Botulinum Toxin-A Injections for Equinus Deformity
Risks, Adverse Effects, Disappointments

Botulinum toxin is the most potent naturally occurring toxin known to humankind.

How many reports of adverse effects does it take to stop the train and do some real research?

What sort of data leads to a commitment to the oath taken by clinicians to "do no harm"?

No one is asking whether building trunk control, improving trunk alignment in function, improving foot alignment and loading, or moving the body COM back over the heels are effective and safer alternatives for contracture management than injecting paralytic toxins into weak muscles to gain temporary mobility without understanding long-term effects on muscle strength and health.

Studies that claim that post-injection recovery of healthy rat muscle occurs in 6 months after injection can be interpreted as he equivalent of 18 human years. http://www.ratbehavior.org/RatYears.htm

Injected CP muscle is transformed and already weak, so if it "recovers" after injection to pre-injection strength, it is still weaker than normal, and there is no evidence that the injected muscle ever achieves normal strength.

Ackman JD, Russman BS, Thomas SS, et al. 2005. Comparing botulinum toxin A with casting for treatment of dynamic equinus in children with cerebral palsy. Dev Med Child Neurol. 47(9): 620-627. [*[AIM: to compare the cumulative efficacy (three treatment sessions. of botulinum toxin A (BTX-A. alone, casting alone, and the combination of BTX-A and casting in the management of dynamic equinus (dynamic???. in ambulatory children with spastic cerebral palsy (CP). Thirty-nine children with spastic CP (mean age 5y 10mo, range 3 to 9y. were enrolled in a multicenter, randomized, double blind, placebo-controlled prospective study. Children were randomly assigned to one of three treatment groups: BTX-A only (B), placebo injection plus casting (C), or BTX-A plus casting (B+C). The dosage for the BTX-A injections was 4U/kg per extremity. Assessments were performed at baseline, 3, 6, 7.5, and 12 months with a total of 3 treatments administered after the evaluations at baseline, 3, and 6 months. Primary outcome measures were ankle kinematics, velocity, and stride length. Secondary outcome measures were ankle spasticity, strength, range of motion, and ankle kinetics. Group B made no significant change in any variable at any time. Groups C and B+C demonstrated significant improvements in ankle kinematics, spasticity, passive range of motion, and dorsiflexor strength. Results of this 1-year study indicate that BTX-A alone provided no improvement in the parameters measured in this study, while casting and BTX-A/casting were effective in the short- and long-term management of dynamic equinus in children with spastic CP]. BTX had NO effect! So why add the pain and expense of the BOTOX??*

Ade-Hall RA, Moore AP. 2000. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. *Cochrane Database Syst Rev.* (2):CD001408. Review. *[CONCLUSIONS: This systematic review has not revealed strong controlled evidence to support or refute the use of BtA for the treatment of leg spasticity in cerebral palsy. Ongoing randomised controlled trials are likely to provide useful data on the short term effects of BtA for leg spasticity. Future research should also assess the longer term use of BtA. Ideally studies should be pragmatic in their approach to dose and distribution of toxin to reflect practise. Outcome measures assessing function and disability would give the most useful information.]*

Antonucci F, Rossi C, Gianfranceschi L, Rossetto O, Caleo M. 2008. Long-distance retrograde effects of botulinum neurotoxin A. J Neurosci. 28(14):3689-96. *[It is widely assumed that BoNT/A remains at the synaptic terminal and its effects are confined to the injection site. Here we demonstrate that catalytically active BoNT/A is retrogradely transported by central neurons and motoneurons and is then transcytosed to afferent synapses, in which it cleaves SNAP-25. SNAP-25 cleavage by BoNT/A was observed in the contralateral hemisphere after unilateral BoNT/A delivery to the hippocampus. Appearance of cleaved SNAP-25 resulted in blockade of hippocampal activity in the untreated hemisphere. Injections of BoNT/A into the optic tectum led to the appearance of BoNT/A-truncated SNAP-25 in synaptic terminals within the retina. Cleaved SNAP-25 also appeared in the facial nucleus after injection of the toxin into rat whisker muscles. Experiments excluded passive spread of the toxin and demonstrated axonal migration and neuronal transcytosis of BoNT/A. These findings reveal a novel pathway of BoNT/A trafficking in neurons and have important implications for the clinical uses of this neurotoxin.] So it migrates to the brain…*

Ateş F, Yucesoy CA. 2014. Effects of botulinum toxin type A on non-injected bi-articular muscle include a narrower length range of force exertion and increased passive force. Muscle Nerve. 49(6):866-78. [The goal of this study was to test the hypothesis that botulinum toxin type A (BTX-A) injection in rat tibialis anterior (TA) muscle affects the mechanics of its bi-articular synergist, both actively and passively. METHODS: Two groups of Wistar rats were tested: control (no BTX-A) and BTX (0.1 U of BTX-A) animals were injected exclusively to the mid-belly of TA. Extensor digitorum longus (EDL) muscle isometric forces were measured after proximal and distal lengthening. RESULTS: Five days after injection, BTX-A administration changed EDL mechanics: (1) active forces decreased (proximal muscle length dependently); (2) length range of active force exertion decreased both proximally and distally; and (3) passive muscle forces increased. CONCLUSIONS: **Effects of BTX-A appear to not be limited to decreased active muscle tone, but may cause also a narrower active range of movement and increased passive resistance.]** Healthy animal muscle, not stiff, transformed CP muscle.

Barber L, Hastings-Ison T, Baker R, et al. 2013. The effects of botulinum toxin injection frequency on calf muscle growth in young children with spastic cerebral palsy: a 12-month prospective study. J Child Orthop. 7(5): 425-433. *[This study was a 12-month prospective investigation of changes in the medial gastrocnemius (MG) muscle morphology in children aged 2-5 years with spastic cerebral palsy (CP) who had received no previous intramuscular injections of botulinum neurotoxin type-A (BoNT-A) and were randomised to receive either single or multiple (three) BoNT-A injections to the gastrocsoleus. MG morphological changes were compared to age-matched typically developing (TD) peers. METHODS: Thirteen children with spastic CP with a mean age of 45 (15) months and 18 TD children with a mean age of 48 (14) months participated in the study. The principal outcome measures were MG muscle volume, fascicle length, pennation angle and physiological cross-sectional area (PCSA), which were obtained using 2D and 3D ultrasound. RESULTS: The single and multiple injection frequency groups significantly increased MG muscle volume at 12 months relative to the baseline by 13 and 15 %, respectively. There were no significant differences in the MG muscle*

volume 28.5 (12.3) versus 30.3 (3.8) ml, fascicle length 48.0 (10.4) versus 44.8 (1.2) mm or PCSA 7.0 (1.2) versus 6.6 (1.7) cm(2) between the single and multiple injection groups, respectively, at 12 months follow-up. The change in MG muscle volume in the single and multiple injection groups was significantly lower than the TD peers by 66 and 60 %, respectively. INTERPRETATION: In young children with spastic CP, naive to BoNT-A treatment, MG muscle growth over 12 months does not appear to be influenced by intramuscular BoNT-A injection frequency. However, MG muscle growth in the spastic CP groups was significantly lower than the age-matched TD peers. It is unclear whether this is an effect of intramuscular BoNT-A injections or reduced growth rates in children with spastic CP in general. ***Controlled investigations and longitudinal studies with multiple measurement time points are required in order to determine the influence of BoNT-A treatment on muscle physiological and mechanical growth factors in young children with spastic CP.****]*

Barclay L. Respiratory Compromise, Death May Be Linked to Botulinum Toxin. Medscape. 2008 Feb;8. Available from: http://www.medscape.com

