin, Neuronox, and Botox all have similar results efficacy for the treatment of lower limb spasticity in children with cerebral palsy.

KEY WORDS: Cerebral Palsy; Spastic Gait; Botox

INTRODUCTION

Cerebral palsy is a term that is nonspecific and used to describe a chronic, static impairment of muscle tone, strength, coordination, or movements due to some type of cerebral insult or injury before birth, during delivery, or in the perinatal period.¹ This condition is caused by abnormal development of the brain or damage to the developing brain that affects the child's ability to control his or her muscles.² Even though the concept of how this condition develops is known, the exact cause of the disease is unknown. Cerebral palsy affects 1.5 to 4 of every 1,000 live births, making cerebral palsy the most common motor disability in childhood.² It is estimated that the average cost of healthcare of a patient with cerebral palsy in their lifetime is \$910,000.² In 2000, it was estimated that the combined lifetime costs for all patients with cerebral palsy totaled \$11.5 billion in direct and indirect costs of having this condition.² Of course, severity manifestations and prognosis vary substantially from patient to patient with cerebral palsy.¹

The most common form of cerebral palsy that accounts for 75% of cases involve spasticity of the limbs.¹ Once the diagnosis is classified as spastic cerebral palsy, there is a term attached to the diagnosis that is used to describe the specific patient's degree of spasticity. The term monoplegia describes the patients with one limb affected.¹ Hemiplegia describes patients that have an arm and leg that are affected on the same side of the body, but the arm is more affected than the leg.¹ Paraplegia describes patients that have both legs affected and both arms unaffected.¹ The last descriptive term used to describe patients with spastic cerebral palsy is quadriplegia, which describes a case where all four limbs are affected equally.¹

The next most common form of cerebral palsy is ataxia, which accounts for around 15% of cases.¹ The most common way the ataxia affects the patients is in fine coordinated movement of the upper extremities, but may also affect the lower extremities and the trunk. Lastly, persistent hypotonia without spasticity accounts for 1% of cases.¹

Many different neurologic deficits tend to occur in the presence of motor deficits that are

caused by cerebral palsy.¹ Seizures occur in up to 50% of these patients, mild retardation in 26% and severe retardation in up to 27%.¹ Many different other disorders coexist in these patients in varying degrees and combinations.¹ Some commonly seen disorders are of language, speech, vision, hearing and sensory perception.¹

The most common finding on physical exam are those of spasticity, hyperreflexia, ataxia, and involuntary movements.² Microcephaly is often present.¹ The patients with spastic hemiplegia type of cerebral palsy can present with the affected arm and leg may be smaller and shorter than the unaffected limbs.¹

Cerebral palsy is a clinical diagnostic term that is used to describe patients with similar symptoms due to a cerebral insult around birth.² The use of laboratory and imaging tests depends on each patient's presenting symptoms, as there is no one diagnostic test for cerebral palsy.¹ One of the more common imaging tests done is an MRI. The MRI scan may be helpful in seeing the full extent of the cerebral injury and can suggest an etiology for the condition.¹ Interest is growing for genetic and metabolic testing, which can be useful to figure out a cause in combination with the history and MRI findings.¹ There are two common findings in a newborn that help diagnose cerebral palsy, even though they are not diagnostic.³ The first being the Apgar score given at 1 and 5 minutes after delivery. It has been shown that when the 5-minute Apgar score is less than 3 the risk of neurological sequelae, such as cerebral palsy is increased substantially.⁴ Another finding in the newborn period that can support the diagnosis of cerebral palsy is umbilical cord blood pH less than 7 and a base deficit greater or equal to 12.3. These findings within the umbilical cord are objective evidence for metabolic acidosis and the worse the acidosis, the more risk that patient has for cerebral palsy.³

The treatment of cerebral palsy has been studied and is an area that is actively researched. All the treatments for cerebral palsy are directed at assisting the patient to attain maximum neurologic functioning with appropriate physical, occupational, and speech therapy as well as medications for spasticity and seizures.¹ The current treatment for spastic cerebral palsy

includes oral antispastic drugs, intrathecal baclofen, surgical treatment such as selective dorsal rhizotomy and deep brain stimulation, and botulinum toxin injection.

