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Title:
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Date:
2021-05-01

Citation:
Graham, K. (2021). Clinical trials of botulinum neurotoxin A: is there a link between funding, pharma, and findings?. Developmental Medicine and Child Neurology, 63 (5), pp.499-. https://doi.org/10.1111/dmcn.14836.

Persistent Link:
https://hdl.handle.net/11343/298207

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Article type : Commentary

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Clinical trials of botulinum neurotoxin A: is there a link between funding, pharma, and findings?

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doi: 10.1111/dmcn.

This commentary is on the original article by Delgado et al. To view this paper visit https://doi.org/10.1111/dmcn.

Should *Developmental Medicine & Child Neurology* publish research funded by the drug industry? This is a highly controversial issue and journals such as the *British Medical Journal* have considered refusing to publish pharma-sponsored research.[1] Clinical trials of botulinum neurotoxin A (BoNT-A) funded by the drug industry are much more likely than publicly funded trials to produce results favourable to the company.[1,2] Would publishing pharma-sponsored studies increase the risk of further distorting the evidence base?[1–3] How does the study by Delgado et al., sponsored by Ipsen, measure up against this background?[4]

Children with upper-limb spasticity secondary to cerebral palsy were randomized to one of three doses of BoNT-A, combined with ‘a personalized, goal-oriented home-exercise

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/DMCN.14836

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therapy program (HETP)'.[4] The doses are intriguing: 2U/kg, 8U/kg, or 16U/kg. According to Ipsen's product information, and in accord with my experience of using this drug, 2U/kg is clearly a subtherapeutic dose and is described by the authors as a control.[4] The authors found there was a significant reduction in modified Ashworth scale (MAS) scores in the 2U/kg (control) group, which was unexpected. Even more startling was the finding that there were no significant differences in functional outcomes (Physician Global Assessment [PGA] and goal attainment scaling [GAS]) between the three groups. The authors explain these findings on the ability of HETP to reduce muscle tone. Perhaps a more plausible explanation is limitations in informed consent and in the outcome measures. Participants in all three groups were told that they would receive an injection of BoNT-A and expected an improvement. The researchers found an improvement. However, this raises questions regarding the process of informed consent, the fidelity of the outcome measures, and blinding.[5] A dose of 2U/kg is subtherapeutic and should have resulted in no measurable effects.[4,5]

Because of the mounting evidence of muscle atrophy and fibrosis in the injected muscle, current recommendations are to use the lowest possible dose of BoNT-A, as infrequently as possible.[5] Given that a dose of 2U/kg plus HETP was as effective for function as the therapeutic doses, this should logically be the preferred dose.[4] I suggest the authors (and Ipsen) change their protocols in the light of these findings.

This study seems to serve the regulators and Ipsen better than researchers and clinicians, as a result of the choice of outcome measures. The primary outcome measure was the MAS, despite its documented shortcomings.[5] The secondary (functional) outcome measures were also psychometrically weak (PGA and GAS).[1–3] None are objective or verifiable. Superior outcome measures are available but were not used.[5]

MAS is a classic surrogate outcome measure and is not very meaningful.[3] Over the last 25 years, studies have shown that BoNT-A reduces MAS scores and replication of this finding is redundant.[5] Pharmaceutical companies choose outcome measures which will showcase their drug in the best light and give the best return on investment.[1,3] These goals are very different from the goals of researchers who want to advance the field beyond where we were 25 years ago. The key question is, are the functional benefits worth the harm to the injected muscle?[5] In my opinion, this study fails to provide the answer.

In conclusion, weighing benefits and drawbacks, the best intervention for clinicians to improve function in children with upper-limb spasticity is 2U/kg plus HETP.[4,5] Researchers should embrace the opportunity to address the evidence gap by designing a study in which a dose of 2U/kg of abobotulinumtoxinA is compared to the outcomes of HETP alone.

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Importantly, journals such as *DMCN* should continue to examine the pros and cons of publishing pharma-sponsored research.[1–3]

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