Caron G, Rouzi T, Grelot L, et al. 2014. Mechano- and metabosensitive alterations after injection of botulinum toxin into gastrocnemius muscle. J Neurosci Res. 92(7):904-14. *[This study was designed to investigate effects of motor denervation by Clostridium botulinum toxin serotype A (BoNT/A) on the afferent activity of fibers originating from* ***the gastrocnemius muscle of rats.*** *Animals were randomized in two groups, 1) untreated animals acting as control and 2) treated animals in which the toxin was injected in the left muscle. Locomotor activity was evaluated once per day during 12 days with a test based on footprint measurements of walking rats (sciatic functional index). At the end of the functional assessment period, electrophysiological tests were used to measure muscle properties, metabosensitive afferent fiber responses to chemical (KCl and lactic acid) injections, electrically induced fatigue (EIF), and mechanosensitive responses to tendon vibrations. Additionally, ventilatory response was recorded during repetitive muscle contractions. Then, rats were sacrificed, and the BoNT/A-injected muscles were weighed. Twelve days postinjection we observed a complete motor denervation associated with a significant muscle atrophy and loss of force to direct muscle stimulation. In the BoNT/A group, the metabosensitive responses to KCl injections were unaltered. However, we observed alterations in responses to EIF and to 1 mM of lactic acid (which induces the greatest activation). The ventilatory adjustments during repetitive muscle activation were abolished, and the mechanosensitive fiber responses to tendon vibrations were reduced. These results indicate that BoNT/A alters the sensorimotor loop and may induce insufficient motor and physiological adjustments in patients in whom a motor denervation with BoNT/A was performed.]* Healthy animal muscle, not stiff, transformed CP muscle.

Chaturvedi SK, Rai Y, Chourasia A, et al. 2013. Comparative assessment of therapeutic response to physiotherapy with or without botulinum toxin injection using diffusion tensor tractography and clinical scores in term diplegic cerebral palsy children. Brain Dev.35(7):647-53. *[The present study was to compare the effects of combined therapy [botulinum (BTX) plus physiotherapy] with physiotherapy alone using diffusion tensor imaging (DTI) derived fractional anisotropy (FA) values of motor and sensory fiber bundles and clinical grade of the disability to see the value of BTX in term children with spastic diplegic cerebral palsy (CP). Clinically diagnosed 36 children participated in the study.* ***All these children were born at term****, and had no history of seizures. The study was randomly categorized into two groups: group I (n=18) - physiotherapy alone and group II (n=18) - physiotherapy plus BTX injection. Quantitative diffusion tensor tractography on all these children was performed on motor and sensory fiber bundles on baseline as well as* ***after 6months of therapy****. Motor function and clinical grades were also measured by gross motor function measures* ***(GMFM) scale*** *on both occasions. We observed significant change in FA value in motor and sensory fiber bundle as well as in GMFM scores at 6months compared to baseline study in both the groups. However, delta change and relative delta change in FA values of sensory and motor fiber bundle as well as GMFM score between group I and group II was statistically insignificant.* ***We conclude that addition of BTX to physiotherapy regimen does not influence the outcome at 6months with similar insult in children with term diplegic spastic CP.*** *This information may influence management of diplegic CP especially in developing countries, where BTX is beyond the reach of these children.]*

Desloovere K, Schörkhuber V, Fagard K, et al. 2012. Botulinum toxin type A treatment in children with cerebral palsy: evaluation of treatment success or failure by means of goal attainment scaling. Eur J Paediatr Neurol. 16(3):229-36. [AIMS: The purpose of this retrospective cohort study was to evaluate the clinical responsiveness of Botulinum toxin type A (BTX-A) treatment in children with CP and specifically delineate features of treatment success and failure. METHODS: **Four hundred and thirty-eight children (251 boys, 187 girls; mean age 8 years 2 months, SD 4 years) were included into the study**. Goal Attainment Scaling (GAS) was used to classify and evaluate treatment efficacy. Two study groups were defined: one group with an excellent response (GAS≥60.0) and one group with a lack of response (GAS≤40.0) to BTX-A. RESULTS: Seventy-five patients (17.1%) had an excellent response and treatment was found to be unsuccessful for 31 patients (7.1%). **Children with a lack of response to BTX-A were significantly older compared to children with a high responsiveness (p=0.0013)**. In the latter group, more children received multi-level injections and fewer children had injections in proximal parts of the lower limb compared to the low responsiveness group (p=0.0024). Moreover, **there was a significant difference in the use of different types of casts between both study groups** (p=0.0263). CONCLUSION: Age, level of treatment and casting seem to be crucial features of BTX-A treatment success or failure in children with CP.]

Dunne J, Singer BJ, Silbert PL, Singer KP. Prolonged vastus lateralis denervation after botulinum toxin type A injection. Mov Disord 2010; 25: 397–401. *[Intramuscular injection of botulinum toxin (BoNT) produces reversible blockade of neuromuscular transmission. In animal experimental models, recovery begins within four weeks and is usually complete by twelve weeks. We present evidence of prolonged denervation following BoNT injection of the vastus lateralis (VL) muscle to correct quadriceps muscle imbalance in patients with chronic anterior knee pain.* ***Needle electromyography data were obtained from 10 subjects who had received a single BoNT treatment 5 to 19 months earlier*** *as part of a clinical trial. Insertional and spontaneous activity, recruitment, and motor unit action potentials were examined. Clear differences between the injected and non-injected VL muscles, which correlated with the time since injection, were identified in all subjects.* ***All 10 subjects studied with needle EMG showed evidence of persisting denervation in the BoNT-A injected VL muscle beyond the period of neuromotor recovery expected from animal experimental studies****.]* Fortuna et al found that in animal studies, recovery was not complete at 6 months, not 12 weeks.

Ellman R[1], Grasso DJ, van Vliet M, et al. 2014. Combined effects of botulinum toxin injection and hind limb unloading on bone and muscle. Calcif Tissue Int. 94(3):327-37. *[Bone receives mechanical stimulation from two primary sources, muscle contractions and external gravitational loading; but the relative contribution of each source to skeletal health is not fully understood. Understanding the most effective loading for maintaining bone health has important clinical implications for prescribing physical activity for the treatment or prevention of osteoporosis. Therefore, we investigated the relative effects of muscle paralysis and reduced gravitational loading on changes in muscle mass, bone mineral density, and microarchitecture. Adult female C57Bl/6J mice (n = 10/group) underwent one of the following: unilateral botulinum toxin (BTX) injection of the hind limb, hind limb unloading (HLU), both unilateral BTX injection and HLU, or no intervention. BTX and HLU each led to significant muscle and bone loss. The effect of BTX was diminished when combined with HLU, though generally the leg that received the combined intervention (HLU+BTX) had the most detrimental changes in bone and muscle. We found an indirect effect of BTX affecting the*

uninjected (contralateral) leg that led to significant decreases in bone mineral density and deficits in muscle mass and bone architecture relative to the untreated controls; the magnitude of this indirect BTX effect was comparable to the direct effect of BTX treatment and HLU. Thus, while it was difficult to definitively conclude whether muscle force or external gravitational loading contributes more to bone maintenance, ***it appears that BTX-induced muscle paralysis is more detrimental to muscle and bone than HLU****.] Healthy animal muscle, not stiff, transformed CP muscle.*

Engström P, Bartonek Å, Tedroff K, et al. 2013. **Botulinum toxin A does not improve the results of cast treatment for idiopathic toe-walking: a** randomized controlled trial. J Bone Joint Surg Am. 95(5):400-7.