The efficacy regarding the use of botulinum toxin injection to increase function in patients with lower limb spasticity from cerebral palsy is a hot topic among healthcare providers. Botulinum neurotoxins are classified into seven categories: A, B, C1, D, E, F, and G.⁵The difference between the categories is their biosynthesis, size, cellular sites of action, binding kinetics, duration of effect and stability.⁵ The two types of botulinum neurotoxin that are currently commercially available are serotypes A and B. The mechanism of action of botulinum is first the toxin enters the nerves by binding to surface protein receptors and undergoing endocytosis into internalized vesicles.⁵ Then, the light chain is released into the nerve cytosol and the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) protein complex is cleaved to inhibit exocytosis of the neurotransmitters such as acetylcholine.⁵The receptor for all types of botulinum toxin A is SV2/SNAP-25.⁵The end result is a chemodenervation of cholinergic neurons, which leads to a localized absence of skeletal muscle activity.⁵Eventually due to nerve sprouts of the chemodenervated nerves there is reestablished chemical contact with their targets and muscles resume activity.⁵The brand name of a specific botulinum toxin is Botox and it is a serotype botulinum toxin A.⁵ Botox is the most commonly used botulinum toxin, as it is the one that has been studied most thoroughly.⁵There are many next brands of botulinum toxin that are becoming available on the market for use, but there are few studies that show if they are as effective as Botox.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not botulinum toxins, besides *Botox* are effective for treating children who have lower limb spasticity from cerebral palsy. The hypothesis about the objective is that the use of other botulinum toxins are also an effective treatment option besides *Botox*, of lower limb spasticity in children with cerebral palsy.

METHODS

The studies that were selected during the construction of this EBM review were two randomized controlled trials and one clinical trial.^{6,7,8} The population studied in the trials included children with cerebral palsy under the age of 18 and have lower limb spasticity. The interventions in each study involved administration of a brand of a serotype A of botulinum toxin. The first study by *Py and et al*, studied the effectiveness of Botox.⁸ In the study done by *Carraro and et al*, the effectiveness of *Xeomin* (a type of botulinum toxin A) verse *Botox* (a type of botulinum toxin A) was studied.⁶ The study done by *Kim and et al* compared the effectiveness of *Neuronox* (a type of botulinum toxin A) and *Botox*.⁷ Neuronox is not currently FDA approved for use of any condition currently in the United States.⁵ The outcome measured that is of particular interest to this EBM review was the number of adverse effects and the improvement of functional ability of the patient. For clarification, each botulinum toxin in this EBM review, is in the serotype of A, but they each have slight individual differences.⁵ A few notable differences between the products are the process by which the product is made, the complex molecular weight uniformity, and the stabilization solubilization pH.⁵ The differences are shown in the chart below:

	Botox	Xeomin	Neuronox
Nonproprietary name (FDA)	Onabotulinum toxin A	Incobotulinum toxin A	Not FDA approved
Process	Crystallization	Chromatography	Chromatography
Complex mw uniformity	-900kD homogenous	-150kD	-150kD
Stabilization/ solubilization pH	Vacuum dried normal saline -7	Vacuum dried normal saline -7.4	lyophilization

Using PubMed databases, three studies were selected. Keywords used in the literature search were “cerebral palsy”, “spastic gait”, and “Botox”. All articles were published in English in peer-reviewed journals and were selected based on significance and application, as well as the condition that outcomes measured were patient oriented outcomes (POEMS). Inclusion and exclusion criteria were similar across all three articles. Inclusion criteria involved studies that were randomized control trials/clinical trials, published after 2011, participations were children with cerebral palsy spastic subtype under the age of 18. Patients were excluded from the study if they had a history of anaphylactic reactions to BoNT-A, a bleeding tendency, or a history of treatment with anticoagulants, aminoglycosides, muscle relaxants, parasympathetic antagonists, or dopaminergic. Individuals who have previously undergone surgery on the muscles or ligaments of the lower extremities who had fixed contracture of the lower limb joints or who exhibited severe athetoid movements were also excluded. **Table 1** demonstrates the demographics of the studies included in this EBM review. The statistic used in all the studies was the p-value.

