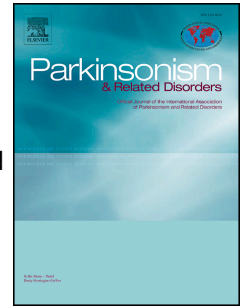


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Title page**Title**

Adverse events with botulinum toxin treatment in cervical dystonia: How much should we blame placebo?

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Abstract

Introduction

Botulinum toxin (BoNT) is the first line therapy for cervical dystonia (CD), with most patients receiving many treatment sessions, and so come to recognize and expect the benefits and harms of BoNT, making it difficult to separate which adverse events (AEs) are driven by BoNT and which come from patients' expectations.

Methods

Using the results of three Cochrane systematic reviews of randomized controlled trials (RCTs) we pooled results to calculate the risk of general and specific AEs associated with BoNT, and the proportion of AEs that cannot be pharmacologically attributed to BoNT.

Results

Fifteen RCTs, enrolling 1604 patients, were included. BoNT was associated with an increased risk of AEs, but 79% of this increased risk cannot be pharmacologically attributed to BoNT.

Conclusions

Patients with CD attach a considerable expectation of harm due to BoNT, reflected in the large proportion of non-pharmacologically-mediated AEs.

Main text

Introduction

Cervical dystonia (CD) is the third most frequent chronic movement disorder and the commonest form of dystonia. It is a disabling condition characterized by involuntary, sustained or intermittent, muscle contractions that cause abnormal head and neck moments and postures. Botulinum toxin type A (BoNT-A)[1] and B (BoNT-B)[2] have been shown to be efficacious compared to placebo in the treatment of adults with this condition. Few trials have compared both serotypes head-to-head in CD[3], without detecting statistically significant or clinically relevant differences in overall efficacy. On the other hand, both serotypes were associated with a significant higher risk of adverse events in comparison to placebo, and differences were found between the two serotypes in the risk of some adverse events[1, 2]. The most clinically relevant adverse events associated with BoNT treatment in CD are well known and to be expected, namely dysphagia and dry mouth, though further concrete evidence of a class effect has been lacking.

Worldwide, the overall benefit-risk profile is considered to be positive, and BoNT treatment is currently the first-line treatment option for CD[4-6]. As the majority of patients will be under treatment for several years, in clinical practice, most patients will have had previous exposure to BoNT. The same applies in the clinical trial setting, where an enriched CD population (previously exposed to BoNT) was almost always used to increase the likelihood of detecting differences with compared to placebo. In this context, where most patients will be able to recognize both the benefits and harms of BoNT treatment, it is difficult to separate which adverse events are pharmacologically driven by BoNT and which represent a nocebo response.

Generally ignored in clinical practice, the nocebo effect is a worsening or harm associated with taking an inert substance and can be thought of as the inverse of the placebo effect, an improvement associated with taking an inert substance. Both the placebo and nocebo effects are thought to be mediated by patients' expectations of the intervention and seem to be directly correlated[7], meaning that the placebo overestimates an intervention's benefit due to positive expectations, while the nocebo overestimates an intervention's harms due to negative expectations.

In this study, we aimed to quantify how much adverse events in the context of CD treatment can be pharmacologically attributed to BoNT rather than to nocebo.

Methods

Using the data from three Cochrane systematic reviews of randomized controlled trials (RCTs) we pooled results to calculate the risk of general and specific AEs associated with BoNT, and the proportion of AEs that could not be pharmacologically attributed to BoNT

Although BoNT-A and BoNT-B have been shown to have a different risk of patients experiencing sore throat/dry mouth in the context of clinical trials, no other statistical significant differences were detected regarding safety and efficacy[3]. Given this, we decided to pool results from RCTs of both BoNT-A and BoNT-B to add power to analyses of a possible class effect, and to further determine to what extent the nocebo response may be responsible for different adverse events.

Briefly, RCTs, blinded, single or multiple dose, parallel-designed, of any duration, assessing the efficacy or safety, or both, of BoNT-A or BoNT-B treatment versus placebo in people with CD were eligible for inclusion in this review. We opted to

exclude crossover trials due to uncertainty about whether this type of study design was appropriate to study chronic fluctuating conditions, as well as methodological concerns with regards to detection and performance bias.