Fortuna R, Vaz MA, Sawatsky A, Hart DA, Herzog W. 2015. A clinically relevant BTX-A injection protocol leads to persistent weakness, contractile material loss, and an altered mRNA expression phenotype in rabbit quadriceps muscles. J Biomech. 48(10):1700-6. *[Botulinum toxin type-A (BTX-A) injections have become a common treatment modality for patients suffering from muscle spasticity. Despite its benefits, BTX-A treatments have been associated with adverse effects on target muscles. Currently, application of BTX-A is largely based on clinical experience, and research quantifying muscle structure following BTX-A treatment has not been performed systematically. The purpose of this study was to evaluate strength, muscle mass, and contractile material* ***six months following a single or repeated (2 and 3) BTX-A injections into the quadriceps femoris of New Zealand white rabbits.*** *Twenty three skeletally mature rabbits were divided into four groups: experimental group rabbits received 1, 2, or 3 injections at intervals of 3 months (1-BTX-A, 2-BTX-A, 3-BTX-A, respectively) while control group rabbits received volume-matched saline injections. Knee extensor strength, quadriceps muscle mass, and quadriceps contractile material of the experimental group rabbits were expressed as a percentage change relative to the control group rabbits. One-way ANOVA was used to determine group differences in outcome measures (α=0.05).* ***Muscle strength and contractile material were significantly reduced in experimental compared to control group rabbits*** *but did not differ between experimental groups. Muscle mass was the same in experimental BTX-A and control group rabbits.* ***We concluded from these results that muscle strength and contractile material do not fully recover within six months of BTX-A treatment****.* [Healthy rabbits, not stiff, transformed gastrocs as in CP.]

Fortuna R, Horisberger M, Vaz MA, Herzog W. 2013. Do skeletal muscle properties recover following repeat botulinum toxin A injections? J Biomech. 46(14): 2426-2433*. [Although considered safe,* ***previous studies have shown that BTX-A injections cause muscle atrophy and deterioration in target and non-target muscles.*** *Ideally, muscles should fully recover following BTX-A treatments, so that muscle strength and performance are not affected in the long-term. However,* ***systematic, long-term data on the recovery of muscles exposed to BTX-A treatments are not available,*** *thus practice guidelines on the frequency and duration of BTX-A injections, and associated recovery protocols, are based on* ***clinical experience with little evidence-based information****. Therefore, the purpose of this study was to investigate muscle recovery following a six months, monthly BTX-A injection (3.5 U/kg) protocol. Twenty seven skeletally mature NZW rabbits were divided into 5 groups: Control (n=5), zero month recovery - BTX-A+0M (n=5), one month recovery - BTX-A+1M (n=5), three months recovery - BTX-A+3M (n=5), and six months recovery - BTX-A+6M (n=7). Knee extensor strength, muscle mass and percent contractile material in injected and contralateral non-injected muscles was measured at each point of recovery. Strength and muscle mass were partially and completely recovered in injected and contralateral non-injected muscles for BTX-A+6M group animals, respectively.* ***The percent of contractile material partially recovered in the injected, but did not recover in the contralateral non-injected muscles. We conclude from these results that neither target nor non-target muscles fully recover within six months of a BTX-A treatment protocol and that clinical studies on muscle recovery should be pursued.****]* [Healthy rabbits, not stiff gastrocs as in CP.]

Fortuna R, Vaz MA, Rehan Youssef A, Longino D, Herzog W. 2011. Changes in contractile properties of muscles receiving repeat injections of botulinum toxin. J Biomech. 44: 39–44. *[Botulinum toxin type A (BTX-A) is a frequently used therapeutic tool to denervate muscles in the treatment of neuromuscular disorders. Although considered safe by the US Food and Drug Administration,* ***BTX-A can produce adverse effects in target and non-target muscles. With an increased use of BTX-A for neuromuscular disorders, the effects of repeat injections of BTX-A on strength, muscle mass and structure need to be known.*** *Therefore, the purpose of this study was to investigate the changes in strength, muscle mass and contractile material in New Zealand White (NZW) rabbits. Twenty NZW rabbits were divided into 4 groups: control and 1, 3 and 6 months of unilateral, repeat injections of BTX-A into the quadriceps femoris. Outcome measures included knee extensor torque, muscle mass and the percentage of contractile material in the quadriceps muscles of the target and non-injected contralateral hindlimbs.* ***Strength in the injected muscles was reduced by 88%, 89% and 95% in the 1, 3 and 6 months BTX-A injected hindlimbs compared to controls. Muscle mass was reduced by 50%, 42% and 31% for the vastus lateralis (VL), rectus femoris (RF) and vastus medialis (VM), respectively, at 1 month, by 68%, 51% and 50% at 3 months and by 76%, 44% and 13% at 6 months. The percentage of contractile material was reduced for the 3 and 6 months animals to 80-64%, respectively, and was replaced primarily by fat. Similar, but less pronounced results were also observed for the quadriceps muscles of the contralateral hindlimbs, suggesting that repeat BTX-A injections cause muscle atrophy and loss of contractile tissue in target muscles and also in non-target muscles that are far removed from the injection site.****]* [Healthy rabbits, not stiff gastrocs as in CP.]

Frick CG, Fink H, Blobner M, Martyn J. 2012. A single injection of botulinum toxin decreases the margin of safety of neurotransmission at local and distant sites. Anesth Analg. 114(1):102-9. *[We tested the hypothesis that a single injection of botulinum toxin not only has local, but also distant effects on muscle function, biochemistry, and pharmacodynamics of atracurium (the same drug). METHODS: Botulinum toxin (2.5 U) was injected into the tibialis muscle of anesthetized rats (n = 26). The contralateral side with no injection served to study distant effects. Control animals (n = 25) received a saline injection. Neuromuscular function, pharmacology, and expression of acetylcholine receptors (nAChRs) were evaluated in the tibialis at 0, 4, and 16 days after injection and in comparison with saline- injected controls. RESULTS: On day 4, botulinum toxin caused complete paralysis of the tibialis, while its contralateral side showed a decrease in absolute twitch tension (1.8 N [1.6; 1.9] vs 3.0 N [2.8; 3.1], Newton, P < 0.05). On day 16, muscle weakness was only present on the toxin-injected side where absolute twitch tension was decreased (0.6 N [0.6, 0.7] vs 3.4 N [3.1, 3.7], P < 0.05). Tibialis mass was decreased on the toxin-injected side at day 4 (1.46 mg/g [1.43, 1.48] vs 1.74 mg/g [1.72; 1.75], P < 0.05) and on day 16 (0.78 mg/g [0.76, 0.79] vs 1.73 mg/g [1.69; 1.77], P < 0.05). Effects distant from the site of injection were seen on day 16, when muscle atrophy was also present in the adjacent gastrocnemius and soleus muscles. Normalized to tibialis mass, specific twitch tension (tension/g muscle) was reduced on the contralateral side at day 4 and on the toxin-injected side at day 16 in relation to saline controls. At day 16, an increased sensitivity to atracurium was seen on the toxin-injected side, evidenced as a decreased ED(50) (0.23 mg/kg [0.13, 0.33] vs 0.72 mg/kg [0.63, 0.82], P < 0.05) and a lower infusion rate (38 µL/kg/min [32, 43] vs135 µL/kg/min [126, 144], P < 0.05), together with a reduced plasma concentration requirement of atracurium (0.5 µg/mL [0.4, 0.7] vs 4.5 µg/mL [3.8, 5.2], P < 0.05) to achieve a steady state 50% reduction in baseline (absolute) twitch tension. ED(50) of atracurium was also decreased on the contralateral side at day 16 in relation to saline controls. The nAChRs in the tibialis were increased on the toxin-injected side to 123 fmol/mg [115, 131] vs 28 fmol/mg [25, 29] (P < 0.05) in time-matched saline-injected controls at day 4 and to 378 [341, 413] vs 27*

fmol/mg [25, 29] (P < 0.05) at day 16. CONCLUSIONS: ***Botulinum toxin has local and distant effects on muscle. The decrease in specific twitch tension indicates that the muscle atrophy alone cannot explain the functional changes; neuromuscular transmission is also impaired.*** *An increased sensitivity to atracurium on the toxin-injected side, despite up-regulation of nAChRs, seems unique to botulinum toxin.]* Healthy animal muscle, not stiff, transformed CP muscle.

