PEER REVIEW HISTORY

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors influencing response to Botulinum toxin type A in patients with idiopathic cervical dystonia: Results from an international, observational study
AUTHORS	Vijay P. Misra, Edvard Ehler, Benjamin Zakine, Pascal Maisonobe and Marion Simonetta-Moreau on behalf of the INTEREST IN CD group

VERSION 1 – REVIEW

REVIEWER	Carlo Colosimo, MD Sapienza University, Rome, Italy I have no competing interests
REVIEW RETURNED	19/02/2012

GENERAL COMMENTS	Ms. by Misra et al., *BMJ Open* This is a large (n=404) international, prospective, study on the factors influencing response to Botulinum toxin type A (BoNT-A) in patients with idiopathic cervical dystonia (CD): This study may be categorized in the group of *Pragmatic trials,* i.e those which are directed at evaluating the effectiveness of a given drug (or intervention) in real life. This is particularly crucial in botulinum toxin therapy for focal dystonia, given the peculiarity of this type of treatment which needs to be very flexible, both in terms of dose and muscles to be injected. Results are largely confirmatory of previous regulatory studies in smaller cohorts: most patients with CD respond favourably to BoNT-A, which is also well-tolerated. A novel finding of this study is that the duration of the clinical effect is probably less than 3 months in most of the CD cases. The paper is well-written and documented. However, I have some remarks: - First paragraph of the introduction: 1) epidemiological data: I suggest keeping only the prevalence figure from the North-American study, since the ESDE study was strongly biased methodologically and possibly under-reported the frequency of dystonia in Europe. 2) The classification of dystonia in primary or secondary is one point, and the co-occurrence of dystonia with other movement disorders is another issue, not necessarily inter-related. - In the introduction, page 5, line 29: in my opinion the main reason for starting a trial as this one is the need to confirm the effectiveness of BoNT-A treatment in the real life, without the constriction in term of doses and muscles to be injected (which were almost always predetermined in all previous regulatory trials). The issue of the scale used for evaluating its effectiveness (TWSTRS, Tsui or others) is probably less relevant

	- Study population: it was reasonable to exclude secondary cases of CD in order to have a homogeneous population to study. However it is not true that secondary cases do not respond to BoNT-A (e.g iatrogenic cases or cases associated with Parkinson's disease may respond well to this treatment). - Injection scheme: Not only median dose, but also the ranges used for the various brands of the toxin should be stated. In addition, can the authors give the mean dose and ranges also for Xeomin (despite the low number of patients treated with this brand)? - Discussion: 1) page 15, line 11...real-life data on response to BoNT-A in CD are sparse...this is a little bit generic. Can the authors comment more in detail about studies similar to the present one, if published? 2) On page 16, lines 29-37: this paragraph is mainly a repetition of what already stated in the previous page. - On Table 1, predominant component: it is unclear to me how to differentiate tremor from *jerk*?

REVIEWER	Shyamal Mehta MD, PhD Assistant Professor, Movement Disorders Department of Neurology Georgia Health Sciences University Augusta, GA 30912 USA Disclosure: consulting relationships with Allergan, Ipsen, Merz and US World Meds.
REVIEW RETURNED	12/03/2012

GENERAL COMMENTS	The authors have conducted a practical study to test the efficacy of botulinum toxin A in cervical dystonia patients based on the new definition by the working group. Although, they met the 3 of the 4 critieria as shown by 97.5%, 73.6% and 69.8% of subjects achieving criterion of magnitude of effect, tolerance (absence of severe related AEs) and subject's CGI. A total of 49.3% of subjects achieved response based on the duration of effect criterion (≥12 weeks between inclusion and subject-rated waning of treatment effect). Overall, 28.6% (95% CI: 24.0% to 33.5%) of subjects were classified as responders to treatment. This is a low number and the authors explanation was that it was due to the subjective nature of the duration of effect question. However, even with just 3 criteria of magnitude of effect, tolerance and CGI - responders were just ~58% which seems low as well. Further explanation of both of these findings needs to be offered in more detail in the discussion section.

