Switching Botulinum Toxin A Products for Patients with Upper Limb Spasticity or Cervical Dystonia: A Review of Clinical Effectiveness
AUTHORS: Ron Pohar, Danielle Rabb


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Context and Policy Issues

Botulinum neurotoxin (BoNT) is a neurotoxin that is produced by fermentation of the anaerobic bacterium *Clostridium botulinum* and is used in medicine for its ability to impair muscle contraction.\(^1\) BoNT exerts its effects in the synaptic cleft by reducing the release of acetylcholine at the motor neuron, which blocks neuromuscular transmission and causes muscle weakness.\(^3\) There are different strains of *Clostridium botulinum* that produce different serotypes of BoNT (type A to type H), which consist of the toxin complexed to a protein.\(^3\) The protein complexes are referred to as progenitor toxins, consisting of the active neurotoxin bound to a nontoxic accessory protein (NAP), from which active neurotoxin must dissociate to exert its pharmacological effects.\(^4\)

In Canada, there are three different BoNT type A (BoNT-A) products that are approved for use in a number of different therapeutic indications:

- **Onabotulinumtoxin A (ONA)** – Marketed as Botox and approved for use in blepharospasm, cervical dystonia (CD), strabismus, focal spasticity, equinus foot, primary hyperhidrosis, chronic migraine and bladder dysfunction.\(^5\)

- **Abobotulinumtoxin A (ABO)** – Marketed as Dysport Therapeutic and approved for use in CD and focal spasticity.\(^6\)

- **Incobotulinumtoxin A (INCO)** – Marketed as Xeomin and approved for use in hypertonicity disorders of the seventh nerve, CD, and upper limb spasticity.\(^7\)

Onabotulinumtoxin A, ABO, and INCO are also available in formulations that are approved for cosmetic indications.\(^8\)-\(^10\) A fourth BoNT-A, Prabotulinumtoxin A, was submitted to Health Canada for review in October of 2017 for a cosmetic indication.\(^11\) It is unclear if approvals for therapeutic indications are also currently being sought.

Cervical dystonia is a form of focal dystonia (a movement disorder characterized by muscle spasms and contractions) that causes significant pain and functional disability. Abnormal neck and head posture with CD impairs the ability to perform activities of daily living. The treatment of choice for this condition is local injections into the muscles with BoNT-A.\(^3\) In ULS, local injections with BoNT-A are used to reduce muscle tone to help improve range of motion, reduce pain and increase function.\(^12\)

The four BoNT-A products have different complex protein structures and differ in their molecular weights, pharmacologic profiles, and potency.\(^2\) Because each BoNT-A product has a different potency, they are not considered interchangeable by Health Canada\(^13\) and dosages may not covert directly on a 1 to 1 basis.\(^2,13\) Each BoNT-A has a different nonproprietary name (generic name) to make it more clear that the products are not interchangeable.\(^13\) However, switching may be necessary for patients who experience secondary nonresponse, develop side effects, or are required to do so for reasons related to drug coverage.\(^14\) For these reasons, it is important to be aware of the evidence to support the efficacy of switching between different BoNT-A products in experienced users.\(^14\) This report will review the evidence of clinical effectiveness of switching BoNT-A products for patients with upper limb spasticity (ULS) and cervical dystonia (CD).
Research Questions

1. What is the clinical effectiveness of switching botulinum toxin A products for patients with upper limb spasticity?

2. What is the clinical effectiveness of switching botulinum toxin A products for patients with cervical dystonia?

Key Findings

No literature was identified that assessed the clinical effectiveness of switching botulinum toxin A products for patients with upper limb spasticity. One systematic review (ONA to ABO), one randomized controlled trial (ABO to ONA), and two nonrandomized studies (ABO to INCO and ONA to INCO) assessed the clinical effectiveness of switching botulinum toxin A products for patients with cervical dystonia. These studies assessed the effects of switching in stabilized patients who had previously responded to treatment. They did not assess a switch in therapy due to secondary failure or adverse effects. Overall, it was generally found that efficacy of botulinum toxin A products was similar following the switch, in terms of functional outcomes and treatment duration. Based on non-randomized studies, similar treatment duration was observed with ONA and INCO at a 1:1 conversion ratio and with ABO and INCO at a conversion ratio of 4:1. However, the systematic review found that for the switch from ONA to ABO, some differences were noted in Tsui Scores, Toronto Western Spasmodic Torticollis Rating Scale, and treatment duration at higher conversion ratios (1:4). An RCT that assessed a switch from ABO to ONA found no statistical differences in functional outcomes (Tsui Scores, Toronto Western Spasmodic Torticollis Rating Scale) four weeks after the switch at conversion ratios of 1:3 and 1:1.7.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval to study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and January 12, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults with upper limb spasticity or cervical dystonia, receiving treatment with a BoNT-A product (abobotulinumtoxinA[Dysport], onabotulinumtoxinA[Botox], or prabotulinumtoxin A [Nabota])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Switching from one botulinum toxin A product to another</td>
</tr>
</tbody>
</table>
### Comparator
Continuous BoNT-A product use (i.e., no switch); pre/post switch comparisons