Glanzman AM, Kim H, Swaminathan K, Beck T. 2004. Efficacy of botulinum toxin A, serial casting, and combined treatment for spastic equinus: a retrospective analysis. Dev Med Child Neurol. 46(12): 807-811. *[Chart review. 55 patients.. With cast number controlled, change in ROM after casting with and without BTX-A was not significantly different.* ***Casting with or without BTX-A improved ROM to a comparable degree, and to a greater degree than BTX-A alone. Casting demonstrated a significantly more robust impact on range of motion than BTX-A alone****]. No difference in effects? So why add the pain, expense, and risks of Botox?*

Lin JP. 2005. Efficacy of botulinum toxin A, serial casting, and combined treatment for spastic equinus: a retrospective analysis. Dev Med Child Neurol. 47(9):635; author reply 635. A letter to the editor pertaining to Glanzman's study.

Grundy Q, Bero L, Malone R. 2013. Interactions between non-physician clinicians and industry: a systematic review. PLoS Med. 10(11): e1001561.

Gough M, Fairhurst C, Shortland AP. 2005. Botulinum toxin and cerebral palsy: time for reflection? Dev Med Child Neurol. 47: 709–712. *[Botulinum toxin A (BTX-A) is increasingly being used in early management of spasticity in ambulant children with cerebral palsy (CP), with the aim of improving function, promoting muscle growth, and delaying the need for surgical intervention. However,* ***there is a lack of evidence about the long-term outcome of BTX-A injections. The focus on spasticity as the predominant problem in younger children with spastic CP may not fully consider the associated muscle weakness. It also raises concern that although BTX-A may improve function in the short term, it has the potential to affect muscle growth and function adversely in the long term.*** *A cautious approach to the early use of BTX-A, with the use of objective outcome measures within a specialized multidisciplinary setting, is recommended, particularly in ambulant children with spastic diplegic CP, until further evidence is available on the long-term outcome of early BTX-A injections in children with CP.]*

Han N, Kim HD, Eom MJ, et al. 2013. Proteomic changes in rat gastrocnemius muscle after botulinum toxin a injection. Ann Rehabil Med. 37(2):157-66. *[To observe the changes in protein expression induced by botulinum toxin A (BoNT-A) injection and to characterize the molecular and cellular action of mechanisms of BoNT-A injection on skeletal muscles using proteomic elements as biomarkers. METHODS: BoNT-A was injected into left gastrocnemius muscles of 12 Sprague-Dawley rats (2 months of age) at a dosage of 5 units/kg body weight. For the controls the same volume of normal saline was injected to right gastrocnemius muscle of each rat.* ***Muscle samples were obtained at 4 time points (3 rats per time point): 3, 7, 14, and 56 day post-injection.*** *To reveal the alterations in muscle protein, we performed 2-dimensional electrophoresis (2DE) and compared Botox group and normal saline group at each time point. Altered protein spots in 2DE were identified using matrix-assisted laser desorption/ionization-time-of-flight mass spectrometer (MALDI-TOF MS) proteomics analysis. RESULTS: Compared with normal saline group, 46 protein spots showed changed protein expression. Twelve protein spots demonstrated increased volume and 34 protein spots demonstrated decreased volume. Among spots of decreased volume, 17 spots showed statistically significant differences. Thirty-eight identified proteins were associated with alterations in energy metabolism, muscle contractile function, transcription, translation, cell proliferation, and cellular stress response. CONCLUSION:* ***BoNT-A gives influences on muscle contractile function and energy metabolism directly or indirectly besides neurotoxic effects****. Proteomic expression provides better understanding about the effect of BoNT-A on skeletal muscle.]* Healthy animal muscle, not stiff, transformed CP muscle.

Haubruck P, Mannava S, Plate JF, et al. 2012. Botulinum Neurotoxin A injections influence stretching of the gastrocnemius muscle-tendon unit in an animal model. Toxins (Basel). 4(8):605-19 *[This study assessed the influence of (BoNT-A) injections on passive biomechanical properties of the muscle-tendon unit. Mouse gastrocnemius muscle (GC) was injected with BoNT-A (n = 18) or normal saline (n = 18) and passive, non-destructive, in vivo load relaxation experimentation was performed to examine how the muscle-tendon unit behaves after chemical denervation with BoNT-A.* ***Injection of BoNT-A impaired passive muscle recovery (15% vs. 35% recovery to pre-stretching baseline, p < 0.05) and decreased GC stiffness*** *(0.531 ± 0.061 N/mm vs. 0.780 ± 0.037 N/mm, p < 0.05) compared to saline controls. The successful use of BoNT-A injections as an adjunct to physical therapy may be in part attributed to the disruption of the stretch reflex; thereby modulating in vivo passive muscle properties. However, it is* ***also possible that BoNT-A injection may alter the structure of skeletal muscle; thus modulating the in vivo passive biomechanical properties of the muscle-tendon unit****.]* Healthy animal muscle, not stiff, transformed CP muscle.

Hong B, Chen M, Hu XY. 2013. Influence of injection of Chinese botulinum toxin type A on the histomorphology and myosin heavy chain composition of rat gastrocnemius muscles. J Zhejiang Univ Sci B. 14(11):983-92. *[In China, Chinese botulinum toxin type A (CBTX-A), a type of BoNT/A, is in widespread clinical use. However,* ***the changes in the morphological and biochemical properties of treated muscles and in remote muscles from the CBTX-A injection site are relatively unknown.*** *Therefore, we investigated the changes in histomorphology and myosin heavy chain (MyHC) isoform composition and distribution in rat gastrocnemius muscles after intramuscular injection of CBTX-A.* ***METHODS:*** *The weakness of the injected muscles was assessed periodically to identify their functional deficiency.* ***RESULTS:*** *Our findings demonstrate that following injection of CBTX-A 5 U into rat gastrocnemius muscles, shifts in MyHC isoform composition emerged on the third day after injection and peaked in the fourth week.* ***The composition remained distinctly different from that of the control group after the twelfth week. More specifically, there was a decrease in the proportion of the type IIb isoform and an increase in the proportions of type IIx, type IIa, and type I isoforms.*** ***CONCLUSIONS:*** *Data revealed that CBTX-A led to* ***a shift in MyHC composition towards slower isoforms and that the MyHC composition remained far from normal six months after a single injection****. However, no noticeable remote muscle weakness was induced.]* Healthy animal muscle, not stiff, transformed CP muscle.

Kay RM, Rethlefsen SA, Fern-Buneo A, Wren TA, Skaggs DL. 2004. Botulinum toxin as an adjunct to serial casting treatment in children with cerebral palsy. J Bone Joint Surg Am. 86-A(11): 2377-2384. *[CONCLUSION: The present study demonstrates the efficacy of serial casting in the treatment of equinus contractures in children with cerebral palsy who are able to walk.* ***Contrary to our hypothesis, the addition of botulinum toxin A to a serial casting regimen led to earlier recurrence of spasticity, contracture, and equinus during gait. The results of the present study suggest that botulinum toxin combined with serial casting for the treatment of fixed contractures will lead to a recurrence of plantar flexor spasticity and equinus contracture by six months in this patient population.*** *While previous research has indicated that the injection of botulinum toxin A is superior to casting for the treatment of dynamic equinus, the present study suggests that serial casting alone is preferable for the treatment of fixed equinus contractures in children with cerebral palsy.]*

Marchand-Libouban H[1], Le Drévo MA, Chappard D. 2013. **Disuse induced by botulinum toxin affects the bone marrow expression profile of bone genes leading to a rapid bone loss.** J Musculoskelet Neuronal Interact. 13(1):27-36. [Molecular events occurring in the bone marrow microenvironment of an immobilized mouse limb after Botulinum toxin (BTX) injection haven't been characterized. **BTX injection induces a localized disuse in which the tissue events have well been characterized. METHODS:** BTX injection was performed in the right quadriceps; saline injection in the left side was used as control. Mice were sacrificed at 0, 7, 14, 21 and 28 days; tibias were used for microCT analysis; bone marrow from femurs for RT-PCR analysis. **RESULTS:** MicroCT revealed bone loss and microarchitectural damages on the immobilized side as from 7d; cortical area tended to be lower on the immobilized limb at 28d. Gene expression of formation factors was altered as from 7 days post-BTX: alkaline phosphatase, Tgfβ1, Lrp5, Sfrp2. Only Sfrp2 and Lrp5 were maintained altered until 28d. Expression of Dkk1 increased from 21d and represented a late inhibitor of formation. Gene expression of resorption markers increased as from 7d (Rankl, Tracp, Il1α, Il1β and Il6) and was maintained until 28d for Tracp and Il6. **CONCLUSION: A localized disuse induces rapid modifications in the bone marrow gene expression leading to bone loss due to an early decrease of formation associated with an increase in resorption**.] Healthy animal muscle, not stiff, transformed CP muscle.