REVIEWER	Antonio Emanuele Elia MD, Neurology 1 Fondazione Istituto Carlo Besta, Milan, Italy
REVIEW RETURNED	12/03/2012

THE STUDY	A definition of "responder" should be added in the abstract.
GENERAL COMMENTS	This is an observational uncontrolled study aimed to develop a definition of treatment response in patients with cervical dystonia after treatment with botulinum toxin type A (BoNT-A) or type B (BoNT-B). The study is of interest, it is well designed and has a high external validity.

	I have these remarks and comments: Abstract: "... the responder definition…" As presented, the sentence is unclear. I suggest to clarify the definition of responder in the outcome measures paragraph. Introduction: o "... classification of CD is based on the primary (idiopathic) or secondary aetiology". I suggest to add a reference. o "...as a first-line treatment option for CD". I suggest to add a reference. o In the "study population" paragraph is written that also patients treated with BoNT-B could be included, accordingly treatment with BoNT-B should be also presented in introduction. Methods: o Study population: The authors should clarify the clinical criteria used for diagnosis of idiopathic and secondary cervical dystonia. o Study assessment: "Subject-rated CGI score at Visit 2 and Visit 3 equal to ..." I suggest to clarify if this criterion was met with improvement in both visit 2 and also visit 3. o "... both the primary and exploratory objectives". Sample size is usually determined on the primary endpoint. Exploratory objectives are not presented before. Are the secondary outcomes ? Results: "...the most strongly associated factors to response were... and 1.5 (not significant) " I suggest to indicate only statistical significant results. Discussion: o "…However, duration of effect…" I suggest to add a comparison with the duration of the effect observed in trials with BoNT in dystonia. o No patient treated with BoNT-B was included, the authors should discuss this. o Other limits of the study should be discussed as the lack of a control group and the decision to include only adverse events considered related to study drug by investigators.

VERSION 1 – AUTHOR RESPONSE

Response to reviewers

Reviewer: 1
Carlo Colosimo, MD
Sapienza University, Rome, Italy

I have no competing interests

This is a large (n=404) international, prospective, study on the factors influencing response to Botulinum toxin type A (BoNT-A) in patients with idiopathic cervical dystonia (CD).

This study may be categorised in the group of Pragmatic trials, i.e. those which are directed at evaluating the effectiveness of a given drug (or intervention) in real life. This is particularly crucial in botulinum toxin therapy for focal dystonia, given the peculiarity of this type of treatment which needs to be very flexible, both in terms of dose and muscles to be injected.

Results are largely confirmatory of previous regulatory studies in smaller cohorts: most patients with CD respond favourably to BoNT-A, which is also well-tolerated. A novel finding of this study is that the duration of the clinical effect is probably less than 3 months in most of the CD cases.

The paper is well-written and documented. However, I have some remarks:

1. First paragraph of the introduction: 1) epidemiological data: I suggest keeping only the prevalence figure from the North-American study, since the ESDE study was strongly biased methodologically and possibly under-reported the frequency of dystonia in Europe. 2) The classification of dystonia in primary or secondary is one point, and the co-occurrence of dystonia with other movement disorders is another issue, not necessarily inter-related.

Response: References to the ESDE study and the following statement have been removed: 'co-morbidity with other movement disorders is common' [Introduction, page 5, paragraph 1].

2. In the introduction, page 5, line 29: in my opinion the main reason for starting a trial as this one is the need to confirm the effectiveness of BoNT-A treatment in the real life, without the constriction in term of doses and muscles to be injected (which were almost always predetermined in all previous regulatory trials). The issue of the scale used for evaluating its effectiveness (TWSTRS, Tsui or others) is probably less relevant.

Response: We agree with the reviewer's comment that confirmation of BoNT-A effectiveness in real-life represents the main rationale for our study, and have reordered sentences within paragraph 3 of page 5 as a consequence.

3. Study population: it was reasonable to exclude secondary cases of CD in order to have a homogeneous population to study. However it is not true that secondary cases do not respond to BoNT-A (e.g iatrogenic cases or cases associated with Parkinson's disease may respond well to this treatment).

Response: Although 'non-response to BoNT-A' was not explicitly stated as a reason for excluding secondary causes of CD, we have supported our rationale for exclusion of CD patients with secondary aetiology by incorporating the following comment from the reviewer 'To create a homogeneous population for study, subjects with secondary CD were excluded from the study, as were subjects with contraindications of BoNT-A treatment' on page 7 [paragraph 3].