### Outcomes
- Functional or disability outcomes (e.g., Toronto Western Spasmodic Torticollis Rating Scale disability subscale score, Modified Ashworth Scale, Tardieu Scale score, active range of motion, Disability Assessment Scale, Modified Frenchay Scale, ease of applying a splint, Goal Attainment Scale, need for restraints)
- Symptoms (e.g., pain, TWSTRS total score)
- Physician Global Assessment
- Treatment response, duration of effect, re-treatment intervals
- Health-related quality of life as measured by validated scales (e.g., SF-36, EQ-5D)
- Harms (e.g., AEs, SAEs, WDAEs, Mortality)

### Study Designs
Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), non-RCTs

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**Exclusion Criteria**

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013.

**Critical Appraisal of Individual Studies**

The included systematic reviews were appraised using the AMSTAR II checklist. Randomized controlled trials (RCTs) were critically appraised using the SIGN 50 checklist, and nonrandomized studies (NRS) were critically appraised using the Downs and Black checklist. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

**Summary of Evidence**

**Quantity of Research Available**

A total of 421 citations were identified in the literature search. Following screening of titles and abstracts, 397 citations were excluded and 24 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 21 publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

**Summary of Study Characteristics**

Details of study characteristics, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

**Study Design**

One systematic review, one RCT, and two NRS met the inclusion criteria for and are summarized in this Rapid Response report. The systematic review included four studies, two of which were relevant for this report. One additional RCT met the inclusion criteria, but was included in the systematic review so was not summarized separately. The systematic review included studies that compared two specific BoNT-Aes, but had no
restriction on study design for inclusion. The included RCT was a randomized, double-blind cross over trial that had three different treatment periods. All patients were initially on ABO, and then received in random sequence continuation with ABO and two different dosages of ONA. Each treatment period lasted 12 weeks in duration (i.e., a single injection). Both NRSs, evaluated a single switch from one BoNT-A to another BoNT-A. One of the NRSs collected data through retrospective chart review and had a mean (SD) follow-up of 91 (31) weeks. The other NRS had a prospective, pre-switch/post-switch design and collected data for an average (SD) of 18.4 (12.4) treatment cycles prior to the switch and for an average (SD) of 9.2 (4.5) cycles post-switch. The authors stated that this was equivalent to approximately 7 years of follow-up. (See Tables A1 and A2, Appendix 2).

Country of Origin
The systematic review was performed by a US-based group. The RCT was performed in Sweden, while the NRSs were performed in the United Kingdom and Germany. (See Tables A1 and A2, Appendix 2).

Patient Population
The systematic review included studies that compared ONA to ABO in a clinical population, but identified only studies in CD (n=3, one of which was not a switching study) and blepharospasm (n=1), with the study in blepharospasm not being relevant to this report. In one of the two studies included in the SR, patients were on a clinically established dose of ONA prior to study initiation. In the other study included in the SR, patients were excluded if they were on BoNT-A within 16 weeks of study enrollment.

The RCT included 46 patients with CD recruited from a university hospital outpatient clinic, previously stabilized on ABO for one year prior to the study. The purpose of switching was to evaluate conversion ratios between products. One NRS included 122 patients with CD from a neurology outpatient clinic, treated with BoNT-A that were then switched to a different BoNT-A when the product used at the clinic changed. The other NRS included 40 patients with CD, from what was described as a BoNT outpatient clinic. In this NRS, all patients were on a BoNT-A at the beginning of the study, but the reason for switching was not stated.