Table 1: Demographics & Characteristics of included studies

Study	Type	#pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Carraro ¹	RCT	35	3-18 years old	Patients had to have a diagnosis of spastic diplegia, hemiplegia or quadriplegia due to CP, as verified by history, clinical/instrumental examination and neuroimaging findings; they were between 3 and 18 year of age.	Subjects were excluded from the study if was present one of the following criteria: peripheral nervous system disorders/ myopathies; previous treatments for spasticity other than BTX-A to the lower limbs (<1 years); previous orthopedic surgery to lower extremities; bone or joint deformities and fixed contractures; medications that could have had an impact on the study findings (es. Intrathecal baclofen, benzodiazepines, muscle relaxant).	0	Botox and incobotulinum
Kim ²	RCT	119	2- 10 years old	Children who had a diagnosis of CP, were aged between 2 and 10 years, and who were classified as Gross Motor Function Classification System (GMFCS) level I, II, or III were eligible for participation in the study. They had to show tiptoeing gait as a result of spastic calf muscles and be able to receive physio-therapy following a standardized protocol for lower limb spasticity. The participants were recruited from individuals who visited the outpatient departments of the	Patients were excluded from the study if they had a history of anaphylactic reactions to BoNT-A, a bleeding tendency, or a history of treatment with anticoagulants, aminoglycosides, muscle relaxants, parasympathetic antagonists, or dopaminergic. Individuals who have previously undergone surgery on the muscles or ligaments of the lower extremities who had fixed contracture of the lower limb joints or who exhibited severe athetoid movements were also excluded.	5	Neuronox and Botox

				university hospitals because of lower limb spasticity resulting from CP.			
Py A-G ⁸	Clinical trial	54	Under 18 y/o	During the period from May 2005 to May 2006, all the ambulatory children examined in outpatient consultations in the spastic diplegia service, consequential to periventricular leukomalacia lesions for which the examining doctor recommended an injection of botulinum toxin in the lower limbs, were seen by the senior doctor in the service who, after a clinical examination, confirmed or rejected the examining doctor's recommendation and suggested injection sites. The injection site could be a single or multiple.	children who had surgery less than three months previous, and children who were not re- evaluated one month after their surgery due to distance concerns.	0	Ultrasound guidance of the botulinum toxin injection

OUTCOMES MEASURED

Outcomes measured were those of patient-oriented evidence that matters (POEMS). The articles all measured outcomes in different ways. *Kim and et al* and *Py and et al*, measured outcomes on the Gross Motor Function measure scale. *Carraro and et al* measured the outcomes by a checklist given to the patient's parents that measured the adverse effects of the treatment. The outcomes measured were the number of adverse effects.

RESULTS

Two randomized, controlled trials, and one clinical trial were analyzed in this review. Each study compared the effectiveness of different versions of botulinum toxin serotype A in children under the age of 18 with lower limb spasticity due to cerebral palsy.

The study done by Py at el was done to show the effectiveness of Botox (onabotulinum toxin).⁸ The study included all ambulatory children examined in outpatient consultations in the spastic diplegia service, from May 2005 to May 2006.⁸ There were 54 children under 18 with diplegia spastic gait cerebral palsy that participated in the study.⁸ In order to determine the injection site of each individual, every child had a visual gait examination and a functional evaluation done using the Gross Motor Function Measure.⁸ The product used was Botox

produced by Allergan Laboratory.⁸The dose was between 5 and 6 UI/kg, according to the marketing