4. Injection scheme: Not only median dose, but also the ranges used for the various brands of the toxin should be stated. In addition, can the authors give the mean dose and ranges also for Xeomin (despite the low number of patients treated with this brand)?

Response: We thank the reviewer for this suggestion. In response, we have incorporated an additional statement in the relevant paragraph on page 12 (Overall, 90% of patients received less than 1000 U of Dysport and 300 U of Botox), which we felt would be of clinical value to the BMJ readership. Furthermore, median dose values for Xeomin were included (with the caveat that small patient numbers may limit full interpretation of these results).

5. Discussion: 1) page 15, line 11...real-life data on response to BoNT-A in CD are sparse...this is a little bit generic. Can the authors comment more in detail about studies similar to the present one, if published? 2) On page 16, lines 29-37: this paragraph is mainly a repetition of what already stated in the previous page.

Response: We have included additional information on recent pragmatic studies by Hefter et al

(2011), Mohammadi et al (2009) and Vivancos (to support the statement that real-life data on response to BoNT-A in CD are sparse [Discussion, page 15, paragraph 2]). The Conclusions paragraph has been modified to eliminate repetition [page 16].

6. On Table 1, predominant component: it is unclear to me how to differentiate tremor from jerk?

Response: We agree that this may difficult to differentiate clinically. Physicians indicated the predominant component of CD based on their clinical judgement.
Tremor was differentiated from jerk to distinguish between more regular rhythmic movement (tremor) as opposed to an irregular random unsustained head movement (jerk).

Reviewer: Shyamal Mehta MD, PhD
Assistant Professor, Movement Disorders
Department of Neurology
Georgia Health Sciences University

Disclosure: consulting relationships with Allergan, Ipsen, Merz and US World Meds.

The authors have conducted a practical study to test the efficacy of botulinum toxin A in cervical dystonia patients based on the new definition by the working group. Although, they met the 3 of the 4 criteria as shown by 97.5%, 73.6% and 69.8% of subjects achieving criterion of magnitude of effect, tolerance (absence of severe related AEs) and subject's CGI. A total of 49.3% of subjects achieved response based on the duration of effect criterion (≥12 weeks between inclusion and subject-rated waning of treatment effect). Overall, 28.6% (95% CI: 24.0% to 33.5%) of subjects were classified as responders to treatment. This is a low number and the authors explanation was that it was due to the subjective nature of the duration of effect question. However, even with just 3 criteria of magnitude of effect, tolerance and CGI - responders were just ~58% which seems low as well.

Further explanation of both of these findings needs to be offered in more detail in the discussion section.

Response: We express our thanks to the reviewer for highlighting an aspect of our findings that requires further explanation. We agree that observed rates of approximately 30% and 60% may appear to be low when considered within the context of currently applied methodology in most clinical studies which are confined to a primary or co-primary endpoint. However, the more criteria that are included in a response definition, the lower the combined response rates will be. To roughly estimate the response rate you multiply each criterion response rate (assuming independence which is not strictly true), for example, in an ideal situation in which a 90% response rate is obtained for each of 4 dimensions, the overall response rate would only be 66%. In our study, as the duration dimension was only achieved by around 50%, this drove the overall response rate much lower, although it improved when considering only 3 dimensions instead of 4. Clinical experience suggests that the level of response achieved with this multimodal response definition is highly encouraging [page 15, Discussion].

Reviewer: Antonio Emanuele Elia
MD, Neurology 1
Fondazione Istituto Carlo Besta, Milan, Italy

A definition of "responder" should be added in the abstract.

This is an observational uncontrolled study aimed to develop a definition of treatment response in patients with cervical dystonia after treatment with botulinum toxin type A (BoNT-A) or type B (BoNT-B). The study is of interest, it is well designed and has a high external validity.

I have these remarks and comments:

Abstract: "... the responder definition…" As presented, the sentence is unclear. I suggest to clarify the definition of responder in the outcome measures paragraph.

Response: The definition of a responder has been clarified within the outcome measures section of the Abstract.

Introduction:
a. "... classification of CD is based on the primary (idiopathic) or secondary aetiology". I suggest to add a reference.