Matak I, Riederer P, Lacković Z. 2012. Botulinum toxin's axonal transport from periphery to the spinal cord. Neurochem Int.; 61(2): 236-9. *[Axonal transport of enzymatically active botulinum toxin A (BTX-A) from periphery to the CNS has been described in facial and trigeminal nerve, leading to cleavage of synaptosomal-associated protein 25 (SNAP-25) in central nuclei. Aim of present study was to examine the existence of axonal transport of peripherally applied BTX-A to spinal cord via sciatic nerve. We employed BTX-A-cleaved SNAP-25 immunohistochemistry of lumbar spinal cord after intramuscular and subcutaneous hind limb injections, and intraneural BTX-A sciatic nerve injections. Truncated SNAP-25 in ipsilateral spinal cord ventral horns and dorsal horns appeared after single peripheral BTX-A administrations, even at low intramuscular dose applied (5 U/kg). Cleaved SNAP-25 appearance in the spinal cord after BTX-A injection into the sciatic nerve was prevented by proximal intrasciatic injection of colchicine (5 mM, 2 µl). Cleaved SNAP-25 in ventral horn, using choline-acetyltransferase (ChAT) double labeling, was localized within cholinergic neurons. These results extend the recent findings on BTX-A retrograde axonal transport in facial and trigeminal nerve.* ***Appearance of truncated SNAP-25 in spinal cord following low-dose peripheral BTX-A suggest that the axonal transport of BTX-A occurs commonly following peripheral application****.]* So BTX migrates out of the injected muscle to the spinal cord…

Minamoto VB, Suzuki KP, Bremner SN, Lieber RL, Ward SR. 2015. Dramatic changes in muscle contractile and structural properties after 2 botulinum toxin injections. Muscle Nerve. 52(4):649-57. ***[****Botulinum toxin is frequently administered serially to maintain therapeutic muscle paralysis, but the effect of repeated doses on muscle function are largely unknown. This study characterized the muscle response to 2 onabotulinum toxin (BoNT) injections separated by 3 months.* ***METHODS:*** *Animal subjects received a single toxin injection (n = 8), 2 BoNT injections separated by 3 months (n = 14), or 1 BoNT and 1 saline injection separated by 3 months (n = 8).* ***RESULTS: The functional effect of 2 serial injections was exponentially greater than the effect of a single injection. While both groups treated with a single BoNT injection had decreased torque in the injected leg by approximately 50% relative to contralateral legs, the double BoNT injected group had decreased torque by over 95% relative to the preinjection level. Both single and double BoNT injections produced clear signs of fiber-type grouping. CONCLUSIONS:*** *These experiments demonstrate a disproportionately greater effect of repeated BoNT injections.]* Healthy animal muscle, not stiff, transformed CP muscle.

Minamoto VB[1], Hulst JB, Lim M, et al. 2007. **Increased efficacy and decreased systemic-effects of botulinum toxin A injection after active or passive muscle manipulation.** Dev Med Child Neurol. 49(12):907-14. *[The effect of physical manipulation on the outcome of neurotoxin (NT) injection was studied in a rat tibialis anterior (TA) model system where dorsiflexion torque could be measured precisely. After determination of initial torque, all rats received a one-time botulinum toxin A (BTX-A) injection (dose 6.0 units/kg in a volume of 100 microL) into the TA midbelly. Four experimental groups were studied: one group was subjected to BTX-A injection alone (BTX-A only, n=8), one was subjected to BTX-A injection followed immediately by 10 isometric contractions (ISO; n=9), and the third was subjected to BTX-A followed immediately by 10 muscle passive stretch/release cycles (PS; n=10). After 1 month, maximum dorsiflexion torque of the injected and contralateral legs was determined followed by quantification of TA fiber area. Post-injection torque was significantly reduced by around 80% in all NT-treated extremities 1 month after injection (p<0.05). While all NT-treated extremities demonstrated a significant torque decrease relative to their pre-injection levels, ISO and PS groups demonstrated significantly lower torques compared with the BTX-A only group which received no physical manipulation (p<0.05) indicating greater efficacy. Perhaps even more surprising was that the ISO and PS groups both demonstrated a significantly smaller contralateral effect compared with the BTX-A only group that received no manipulation (p<0.05) indicating a decreased* ***systemic-effect.*** *Muscle fiber size generally correlated with dorsiflexion torque. These data demonstrate that both neuromuscular activity (seen in the ISO group) and muscle movement (seen in the PS group) increased the efficacy of BTX-A and decreased the systemic side effects.]* **Systemic effects…??? So it leaks out of the injected muscle.** Healthy animal muscle, not stiff, transformed CP muscle.

Mohamed KA, Moore AP, Rosenbaum L. Adverse events following repeated injections with Botulinum toxin A in children with spasticity. Dev Med Child Neurol 2001; 43: 791–2. ***Awful details of adverse episodes and still thinks it is safe.***

Naidu K, Smith K, Sheedy M, Adair B, Yu X, Graham HK. 2010. Systemic adverse events following botulinum toxin A therapy in children with cerebral palsy. Dev Med Child Neurol. 52(2):139-44. *[We studied the incidence of* ***incontinence and respiratory events*** *in children with cerebral palsy who received injections of botulinum toxin A (BoNT-A). METHOD: We used multivariable logistic regression to investigate relationships between (BoNT-A) dose, Gross Motor Function Classification System (GMFCS) level, and the incidence of bladder or bowel incontinence, unplanned hospital admission, emergency department consultation or prescription of antibiotics for respiratory symptoms, and diagnosis of upper respiratory tract infection. RESULTS: Of 1980 injection episodes in 1147 children (mean age 4y 7mo, SD 1y 10mo, range 9mo-23y), 488 (25%) were in children with unilateral involvement and 1492 (75%) in children with bilateral involvement. At the time of injection 440 (22.2%) of children were at GMFCS level I, 611 (30.9%) were at level II, 330 (16.7%) were at level III, 349 (17.6%) were at level IV, and 250 (12.6%) were at level V. The incidence of serious adverse events was low, with* ***19 episodes of incontinence (1% of injection episodes) and 25 unplanned hospital admissions due to respiratory symptoms (1.3%).*** *Incontinence typically resolved spontaneously 1 to 6 weeks after injection. The incidence of adverse events was associated with GMFCS level and dose of BoNT-A. INTERPRETATION: The incidence of serious adverse events was low but suggests systemic spread as well as a procedural effect. We recommend reviewing upper dose limits for children at all GMFCS levels, particularly those at levels IV and V with a history of aspiration and respiratory disease. In these children, alternatives to mask anaesthesia may be particularly important.]*

Moon YM, Kim YJ, Kim MK, et al. 2015. Early effect of Botox-A injection into the masseter muscle of rats: functional and histological evaluation. Maxillofac Plast Reconstr Surg. 37(1):46. **[Reduced muscle volume persisted after recovery of use.]** Healthy animal muscle, not stiff, transformed CP muscle.

Naumann M, Albanese A, Heinen F, Molenaers G, Relja M. 2006. Safety and efficacy of botulinum toxin type A following long-term use. Eur J Neurol 2006; 13: 35–40. *[Botulinum toxin serotype A (BoNT-A) has long heritage of use leading to confidence in its safety and efficacy. The application of BoNT-A does not lead to persistent histological changes in the nerve terminal or the target muscle. Clinical trials defined the safety and tolerability profile of BoNT-A across common therapeutic indications and* ***showed an incidence of adverse events of approximately 25% in the BoNT-A-treated group compared with 15% in the control group. Focal weakness was the only adverse event to occur more often following BoNT-A treatment.]*** Since when is weakness OK?