recommendation for each different muscle.⁸The dilution of 100 units, was carried out in 1 to 2 ml of 0.09% physiological serum, with a minimal volume of 0.3mL per injection.⁸ Of the 54 children given Botox injections in their lower limbs, 85% of them were evaluated with the GMFM before and after the injections.⁸The remaining 15% either had difficulty understanding the instructions or were opposed to treatment during the procedure.⁸ Only one undesirable effect was reported by the patients.⁸ The overall clinical effectiveness was good in 51% of the children.⁸The clinical improvement was better in cases of injections to the hamstring muscle (57%) and/or the gastrocnemius muscle 57%.These findings show a significant p-value of 0.04.⁸ The best clinical improvement was in children under 6 (53%) and over 12.⁸The effectiveness of the treatment all increased with increased doses.⁸ Patients injected with over 0.8IU/kg per muscle was statically significantly better than injection doses of under 0.8 UI/kg per muscle, the p-value was < 0.05.⁸ Overall there was a 24% improvement of the GMFM scores in the children treated.⁸

In the study by Carraro et al⁶ there were 35 patients recruited and the study was performed at an institute for rehabilitation and treatment.⁶ All patients completed the study and they were all treated by the same physician.⁶ All the patients had the diagnosis of spastic diplegia, hemiplegia, or quadriplegia due to cerebral palsy, as verified by history, clinical/instrumental examination and neuroimaging findings. All the participants were between the ages of three and eighteen.⁶ All the participants in the study had clinical indication to have treatment with BTX-A in the gastrocnemius muscle.⁶The participants were randomized to either the study group (incobotulinum toxin A) or the control group (onabotulinum toxin A). Both of the groups were injected with 5units/kg on the gastrocnemius (medialis and lateralis) muscles with a clinical conversion ratio of 1:1 for onabotulinum toxin A and incobotulinum toxin A.⁶ The study group had a total of 17 participants, and the control group had 18 participants.⁶ The two groups were well balanced regarding demographics.⁶ All adverse events were recorded by the patient's parents in the form of a checklist at baseline, 48hours after procedure, 10 days after, and 3 months after.⁶ The checklist had the most common side effects listed such as fever,

fatigue, general and local muscle pain, diarrhea, ecchymosis.⁶ The form also had a blank area for parents to add any additional side effects that their child experienced.⁶ The adverse effects were define as “severe” if they were fatal or life-threatening or if they resulted in functional disability or hospitalizations of the patient.⁶ The adverse effect was termed “local” if they were confined to the site of the injection.⁶ Throughout the study there were no severe adverse effects noted by any of the parents of the participants. The most common “local adverse effect was fatigue among the study and control group.⁶ **Table 2** demonstrates the statistical information from the study.

Table 2: Frequency of local adverse events⁶

	Within the first 48hours			Within the first 10 days			Within the first 3 months		
At Least one local adverse event	Study group	Control group	P values	Study group	Control group	P values	Study group	Control group	P values
	6	7	0.56	8	6	0.72	0	3	0.11

As shown by the results in the table 2, the study group (incobotulinum toxin A) and the control group (onabotulinum toxin A) had similar numbers of adverse effects with slightly less adverse effects within the study group overall.

The study done by Kim et al, included 127 total children with cerebral palsy, who presented at three university hospitals with lower limb spasticity.⁷ The 127 children were then assessed for eligibility and 119 were eligible.⁷ The study was done to access the difference of adverse events and effectiveness of Neuronox compared with Botox for the treatment of lower limb spasticity in cerebral palsy.⁷ The mean age of the participants was 4.33 years old, and the study had 43 females and 76 males.⁷ Participants were randomly assigned to a treatment group. 60 patients were treated with Neuronox and 59 with Botox.⁷ Each group received the treatment in the calf muscles at a dose of 4U/kg for those with hemiplegia (40) and 6U/kg of those patients