We searched CENTRAL, MEDLINE, and Embase from inception through May 2018 using keywords and MeSH terms related to BoNT, CD, and RCTs. We also searched the main conference proceedings in the field of movement disorders. For more details on the systemic review methods please refer to previous studies[1-3].

We firstly compared groups treated with BoNT versus placebo regarding the proportion of participants reporting one or more adverse event of any type reported in at least two RCTs.

Meta-analyses were conducted on the R software[8], and the threshold for statistical significance (type I error) was established at 5%. Firstly, we used the Paule-Mandel random effects model to pool the risk ratio (RR) and a 95% confidence interval (95% CI) of all reported adverse events. Second, for pooling the frequency and 95% CI of adverse events in the placebo arms, we applied a Freeman-Tukey transformed proportion and pooled data using the Paule-Mandel random effects model.

Heterogeneity was assessed with the I^2 statistic[9]. We further calculated the number needed to treat to cause harm (NNTH) and the proportion of symptoms nonpharmacological[10, 11] (PSN) for all types of adverse events whose risks were significantly increased due to BoNT treatment. We explored the difference between serotypes using subgroup analyses via trials of BoNT-A versus placebo against trials of BoNT-B versus placebo.

PSN is defined as the proportion of symptoms not attributable to the pharmacological action of an intervention, i.e. in the present case we can deduce the proportion of

adverse events that can truly be attributed to BoNT. PSN is calculated as below [10, 11]:

$$(1) PSN = \left[1 - \frac{(\rho_{BoNT} - \rho_{placebo})}{\rho_{BoNT}} \right] \times 100\%$$

ρ_{BoNT} is the pooled probability of a certain event in the BoNT arm, $\rho_{placebo}$ is the pooled probability of the same event in the placebo arm.

Results

We included 12 RCTs, 8 comparing BoNT-A versus placebo and 4 comparing BoNT-B versus placebo (Table 1). Most trials were of short duration and assessed only the clinical profile of BoNT after a single treatment session.

Table 2 summarizes the results of the comparative analysis between BoNT and placebo arms. Overall, randomization to BoNT increased the risk of patients experiencing any adverse event (RR 1.14; 95% CI 1.05 to 1.25; $I^2=11\%$; 9 trials), weakness (RR 1.78; 95% CI 1.08 to 2.94; $I^2=0\%$; 6 trials), dry mouth (RR 3.00; 95% CI 1.49 to 6.04; $I^2=18\%$; 7 trials), and dysphagia (RR 3.68; 95% CI 2.21 to 6.12; $I^2=0\%$; 12 trials). There was no evidence of difference between the BoNT and placebo arms for the other adverse events. Subgroup analyses revealed that BoNT-A and BoNT-B were different regarding the risk of dry mouth ($p=0.03$), with BoNT-B contributing more heavily to the overall increased risk of this adverse event. We found no further evidence of a difference between BoNT-A and BoNT-B regarding other adverse events.

The PSN was 79% for overall adverse events, being 67% for weakness, 26% for dry mouth (combining BoNT-A and BoNT-B trials), and 21% for dysphagia. The PSN for dry mouth using BoNT-A was 50%, while for dry mouth using BoNT-B was 11%.

The analyzed results refer exclusively to the results of a single treatment session. As only one trial conducted more than one treatment session, we are unable to study the effect of previous treatments.

Discussion

For the adverse events at a statistically significant increased risk with BoNT we calculated the PSN, which can be used by patients and clinicians during interactions to determine preferences regarding safety and tolerability. By capturing additional trial information, we attempted to explore the presence of a class effect of BoNT. This additional power confirms that weakness, dry mouth, and dysphagia are the only reported specific adverse events that are increased in people treated with BoNT for CD. However, the nocebo response that we quantified was the addition of the nocebo effect and the Hawthorne effect[12], though as trials did not include a non-intervention arm, we are unable to assess the nocebo effect in isolation. It is relevant to consider recent evidence studying the Hawthorne effect, which shows that little can be securely known about the conditions under which it operates, the mechanisms of action, or its magnitude[13].