Response: A supporting reference (Albanese et al, 2010) has been added to the relevant sentence in addition to an example of the type of secondary aetiology on which a classification of CD is based [Introduction, page 5].

b. "...as a first-line treatment option for CD". I suggest to add a reference.

Response: A supporting reference (Costa et al, 2005) has been added to the relevant sentence [Introduction, page 5].

c. In the "study population" paragraph is written that also patients treated with BoNT-B could be included, accordingly treatment with BoNT-B should be also presented in introduction.

Response: We have added a statement regarding BoNT-B treatment in the Introduction [page 5].

Methods:
a. Study population: The authors should clarify the clinical criteria used for diagnosis of idiopathic and secondary cervical dystonia.

Response: An established diagnosis of idiopathic CD was an inclusion criterion for study entry. Furthermore, in line with the non-interventional nature of this study, differentiation of idiopathic versus secondary CD was determined according to the Investigator's clinical diagnosis based on clinical history, examination and relevant investigations.

b. Study assessment: "Subject-rated CGI score at Visit 2 and Visit 3 equal to ..." I suggest to clarify if this criterion was met with improvement in both visit 2 and also visit 3.

Response: We have qualified that response was defined as 'Improvement in subject-rated CGI score at Visit 2 and 3…' [page 8, paragraph 2].

c. "... both the primary and exploratory objectives". Sample size is usually determined on the primary endpoint. Exploratory objectives are not presented before. Are the secondary outcomes?

Response: We have provided further clarification of the exploratory objectives in the 'Sample size' section of the methods [page 8]. Additionally, a sentence has been incorporated at the end of the

Introduction to introduce the objective of conducting an exploratory analysis of prognostic factors [page 6]. Sample size was not specifically determined on the basis of secondary endpoints (improvements in TWSTRS total and Severity, Disability and Pain subscale scores, tremor [as measured by TSUI score] and CDIP-58).

The sample size justification was primarily driven by the primary objective and the precision of at most 5%. In addition, it was ensured that this sample size would allow to look for potential prognosis factors with a reasonable power given a minimum targeted odds ratio of 2 (assumed as clinically relevant).

Results: "...the most strongly associated factors to response were... and 1.5 (not significant) " I suggest to indicate only statistical significant results.

Response: The relevant paragraph has been modified to exclude the non-significant association with absence of baseline head tremor.

Discussion:
a. "…However, duration of effect…" I suggest to add a comparison with the duration of the effect observed in trials with BoNT in dystonia.

Response: Corresponding text in the discussion has been supplemented with additional information on the duration of effect of BoNT-A treatment observed in controlled trials [page 15, paragraph 2].

b. No patient treated with BoNT-B was included, the authors should discuss this.

Response: A minority of patients (5.7%) were previously treated with BoNT-B; the treatment history section of the Results has been amended accordingly [page 12].

c. Other limits of the study should be discussed as the lack of a control group and the decision to include only adverse events considered related to study drug by investigators.

Response: We have provided a discussion of the limitations arising from the design of a non-interventional study, which by its nature does not include a placebo-control treatment arm [Discussion, page 16, last paragraph]. However, we would suggest that our reporting of treatment-related adverse events reflects real-life practice, whereby, in the main, only related adverse events are likely to influence the course of BoNT-A therapy. Furthermore, as this study was conducted in-line with good pharmaco-epidemiological practice the data collected only recorded treatment-related adverse events.

VERSION 2 – REVIEW

REVIEWER	Carlo Colosimo, MD Sapienza University, Rome, Italy I have no competing interests
REVIEW RETURNED	16/04/2012

The reviewer completed the checklist but made no further comments.

REVIEWER	Antonio Emanuele Elia Besta Neurological Institute, Milan, Italy
REVIEW RETURNED	14/05/2012

GENERAL COMMENTS	This is an observational uncontrolled study aimed to develop a definition of treatment response in patients with cervical dystonia after treatment with botulinum toxins. The study is of interest, it is well designed and has a high external validity. Minor points: 1) Reference number 5 was published in 2011 2) Page 13: "wasage" 3) Page 16: "... as the absence of a placebo-controlled group", I suggest to change as "... as the absence of a control group"