with diplegia (79).⁷ All participants were treated by experienced physicians.⁷ Assessments were performed at baseline (V1), and at 4(V2), 12(V3), and 24(V4) weeks.⁷ The outcomes were measured by using the Gross Motor Function Measure 88 (GMFM-88), and was measured at baseline and every other interval.⁷ After the treatments the GMFM scores increased significantly at all follow up visits.⁷ The Neuronox group showed a mean increase of 2.14 at V2, 3.77 at V3, and 4.76 at V4.⁷ The botox group showed mean increases of 2.65 at V2, 5.25 at V3, and 6.63 at V4.⁷ There was no significant difference in the change in the GMFM scores between the treatment groups at V2, $p=0.41$.⁷ At V3 and V4, Botox showed a larger increase in the GMFM score than the Neuronox group, $p=0.03$.⁷ The frequency of adverse events was not significantly different between the two groups. The 119 participants that underwent the original evaluation, 101 completed the study without violation of protocol.⁷ Eight individuals in the Neuronox group were excluded after the intervention, one due to adverse events, two retracted their consent, three didn't attend the scheduled follow up, and two were classified as protocol violators.⁷ Six individuals in the Botox group were excluded after the intervention, one was excluded because of an adverse outcome, four retracted their consent, and one didn't attend the scheduled follow up.⁷ Also, two individuals in each group were excluded after the final evaluation because of violation of study protocol.⁷ According to the study Neuronox is not inferior to Botox.⁷ Neuronox is not currently FDA approved in the United States.

DISCUSSION

The study by Py et al, showed that Botox is an effective treatment for diplegia spastic gait cerebral palsy. The reasoning for the best clinical improvement found in children under six can be explained by the fact that the fibrotic and retractile phenomena are less significant in younger children, allowing the effects of the treatment to be noted to a greater extent.⁸ It can also be explained by motor development being greater in that study population, so when the problematic spasticity is eliminated there is a more rapid influence in overall function.⁸ The effectiveness of the treatment was also better in children over 12, which was more surprising.⁸ This could be explained by that fact that many of the

children over 12 have already had musculotendinous surgical treatment in their lower limbs, which helped the practitioner target more precisely the muscles to be injected.⁸ The main limitation of this study is that it was not a double-blind study, which in turn makes the results less reliable.⁸ Two more limitations to the study include that the post-evaluation took place at 3 to 4 weeks after the injection, which could have been too early to see complete results, and the percent of improvement could have been lower in the patients where the dose of the injection was lower per muscle, due to multiple muscle injections and the cumulative dose for all participants being 6IU/kg of botox.⁸

The study by Carraro et al showed that incobotulinum toxin A doesn't have more adverse effects and is equally beneficial as onabotulinum toxin A.⁶ The study did not detect any important difference in safety between these two formulations of BTX-A for the treatment of lower limb spasticity in children under 18 with cerebral palsy.⁶ The study as a whole produced an increase in adverse events relative to other similar studies.⁶ Within the whole cohort at 48 hours, 48.6% of patients experienced an adverse event, 47.8% in the first ten days and 11.8% in the first three months.⁶ There were a few limitations to the study. The first being that there was no placebo group, which means that not all adverse events can be directly linked to the treatment.⁶ Another limitation of the study is that the parents were given an articulated list of adverse events, which could have caused the patients to believe that a certain symptom was from the treatment only because it was listed on the form.⁶ The last limitation of this study was the small sample size that participated in the treatments.⁶ At this point, incobotulinum toxin A is not currently being used in the United States for treatment of spastic gait cerebral palsy but this study does show that it could have a place in the treatment of this condition in the future.⁶ Further studies need to be done to confirm the safety and effectiveness of incobotulinum toxin A.

The study by Kim et al, showed Neuronox to be just as effective as Botox. The study as a whole showed improvement in all children treated in both treatment groups for lower limb spasticity

from cerebral palsy.⁷The results of this study are similar to those of previous studies done on Botox.⁷ The study had a few notable limitations that could have altered the results. One limitation was that the study was not controlled with a placebo group, which is necessary in order to show the net effect of the drug.⁷ Another limitation of the study was that the protocol did not apply variable doses of either treatments.⁷ According to the severity of each patient's spasticity, different doses would produce more optimal outcomes.⁷The dose of 4U/Kg could have been insufficient in some cases.⁷ This study was the first well designed, strictly conducted phase III clinical trial to validate the effectiveness of Neuronox for lower limb spasticity in cerebral palsy.⁷The results of this study are expected to provide physicians with more choices for the treatment of spasticity in cerebral palsy in the future.⁷