Interventions and Comparators
The systematic review included two RCTs that were relevant to this Rapid Response, both of which assessed the outcomes associated with switching from ONA to ABO. The included RCT assessed a switch of ABO to ONA at two different conversion ratios of ABO:ONA (1.7:1 and 3:1). One NRS assessed a switch from ABO to INCO at a conversion ratio of 4:1, while the other assessed a switch from ONA to INCO at a conversion ratio of 1:1.

Outcomes
The systematic review reported adverse effects and clinical efficacy outcomes (including function and treatment duration). The RCT reported functional outcomes including the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), Tsui scale, and the Movement Energy Index (MEI). The NRSs reported on duration of effect and patient ratings of efficacy.
Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3 Table 3A (Systematic Reviews), Table 4A (Randomized Controlled Trials) and Table 5A (Nonrandomized Studies).

Systematic Reviews

The systematic review provided a narrative summary of findings. Limited detail of the systematic review methodology was reported. There were no details on data extraction (for example if a standard form was used or if data extraction was performed in duplicate), no statement as to whether the review methods were established prior to the conduct of the review, and the PICO dimensions were not presented. However, there was a rationale for the selection of study designs (any clinical study was included) and the study screening and selection was in duplicate. It was unclear, however, if the grey literature had been searched and the time frame for the database search was not reported. Further, while it was stated the risk of bias of the included studies was assessed, this information was not presented or considered when making conclusions. The selection criteria were not described in clear detail (i.e., the PICO dimensions were not clearly presented).

Randomized Controlled Trials

The RCT had some limitations as well. The method of allocation concealment was not described and the description of blinding was unclear. It was also unclear if the patients received any additional medications that could potentially impact study outcomes. There was no formal analysis of carry-over effects between treatments in the trial and no washout period between dosing. Each treatment period appeared to be a single dose of each BoNT-A (ABO, ONA 1:3, ONA 1: 1.7), but was not entirely clear. Strengths of this RCT included the use of multiple standardized scales to assess outcomes (TWSTRS and Tsui Score), a complete follow-up (there appeared to be no missing data) and an intention-to-treat analysis.

Nonrandomized Studies

Both of the NRS clearly described the research question, dosing and conversion ratios for the different BoNT-As that were compared in the studies, and had complete reporting (no loss to follow-up). The main limitations of Grosset et al., 2015 was that the chart review included other conditions in addition to CD. For some outcomes, data were presented for the CD group only, but for other outcomes only the combined data were available. As well, results were presented descriptively, without statistical testing. There were some issues with outcome reporting in that reporting of adverse events was limited. Also, given that the switch was open-label, there is the potential for bias in the reporting of some subjective outcomes related to efficacy. Adherence to treatment was not reported. Similar limitations were noted with Dressler et al., in that the study also involved an open-label switch of treatment, which could potentially bias the reporting of outcomes such as patient reported deterioration of effect. Further, functional outcomes were not measured using standardized measures such as the TWSTRS or Tsui Score and adverse effects were not assessed. Instead, the study measured only duration of effect defined as the time between injection of BoNT-A and the onset of the decrease of the therapeutic effect as reported by the patient, and the injection interval (the actual time between injections). The study tested the equivalence of the two BoNT-A, but no rationale was provided for the selection of the equivalence margin.
Summary of Findings

What is the clinical effectiveness of switching botulinum toxin A products for patients with upper limb spasticity?

No relevant literature was identified that evaluated the clinical effectiveness of switching botulinum toxin A products for patients with upper limb spasticity.

What is the clinical effectiveness of switching botulinum toxin A products for patients with cervical dystonia?

Systematic Reviews

The systematic review included two relevant studies, one of which was a double-blind, randomized cross-over trial in patients with CD and had three treatment periods: ONA at the patient’s usual effective dose, ABO at a conversion ratio of 1:3 and ABO at a conversion ratio of 1:4. Outcomes were assessed one month after each injection. Tsui scores (which are a measure of amplitude and duration of sustained movements, shoulder elevation, and tremor) were found to be statistically higher (improved) with both dosages of ABO compared to ONA. The improvement in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) (which evaluates clinical severity, disability, and pain) was also statistically significant. The mean duration of action was longer with ABO (1:4) by 25 days ($P=0.02$), but by 7 days for ABO (1:3) ($P=0.04$) than with ONA. The rates of treatment emergent adverse effects (AEs) were also higher with ABO (1:3) (33%) and ABO (1:4) (36%) than with ONA (17.6%) (Appendix 3 Table 6A).