Omprakash Hm, Rajendran Sc. 2008. Botulinum Toxin Deaths: What is the Fact? J Cutan Aesthet Surg. 1(2): 95-7. ***Not much info on CP uses.***

Papavasiliou AS, Nikaina I, Foska K, Bouros P, Mitsou G, Filiopoulos C. 2013. Safety of botulinum toxin A in children and adolescents with cerebral palsy in a pragmatic setting. Toxins (Basel). 5(3):524-36. *[This retrospective study aimed to examine the safety of botulinum toxin A (BoNT-A) treatment in a paediatric multidisciplinary cerebral palsy clinic. In a sample of 454 patients who had 1515 BoNT-A sessions, data on adverse events were available in* ***356 patients and 1382 sessions; 51 non-fatal adverse events were reported (3.3% of the total injections number, 8.7% of the patients).*** *On five occasions, the adverse reactions observed in GMFCS V children were attributed to the sedation used (rectal midazolam plus pethidine; buccal midazolam) and resulted in prolongation of hospitalization.* ***Of the reactions attributed to the toxin, 23 involved an excessive reduction of the muscle tone either of the injected limb(s) or generalized; others included local pain, restlessness, lethargy with pallor, disturbance in swallowing and speech production, seizures, strabismus, excessive sweating, constipation, vomiting, a flu-like syndrome and emerging hypertonus in adjacent muscles.*** *Their incidence was associated with GMFCS level and with the presence of epilepsy (Odds ratio (OR) = 2.74 - p = 0.016 and OR = 2.35 - p = 0.046, respectively) but not with BoNT-A dose (either total or per kilogram). In conclusion, treatment with BoNT-A was safe; adverse reactions were mostly mild even for severely affected patients. Their appearance did not necessitate major changes in our practice.]*

Park C, Park K, Kim J. 2015. Growth effects of botulinum toxin type A injected unilaterally into the masseter muscle of developing rats. J Zhejiang Univ Sci B. 16(1):46-51. *[AIM: To evaluate the effects of botulinum toxin type A (BTX-A) on mandible skeletal development by inducing muscle hypofunction.* ***METHODS:*** *Four-week-old Sprague-Dawley rats (n=60) were divided into three groups: Group 1 animals served as controls and were injected with saline; Group 2 animals were injected unilaterally with BTX-A (the contralateral side was injected with saline); and Group 3 animals were injected bilaterally with BTX-A. In Group 2, the saline-injected side was designated the control side (Group 2-1), whereas the BTX-A-injected side was designated the experimental side (Group 2-2). After four weeks, the animals were sacrificed, dry skulls were prepared, and mandibles were measured.* ***RESULTS:*** *In the unilateral group,* ***the experimental side (Group 2-2) had reduced dimensions for all mandible measurements compared with the control side (Group 2-1), suggesting a local effect of BTX-A on mandible growth, likely due to muscle reduction****.]* Healthy animal muscle, not stiff, transformed CP muscle.

Park ES, Sim E, Rha DW, Jung S. 2014. Architectural changes of the gastrocnemius muscle after botulinum toxin type a injection in children with cerebral palsy. Yonsei Med J. 55(5):1406-12. *[Thirteen children with CP who received a BoNT-A injection into their GCM to treat equinus were recruited (9 males and 4 females). Architectural changes in both the medial and lateral heads of the GCM from a total of 20 legs were assessed using B-mode, real-time US. Muscle thickness (MT), fascicle length (FL), and fascicle angle (FA) were measured over the middle of the muscle belly in both a resting and neutral ankle position. Measures at 1 and 3 months after the injection were compared with baseline data taken before the injection. RESULTS: The mean age of the subjects was 5.8 (±1.6) years….****The MT and FA of both the medial and lateral heads of the GCM were significantly reduced for both neutral and resting ankle positions at 1 and 3 months after the injection.*** *The FL of both the medial and lateral heads of the GCM were significantly increased in a resting position (p<0.05), but not in a neutral position.]*

Pin TW, Elmasry J, Lewis J. 2013. Efficacy of botulinum toxin A in children with cerebral palsy in Gross Motor Function Classification System levels IV and V: a systematic review. Dev Med Child Neurol. 55(4):304-13. *[AIM: Previous studies have shown the efficacy of botulinum toxin type A (BoNT-A) in the management of ambulant individuals with cerebral palsy (CP). There is little evidence on its use in non-ambulant children with CP. This review aimed to investigate indications and efficacy for BoNT-A use in managing pain, care, and comfort, and improving function in children with CP in Gross Motor Function Classification System (GMFCS) levels IV and V.* ***METHOD:*** *Electronic databases were searched from the earliest available date to June 2012 using a combination of subject headings and free text. Inclusion criteria consisted of studies with (1) participants aged 18 or under, (2) participants with CP in GMFCS levels IV and V, (3) participants receiving BoNT-A treatment, and (4) studies published in English-language peer-reviewed journals.* ***RESULTS:*** *The search resulted in a total of 814 studies, of which 19 met the inclusion criteria. Eighteen studies provided level IV or V evidence and one level I evidence according to the American Academy for Cerebral Palsy and Developmental Medicine guidelines for the development of systematic reviews. Most of the studies were of weak to moderate methodological quality.* ***INTERPRETATION:*** *The evidence that BoNT-A is effective in reducing postoperative pain in children with CP in GMCFS levels IV and V is limited, with only one level I study identified. Remaining indications were general pain reduction, maintaining hip integrity, achieving functional changes, and goal attainment. A high percentage of participants in the studies showed positive changes in these areas.* ***With the poor level of evidence of the included studies, no definite conclusion could be drawn on the indications for BoNT-A use in children with CP in GMCFS levels IV and V. Further investigation by rigorous studies is required****.]* **Free Article**

Ramirez-Castaneda J, Jankovic J, Comella C, et al. 2013. Diffusion, spread, and migration of botulinum toxin. Mov Disord. 28(13): 1775-83. *[The efficacy and safety of BoNT depends on accurate selection and identification of intended targets but also may be determined by other factors, including physical spread of the molecule from the injection site, passive diffusion, and migration to distal sites via axonal or hematogenous transport. The passive kinetic dispersion of the toxin away from the injection site in a gradient-dependent manner may also play a role in toxin spread. In addition to unique properties of the various BoNT products, volume and dilution may also influence local and systemic distribution of BoNT.* ***Most of the local and remote complications of BoNT injections are thought to be due to unwanted spread or diffusion of the toxin's biologic activity into adjacent and distal muscles.*** *Despite widespread therapeutic and cosmetic use of BoNT over more than three decades,* ***there is a remarkable paucity of published data on the mechanisms of distribution and its effects on clinical outcomes.****]*

Ryll U, Bastiaenen C, De bie R, Stall B. 2011. Effects of leg muscle botulinum toxin A injections on walking in children with spasticity-related cerebral palsy: a systematic review. Dev Med Child Neurol. 53(3): 210-216. Review. *[Eight trials were included. Trials comparing BoNT-A plus usual care or physiotherapy versus usual care or physiotherapy alone showed moderate evidence for functional outcomes at 2 to 6, 12, and 24 weeks follow-up in favour of BoNT-A.* ***Studies comparing BoNT-A versus casting showed strong evidence for no difference in effects between these interventions.*** *A limitation of our review was the exclusion of studies not published in English, Dutch, or German. The heterogeneity of the included studies, especially for outcome measures and follow-up assessments, prompted us to refrain from statistical*

pooling, which might also be considered a limitation. INTERPRETATION: The use of BoNT-A with usual care or physiotherapy seems to improve walking of children with CP, but ***results should be appraised carefully owing to the limited quality of included trials.]***