As had been previously reported, subgroup analysis demonstrated that BoNT-B is associated with a greater increase in the risk of dry mouth than BoNT-A[3], and showed no other differences between BoNT-A and BoNT-B. This effect of BoNT-B is almost exclusively due to the pharmacological action of BoNT-B and has a small

nocebo response. This finding suggests, albeit indirectly, that BoNT-B may be associated with greater efficacy in treating sialorrhea. We know of a Cochrane review that is currently underway, and look forward to seeing whether or not its conclusions are in line with the work done in this area[14].

Beyond weakness, dry mouth, and dysphagia, which occur in 9%, 19%, and 14% of BoNT-treated patients, there is compelling evidence that additional adverse events are largely due to the negative expectations that patients have regarding treatment, the so-called nocebo effect.

Although almost 70% of people with CD will report having an adverse event, comparatively few of these can genuinely be attributed to the pharmacological effect of BoNT according with our results. Regarding the two most clinically relevant adverse effects of BoNT in CD, namely dysphagia and dry mouth, it will not come as a surprise that most of these events are due to the pharmacological action of the drug. Regarding weakness, although at a legitimately increased risk in people receiving treatment, only around 30% can be attributed to botulinum toxin.

Considering placebo response as the percentage improvement from baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), the most widely used rating scale in CD[15], we found a 3.9-point improvement in the placebo arm of RCTs, equivalent to an approximately 11% improvement. It is of interest to compare the large nocebo response (53%) to the comparatively modest placebo response, as the dissonance seems to suggest that patients with CD attach a low expectation of improvement, reflected in the diminutive placebo response, despite a more considerable expectation of harm, as seen by the considerable nocebo response.

Our results are supported by the largest pooled analysis of data from interventional studies in CD, and by a low degree of statistical heterogeneity on the analyses performed. On the other hand, there is some clinical heterogeneity in regards to the intervention (merging data from BoNT-A and BoNT-B), different equivalent dosages used in different trials, and different baselines characteristics. That being said, a certain extent of clinical heterogeneity is helpful in extrapolating our results to a larger and more diverse population.

Authors' roles

1. Research project:
 - a. Conception, GSD
 - b. Organization, GSD
 - c. Execution, GSD, FBR
2. Statistical Analysis:
 - a. Design, GDS
 - b. Execution, GSD, FBR
 - c. Review and Critique, JJF, JC
3. Manuscript Preparation:
 - a. Writing of the first draft, GSD
 - b. Review and Critique, GSD, FBR, JJF, JC

(GSD, Gonçalo S Duarte; FBR, Filipe B Rodrigues; JJF, Joaquim J Ferreira; JC, João Costa)

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Table 1. Summary of included trials comparing botulinum toxin (BoNT-A and BoNT-B) *versus* placebo