The second study included in the SR was also a double-blind, randomized cross-over trial that compared switching from ONA to ABO at a conversion ratio of 1:2.5 in patients with CD. Outcomes were assessed one month after each injection. For the Tsui Score, there was no statistical difference in change from baseline to one month post-injection ($P=0.09$). Similarly, for the TWSTRS, differences in change from baseline were not statistically significant. The Clinical Global Impression Scale and Patient Global Impression Scale also showed no statistical differences between groups and adverse effects were similar (Appendix 3 Table 6A).

The authors concluded that the conversion dose should be 2.5 to 3.0 units of ABO per unit of ONA, but that a number of factors would be used to determine the appropriate ratio when switching a patient between BoNT-A products.

Randomized Controlled Trials

Rystedt et al. (2015) compared the a number of functional outcomes in a cross-over trial with three treatment periods: staying on ABO, switch to ONA (conversion ratio ONA:ABO of 1:3 – referred to as ONA 1:3) and switch to ONA (conversion ratio ONA:ABO of 1:1.7 – referred to as ONA 1:1.17). Outcomes were assessed four and 12 weeks after the switch. The statistical analysis was presented for four weeks after the switch for the TWSTRS, where no statistical differences were found between either dose of ONA and ABO. For Tsui Score and the Movement Energy Index (MEI), there were no statistical comparisons presented between time periods, but results were described as nonsignificant. The MEI is an estimate of the mechanical power and work involved in the movements of the head. A post-hoc analysis of patients assessment of treatment effect suggested that treatment duration might be shorter with ONA (1:3) compared with ONA (1:1.7) and ABO. Adverse effects were similar across treatment groups with the exception of dry mouth, which was
highest with ONA (1:3). The authors concluded that further work was needed to validate the conversion ratio, but it may be lower than 1:3 as this ratio may have resulted in suboptimal efficacy of ONA (Appendix 3 Table 7A).

**Nonrandomized Studies**

Grosset et al., (2015) analyzed the conversion of patients from ABO to INCO at a ratio of 4:1 retrospectively and found that the injection interval remained the same on average in the time periods before and after the switch. Further, 93% of patients rated the efficacy of INCO to be good to excellent (on a seven point rating scale). The most common adverse effects were pain at the injection site and bruising, but were only reported for the period after the switch. The authors concluded that the therapeutic efficacy, duration of action and adverse effect profile were good with switching.

Dressler et al., (2014) assessed the duration of treatment and injection interval when switching from ONA to INCO and found that both met the pre-determined criteria for therapeutic equivalence, with the 95% confidence interval for the difference falling within the range of ±1.5 weeks. The authors concluded that a 1:1 conversion ratio between ONA and INCO was appropriate.

**Limitations**

No literature was identified that assessed the efficacy and harms of switching between BoNT-A products in patients with upper limb spasticity.

For the evidence in CD, there were some limitations to the included literature that should be noted. Importantly, the studies included patients who were previously stabilized on one BoNT-A and then switched to a different BoNT-A for the purpose of assessing comparative efficacy and/or equivalency of two products at set conversion ratios, or switched patients due to a change in the product that was used in a clinic setting. Thus, these patients were not switched for therapeutic reasons such as an adverse effect or secondary therapeutic failure. As such, the included studies do not provide evidence of similar efficacy when switching between BoNT-A products in these clinical situations.

The systematic review sought to compare only ONA to ABO and included two RCTs that were relevant to this Rapid Response report. It provided no evidence on the efficacy of switching between other BoNT-A formulations. For the other BoNT-A formulations, the amount of evidence for each comparison was sparse with the switches from INCO to ABO and from ONA to INCO being assessed in one NRS study each. Further, these studies had limitations in that the comparison of INCO to ABO included a mixed population such that approximately 47% of patients had CD while the rest had other conditions. The results for the CD population were presented for the injection interval, but they were not available for the other study outcomes. Further, for the injection interval, data were only displayed graphically by condition, without numerical values, so were not included in this Rapid Response report. Results did, however, appear to be similar for the various conditions and similar to the numerical values reported for the overall population. For other outcomes, where data were not presented according to condition, it is not known if the results for the overall population would be generalizable to CD. For the NRS that assessed a switch from ONA to INCO, the study included on 40 participants. Moreover, the NRS were open-label in design, which has the potential to bias more subjective measures such as adverse effect reporting, patient reported measures of duration of effect, and functional outcomes. Switching from ABO to ONA was assessed in one RCT that included two different...
conversion ratios using a double-blind, randomized cross-over design. While this study was a stronger design than the NRSs, its authors noted several important limitations including a lack of washout period between treatments, no formal assessment of carryover effects and a low initial dose of ABO, which subsequently resulted in an insufficient dose of ONA when converted according to the predetermined ratios.