Shoemaker CB, Oyler GA. 2013. Persistence of Botulinum neurotoxin inactivation of nerve function. Curr Top Microbiol Immunol. 364:179-196. *[The* ***extraordinary persistence of intoxication occurring after exposure to some Botulinum neurotoxin (BoNT)*** *serotypes is both a therapeutic marvel and* ***a biodefense nightmare.*** *Understanding the mechanisms underlying BoNT persistence will offer new strategies for improving the efficacy and extending the applications of BoNT therapeutic agents* ***as well as for treating the symptoms of botulism****. Research indicates that the persistence of BoNT intoxication can be influenced both by the ability of the toxin protease or its cleaved soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein substrate to resist turnover. Protease turnover seems to be mediated in part by the ubiquitin-proteasome system (UPS) and efforts to manipulate the UPS may prove to be an effective strategy for improving therapeutic utility of BoNT products and in the development of botulism antidotes.]*

Schroeder AS, Ertl-Wagner B, Britsch S, et al. 2009. Muscle biopsy substantiates long-term MRI alterations one year after a single dose of botulinum toxin injected into the lateral gastrocnemius muscle of healthy volunteers. Movement disorders.24(10):1494-503.*[Despite numerous clinical and experimental studies on botulinum toxin type A (BoNT/A), long-term alterations of muscle texture and fine structure following BoNT/A treatment have thus far not been studied in normal human skeletal muscle. After obtaining institutional review board approval, we performed a prospective, placebo-controlled, double-blinded follow-up study on* ***two healthy adults*** *using magnetic resonance imaging (MRI) and muscle biopsy to visualize long-term alterations after a single BoNT/A injection into the lateral head of the gastrocnemius muscle. MRI disclosed a high-signal-intensity pattern in short tau inversion recovery sequences, and a reduction of the cross-sectional area in the BoNT/A-injected, but not in the saline-injected contralateral control muscle (at 6 to 9 months in volunteer A: 73%, in B: 62%; at 12 months in A: 88%, and in B: 78%).* ***Enzyme histochemistry, 12 months after injection, confirmed neurogenic atrophy of muscle fibers only in the BoNT/A-injected muscle. Electron microscopy revealed additional degenerative changes at the neuromuscular junction. The*** *data confirm that MRI is a suitable tool to monitor the long-term effect of BoNT/A on skeletal muscle.* ***Neurogenic muscle atrophy following a single BoNT/A injection should be taken into consideration when repeated BoNT/A injections into the same muscles are proposed****.]*

Seehusen DA, Koren KG .2013. Impact of industry sponsorship on research outcomes**.** Am Fam Physician. 88(11):746.

Sheean GL. 2001. Botulinum treatment of spasticity: why is it so difficult to show a functional benefit? Curr Opin Neurol. 14(6):771-6.

Simpson DM, Blitzer A, Brashear A, et al. 2008. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurol. 70(19): 1699-1706*. [RECOMMENDATIONS: Botulinum neurotoxin should be offered as a treatment option for the treatment of cervical dystonia (Level A), may be offered for blepharospasm, focal upper extremity dystonia, adductor laryngeal dystonia, and upper extremity essential tremor (Level B), and may be considered for hemifacial spasm, focal lower limb dystonia, and motor tics (Level C). While clinicians' practice may suggest stronger recommendations in some of these indications,* ***evidence-based conclusions are limited by the availability of data.]***

Simpson DM, Gracies JM, Graham K, et al. 2009. Assessment: botulinum neurotoxin for the treatment of spasticity (an evidence-based review). Neurol. 73(9):736-7; author reply 737-738. ***Authors admit affiliation with Allergan, do not investigate studies of physiologic change or strength loss in muscle tissue.*** Wow.

Sung Sung KH, Chung CY, Lee KM, et al. 2013. Conflict of interest in the assessment of botulinum toxin A injections in patients with cerebral palsy: a systematic review. *J Pediatr Orthop.* 33(5):494-500. *[****Fifteen (53.6%) of the 28 industry-sponsored studies had favorable conclusions, whereas only 5 (20%) of the 25 non-industry-sponsored studies had favorable conclusions. The efficacy of using botulinum toxin A injections in cerebral palsy (CP) is controversial.*** *The financial conflict of interest related to medical research can affect the conclusion of an evidence-based review. This study was performed to determine as to what proportion of studies on botulinum toxin A injections in patients with CP was sponsored by the industry and whether the assessments of botulinum toxin injection in CP were associated with industry support. METHODS: Studies were identified with a search of the PubMed database (January 1991 to November 2011). All prospective, comparative, English language studies on the use of botulinum toxin A injections in patients with CP were included. A total of 374 articles were screened, 128 potentially eligible full articles were retrieved, and 66 studies met our inclusion criteria. The funding sources of the articles were reviewed, and qualitative conclusions regarding the effect of botulinum toxin A injection were classified as being either favorable, neutral, or unfavorable. RESULTS: Of 66 eligible articles, 28 were funded by the industry, and 25 were not. The other 13 studies did not include information on the funding source. A significant association was observed between the funding source and qualitative conclusions (P=0.042). Fifteen (53.6%) of the 28 industry-sponsored studies had favorable conclusions, whereas only 5 (20%) of the 25 non-industry-sponsored studies had favorable conclusions. CONCLUSIONS: About half of studies on the effect of botulinum toxin A in CP were sponsored by the industry. This systematic review revealed that the qualitative conclusions in those studies are more favorable to the use of the botulinum toxin A than the non-industry-sponsored studies.* ***Clinicians should be aware of an industry-related conflict of interest regarding reports on the efficacy of botulinum toxin A injections in patients with CP.]***

Tedroff K, Granath F, Forssberg H, Haglund-Akerlind Y. 2009. Long-term effects of botulinum toxin A in children with cerebral palsy. Dev Med Child Neurol. 51(2): 120-127. *[The long-term effects of botulinum toxin A (BoNT-A) treatment in children with cerebral palsy (CP) are still elusive. We studied a prospective clinical cohort of 94 children with different subtypes (50% spastic diplegic CP, 22% hemiplegic CP, 25% tetraplegic CP, 3% dyskinetic CP), sex (55% male, 45% female), severity according to Gross Motor Function Classification System (29% Level I, 15% Level II, 16% Level III, 17% Level IV, 23% Level V), and age (median 5y 4mo, range 11mo-17y 8mo). The longest follow-up time was 3 years 7 months (median 1y 6mo) and included a maximum of eight injections per muscle (median two injections to a specific muscle). Outcome measurements were muscle tone (Modified Ashworth Scale) and joint range of motion (ROM). Assessments were made at a minimum before and 3 months after each injection. Ninety-five per cent confidence intervals for differences from baseline were used to identify significant changes. BoNT-A injections induced reduction of long-term spasticity in all muscle-groups examined: the gastrocnemius, hamstring, and adductor muscles. The reduction in tone was most distinct in the gastrocnemius muscle, and each repeated injection produced an immediate reduction in muscle tone. However, improvement in ROM was brief and measured only after the first injections, whereupon the ROM declined. Thus,* ***the results suggest that BoNT-A*** *can be effective in reducing muscle tone over a longer period, but* ***not in preventing development of contractures in spastic muscles.*** *The dissociation between the effects on muscle tone and ROM indicates that development of contractures is not coupled to increased muscle tone only, but might be caused by other mechanisms.]*