Trial	BoNT	n	Follow-up (weeks)	% Female	Baseline disability score	Previous BoNT treatment?
BoNT-A trials						
Charles 2012	OnabotulinumtoxinA	170	10	BoNT-A 70%; placebo 80%	CDSS BoNT-A 9.2 (4.8); placebo 9.3 (4.2)	Yes
Comella 2011	IncobotulinumtoxinA	233	20	BoNT-A 120U 51%; BoNT-A 240U 54%; placebo 49%	TWSTRS total BoNT-A 120U 42.6 (9.7) BoNT-A 240U 42.1 (9.3) placebo 41.8 (7.9)	Yes
Greene 1990	OnabotulinumtoxinA	55	12	BoNT-A 61%; placebo 67%	BoNT-A 7% mild, 71% moderate, 21% severe; placebo 11% mild, 48% moderate, 41% severe	No
Poewe 2000	AbobotulinumtoxinA	75	8	Overall 48%	Tsui modified BoNT-A 250U 14.3; BoNT-A 500U 13.1; BoNT-A 1,000U 14.5; placebo 14.4	Yes
Poewe 2016	AbobotulinumtoxinA	369	12	BoNT-A 64%; placebo 63%	TWSTRS total BoNT-A 46 (9); placebo 47 (9)	Yes
Truong 2005	AbobotulinumtoxinA	80	20	BoNT-A 62%; placebo 63%	TWSTRS total BoNT-A 45.1 (8.7); placebo 46.2 (9.4)	Yes
Truong 2010	AbobotulinumtoxinA	116	12	BoNT-A 67%; placebo 62%	TWSTRS total BoNT-A 43.8 (8.0); placebo 45.8 (8.8)	Yes
Wissel 2001	AbobotulinumtoxinA	68	16	BoNT-A: 46%; placebo 56%	Tsui BoNT-A 11.1(1.7); placebo 11.5 (1.8)	Yes
BoNT-B trials						
Brashear 1999	RimabotulinumtoxinB	109	16	BoNT-B 63%; placebo 58%	TWSTRS total BoNT-B 5000U 46.4 (10.4); BoNT-B 10000U 46.9 (9.6); placebo 43.6 (9.0)	Yes
Brin 1999	RimabotulinumtoxinB	77	16	BoNT-B 69%; placebo 68%	TWSTRS BoNT-B 52.8 (8.6); placebo 51.2 (9.5)	Yes
Kaji 2013	RimabotulinumtoxinB	130	16	BoNT-B 41%; placebo 36%	TWSTRS total BoNT-B 2500U 43.9 (14.7); BoNT-B 5000U 43.2 (9.7); BoNT-B 10000U 42.4 (8.8)	Partially
Lew 1997	RimabotulinumtoxinB	122	16	Overall 67%	TWSTRS total BoNT-B 2500U 45.6; BoNT-B 5000U 45.2; BoNT-B 10000U 47.5; placebo 45.5	Yes

Table 2. Analysis of adverse events reported. BoNT, botulinum neurotoxin; 95% CI, 95% confidence interval; n, number of participants; NA, not applicable; NNTH, number needed to treat to cause harm; PSN, proportion of symptoms nonpharmacological; RCT, randomized controlled trial; RR, risk ratio.

Events reported (in at least two RCTs)	Number of RCTs	BoNT arm			Placebo arm			RR (95% CI)	I ²	P value for subgroup difference between BoNT-A and BoNT-B	NNTH (95% CI)	What percentage of patients had this event due to the pharmacological effect of BoNT?	PSN (95% CI)
		n	N	Proportion	n	N	Proportion						
BoNT increases risk of the following events compared to placebo													
Overall adverse events	9	409	696	0.67	233	422	0.53	1.14 (1.05 to 1.25)	11	0.52	13 (8 to 38)	21	79
Weakness (all BoNT-A)	6	47	522	0.09	17	301	0.06	1.78 (1.08 to 2.94)	0	NA	21 (9 to 208)	33	67
Dry mouth (overall)	7	75	427	0.19	14	233	0.05	3.00 (1.49 to 6.04)	18	0.03	10 (4 to 41)	74	26
Dysphagia	12	124	913	0.14	15	532	0.03	3.68 (2.21 to 6.12)	0	0.22	12 (7 to 28)	79	21
Dry mouth (BoNT-B only)	4	49	301	0.18	3	137	0.02	7.12 (2.46 to 20.62)	0	NA	8 (3 to 34)	89	11
No statistically significant difference between BoNT and placebo													
Dry mouth (BoNT-A only)	3	26	126	0.20	11	96	0.10	1.66 (0.78 to 3.51)	5	NA	NA	NA (50)	NA (50)
Injection site pain	11	83	825	0.10	40	450	0.09	1.44 (0.94 to 2.20)	0	0.99	NA	NA	NA
Headache	9	51	680	0.08	25	387	0.06	1.27 (0.79 to 2.05)	0	0.91	NA	NA	NA
Flu-like syndrome	10	75	846	0.09	42	467	0.09	1.20 (0.65 to 2.22)	48	0.36	NA	NA	NA

Highlights

- 21% of adverse events with botulinum toxin (BoNT) in cervical dystonia are due to BoNT
- 53% of patients reported adverse events when taking placebo (nocebo response)
- The placebo response (improvement with placebo) was only 11%
- BoNT-A and BoNT-B have similar safety profiles, except regarding dry mouth, more with BoNT-B