CONCLUSION

The trials analyzed in this EBM review showed that the different types of botulinum toxin A all showed significant improvement in the treatment of lower limb spasticity from cerebral palsy.^{6,7,8} The study Carraro et al showed that incobotulinum toxin A (Xeomin) was just as effective for the treatment of spasticity for cerebral palsy, as onabotulinum toxin A(Botox).⁶ The study by Kim et al, showed the Neuronox was just as effective as Botox.⁷ Lastly, the study by Py et al, provided clear evidence that onabotulinum toxin A (Botox), was even an effective treatment of spastic gait in cerebral palsy in the first place.⁸

Future study is warranted to definitively evaluate the efficacy of different types of botulinum toxin A in the treatment of lower limb spasticity in cerebral palsy. All of the aforementioned studies have a small population size and various limitations that reduce the significance of the results. Additional studies should include a larger population and should be double-blind trials to make the results more reliable. This treatment should be continually investigated because it could change the treatment options for children with issues of lower limb spasticity from cerebral palsy.

REFERENCES

1. Kedia S, Knupp K, L. Schreiner T, Yang ML, Toler J, G. Moe P. Neurologic & Muscular Disorders. In: Hay WW, Jr., Levin MJ, Deterding RR, Abzug MJ. eds. *CURRENT Diagnosis & Treatment Pediatrics*, 23e New York, NY: McGraw-Hill; . <http://accessmedicine.mhmedical.com/content.aspx?bookid=1795§ionid=125744005>. Accessed November 23, 2017.
2. Cerebral Palsy (CP). Centers for Disease Control and Prevention <https://www.cdc.gov/ncbddd/cp/data.htm> l. Published May 2, 2016. Accessed October 4, 2017
3. Diseases and Injuries of the Term Newborn. In: Cunningham F, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS. eds. *Williams Obstetrics, Twenty-Fourth Edition* New York, NY: McGraw-Hill; 2013. <http://accessmedicine.mhmedical.com/content.aspx?bookid=1057§ionid=59789175>. Accessed November 24, 2017.
4. Dijkhoorn MJ, Visser GHA, Fidler VJ, et al: Apgar score, meconium and acidemia at birth in relation to neonatal neurological morbidity in term infants. *Br J Obstet Gynaecol* 86:217, 1986
5. Glogau RG. Chapter 255. Botulinum Toxin. In: Goldsmith LA, Katz SI, Gilchrist BA, Paller AS, Leffell DJ, Wolff K. eds. *Fitzpatrick's Dermatology in General Medicine*, 8e New York, NY: McGraw-Hill; 2012. <http://accessmedicine.mhmedical.com/content.aspx?bookid=392§ionid=41138996>. Accessed November 24, 2017.
6. Carraro E, Trevisi E, Martinuzzi A. Safety profile of incobotulinum toxin A [Xeomin®] in gastrocnemius muscles injections in children with cerebral palsy: Randomized double-blind clinical trial. *European Journal of Pediatric Neurology*. 2016;20(4):532-537. doi:10.1016/j.ejpn.2016.04.008.
7. Kim K, Shin H-I, Kwon BS, Kim SJ, Jung I-Y, Bang MS. Neuronox versus BOTOX for spastic equinus gait in children with cerebral palsy: a randomized, double-blinded, controlled multicentre clinical trial. *Developmental Medicine & Child Neurology*. 2010;53(3):239-244. doi:10.1111/j.1469-8749.2010.03830.x.
8. Py A-G, Addeen GZ, Perrier Y, Carlier R-Y, Picard A. Evaluation of the effectiveness of botulinum toxin injections in the lower limb muscles of children with cerebral palsy. Preliminary prospective study of the advantages of ultrasound guidance. *Annals of Physical and Rehabilitation Medicine*. 2009;52(3):215-223. doi:10.1016/j.rehab.2009.02.005.