Tsai SW, Tung YT, Chen HL, et al. 2016. Myostatin propeptide gene delivery by gene gun ameliorates muscle atrophy in a rat model of botulinum toxin-induced nerve denervation. Life Sci. pii: S0024-3205(15)30147-8. [Epub ahead of print] *[****Muscle atrophy is a common***

symptom after nerve denervation. *Myostatin propeptide, a precursor of myostatin, has been documented to improve muscle growth. However, the mechanism underlying the muscle atrophy attenuation effects of myostatin propeptide in muscles and the changes in gene expression are not well established. We investigated the possible underlying mechanisms associated with myostatin propeptide gene delivery by gene gun in a rat denervation muscle atrophy model, and evaluated gene expression patterns.* ***MAIN METHODS:*** *In a rat botulinum toxin-induced nerve denervation muscle atrophy model, we evaluated the effects of wild-type (MSPP) and mutant-type (MSPPD75A) of myostatin propeptide gene delivery, and observed changes in gene activation associated with the neuromuscular junction, muscle and nerve.* ***KEY FINDINGS:*** *Muscle mass and muscle fiber size was moderately increased in myostatin propeptide treated muscles ($p<0.05$). And enhancement of the gene expression of the muscle regulatory factors, neurite outgrowth factors (IGF-1, GAP43) and acetylcholine receptors was observed. Our results demonstrate that myostatin propeptide gene delivery, especially the mutant-type of MSPPD75A, attenuates muscle atrophy through myogenic regulatory factors and acetylcholine receptor regulation.* ***SIGNIFICANCE:*** *Our data concluded that myostatin propeptide gene therapy may be a promising treatment for nerve denervation induced muscle atrophy.]* Healthy animal muscle, not stiff, transformed CP muscle. **So, until then, we'll see muscle more atrophy following BTX injection into CP gastrocs...**

Tsai FC[1], Hsieh MS, Chou CM. 2010. Comparison between neurectomy and botulinum toxin A injection for denervated skeletal muscle. J Neurotrauma. 27(8):1509-16. *[****Neurectomy and botulinum toxin A (BoNT-A) injection cause denervated muscle atrophy,*** *but questions remain about their clinical utility. We investigated time-series alterations of rat muscle weight, functional deficits, signaling pathways, and microscopic structures, to gain an understanding of the clinical implications. Between 2008 and 2009, the maximal calf circumference of patients for calf reduction either by neurectomy or BoNT-A injections were recorded for study. A rat skeletal muscle model was established through repeated or dose-adjusted BoNT-A injections and neurectomy. The survival, apoptosis (natural cell death) pathways, functional deficits, and microscopic structures were investigated using Western blot, sciatic functional index (SFI), and transmission electron microscopy (TEM), respectively.* ***The rat muscle weight ratio of the BoNT-A group had recovered to 89.3 +/- 3.8% by week 58, but it never recovered in the neurectomy group. Muscle weight reduction by BoNT-A not only depended on the dose, but additive effects were also obtained through repeated injections.*** *Rat SFI demonstrated rapid recovery in both groups. Molecular expressions showed a coherent and biphasic pattern. p-Akt and apoptosis-inducing factor (AIF) were upregulated significantly, with a peak at 8 weeks in the neurectomy group ($p < 0.01$), but cleaved caspase-9 and caspase-3 showed no significant changes in either group.* ***TEM findings showed irreversible and reversible inner-structure disruption and sarcomere discontinuity in the neurectomy and BoNT-A groups, respectively****. We demonstrated that* ***denervation induced lasting muscle weight and structural changes of different degrees.*** *Muscle weight reduction by BoNT-A was related to frequency and dose. AIF-mediated caspase-independent apoptosis was significantly different for neurectomy and BoNT-A injection.]* Healthy animal muscle, not stiff, transformed CP muscle.

Wasiak J, Hoare B, Wallen M. 2004. Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy. Cochrane Database Syst Rev. 4:CD003469. *[SELECTION CRITERIA: All randomised controlled trials (RCTs) comparing intramuscular BtA injections into any muscle group of the upper limb with placebo, no treatment or other interventions.DATA COLLECTION AND ANALYSIS: Two authors using standardised forms extracted the data independently. Each trial was assessed for internal validity with differences resolved by discussion. Data was extracted and entered into RevMan 4.2.3.MAIN RESULTS: Two trials met the inclusion criteria, each having short-term follow up, a small number of subjects and using a single set of injections. The study by Corry 1997 compared BtA with an injection of normal saline and found promising results in elbow extension, elbow and wrist muscle tone. At three months, encouraging results for wrist muscle tone and grasp and release were noted. The trial reported median change, range of changes and the difference in these measures between groups. The study by Fehlings 2000 compared BtA with no intervention. When data were analysed no treatment effect was found for quality of upper limb function, passive range of motion, muscle tone, grip strength or self-care ability.* ***REVIEWERS' CONCLUSIONS: This systematic review has not found sufficient evidence to support or refute the use of intramuscular injections of BtA as an adjunct to managing the upper limb in children with spastic cerebral palsy. Only one of the two identified RCTs reported some promising results in support of reduced muscle tone following BtA injections. Further research incorporating larger sample sizes, rigorous methodology, measurement of upper limb function and functional outcomes is essential.*** *]*

Williams SA, Reid S, Elliott C, Shipman P, Valentine J. 2013. Muscle volume alterations in spastic muscles immediately following botulinum toxin type-A treatment in children with cerebral palsy. Dev Med Child Neurol. 55(9):813-20. *[METHOD: Fifteen children (10 males, five females; age range 5-11y, mean age 8y 5mo, SD 1y 10mo) with spastic diplegic CP [Gross Motor Function Classification System Levels I (n=9) and II (n=6)] receiving BoNT-A injections for spasticity management were included.* ***None of the children was a first-time receiver of BoNT-A.*** *Magnetic resonance imaging and Mimics software assessed muscle volume, timed 2 weeks before and 5 weeks after injection. All participants received BoNT-A bilaterally to the gastrocnemius muscle, and five participants also received BoNT-A bilaterally to the medial hamstring muscles. Functional assessment measures used were the 6-Minute Walk Test (6-MWT), the Timed Up and Go (TUG) test, and hand-held dynamometry.* ***RESULTS:*** *Whilst total muscle group volume of the injected muscle group remained unchanged, a* ***4.47% decrease in the injected gastrocnemius muscle volume*** *($p=0.01$) and* ***a 3.96% increase in soleus muscle volume ($p=0.02$) was evident following BoNT-A.*** *There were no statistically significant changes in function after BoNT-A as assessed by the TUG. There was also no statistically significant change in distance covered in the 6-MWT. Muscle strength, as assessed using hand-held dynamometry was also not statistically different after BoNT-A treatment.* ***INTERPRETATION:*** *Muscle volume decreases were observed in the injected muscle (gastrocnemius), with synergistic muscle hypertrophy that appeared to compensate for this decrement. The 4% to 5% decrease in the volume of BoNT-A injected muscles are not dramatic in comparison to reports in recent animal studies, and are a positive indication for BoNT-A, particularly as it also did not negatively alter function.]* **They were all already weakened by earlier BTX injections! So they were equally week 5 weeks after this one?**

Willoughby K, Ang SG, Thomason P, Graham HK. 2012. The impact of botulinum toxin A and abduction bracing on long-term hip development in children with cerebral palsy. Dev Med Child Neurol. 54(8):743-7. *[RESULTS: Forty-six children with bilateral spastic CP (31 males, 15 females; 10 with diplegia, 36 with quadriplegia; mean age at enrolment of 3 y 2 mo, mean age at most recent clinical review 13 y 11 mo [range 10 y 6 mo-16 y 8 mo]; three children in Gross Motor Function Classification System level II, 11 in level III, 20 in level IV, 12 in level V) were followed for a mean of 10 years 10 months from recruitment to the trial. Mean migration percentage was 15.9% in the BoNT-A group and 15.2% in the comparison group ($t = 0.26$, $p = 0.79$). Eighty-nine percent of hips in the treatment group and 91% hips in the comparison group had satisfactory development, using a valid scale (Mann-Whitney U test = 867.50, $z = -1.59$, $p = 0.11$). Forty children had preventive surgery (21 treatment group, 19 comparison group) and 18 children had reconstructive surgery (10 treatment, 8 comparison). INTERPRETATION:* ***In children with bilateral spastic CP, early treatment with BoNT-A and hip abduction bracing does not reduce the need for surgery or improve hip development at skeletal maturity.]***