The reporting of harms was generally quite limited and was focused only on a few key outcomes. Thus, the evidence for comparative adverse effects remains uncertain.

Conclusions and Implications for Decision or Policy Making

Given the number of BoNT-A products available in Canada and the potential for more to become available, it is important to have an understanding of the comparative clinical effectiveness of these products for specific indications. As well, it is important to be aware of how to convert between dosages. One systematic review and three clinical studies assessed the efficacy of switching stabilized patients from one BoNT-A product to a different one. They did not, however, compare the efficacy of these products in patients who experience adverse effects or a secondary therapeutic failure with one BoNT-A and switch to a different product.

Limited evidence was available that assessed the clinical effectiveness of switching BoNT-A products for patients with CD. The NRSs found that the efficacy was similar when switching from ABO to INCO and ONA to INCO in terms of duration of effect. The impact on functional outcomes, such as the TWSTRS or Tsui Score, was not assessed in these studies. The RCT assessed switching from ABO to ONA and found that after four weeks of treatment, functional outcomes were not statistically different between treatments. However, duration of effect may have been shorter with ONA at a conversion ratio of 1:3 based on TWSTRS scores twelve weeks after treatment. The results of the SR supported a conversion ratio of 1.25 to 1.3 for ONA to ABO.

Harms data were poorly reported and somewhat uncertain, but did not identify any major differences between products.

No evidence was identified that assessed the effectiveness of switching botulinum toxin A products for patients with upper limb spasticity.
References


Appendix 1: Selection of Included Studies

421 citations identified from electronic literature search and screened

397 citations excluded

24 potentially relevant articles retrieved for scrutiny (full text, if available)

1 potentially relevant report retrieved from other sources (grey literature, hand search)

25 potentially relevant reports

21 reports excluded:
- irrelevant comparator (12)
- already included in at least one of the selected systematic reviews (1)
- other (review articles, editorials) (8)

4 reports included in review
### Appendix 2: Characteristics of Included Publications

#### Table 1A: Characteristics of Included Systematic Reviews

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Types and Numbers of Primary Studies Included</th>
<th>Population Characteristics</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
</table>
| DashtiPour et al., 2016
t (United States) | Comparative clinical trials, systematic reviews, meta-analyses that assessed the dose conversion of ONA to ABO. Four RCTs were included total; three of which were in CD. Of the CD trials, two were relevant as they had crossover designs. The over was a parallel group RCT so did not match the selection criteria for this Rapid Response. | Any clinical population that had compared the BoNT-A’s ONA and ABO for a therapeutic use in a medical field was eligible for inclusion, but studies were only identified in CD (n=3) and blepharospasm (n=1) | Switch to ABO | Switch from ONA | Dosing practices, dosing conversions, AEs, clinical efficacy outcomes |

ABO= Abobotulinumtoxin A; AE= Adverse effect; BoNT-A= Botulinum neurotoxin A; CD= Cervical dystonia; ONA= Onabotulinumtoxin A; RCT= Randomized controlled trial

#### Table 2A: Characteristics of Included Clinical Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design</th>
<th>Patient Characteristics, Sample Size (n)</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Conversion Ratio</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
</table>
| Rystedt et al., 2015
t (Sweden) | Double-blind, randomized cross-over trial | Received three different treatments in random order: two different dosages of ONA | Switch to ONA at 1.7:1 conversion ratio | Switch to ONA at 3:1 conversion ratio | ABO dose applied at last treatment session prior to study (continuing treatment). | 1.7:1 ABO:ONA 3:1 ABO:ONA | TWSTRS, Tsui scale, MEI assessed 4 and 12 weeks after each treatment. SF-36 and FDQ were also listed as outcomes but no data were |
<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design</th>
<th>Patient Characteristics, Sample Size (n)</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Conversion Ratio</th>
<th>Clinical Outcomes</th>
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<tbody>
<tr>
<td>and one dose of ABO (six possible sequences). Each treatment period was 12 weeks (a single injection of each drug).</td>
<td>treated at a university hospital outpatient clinic Average age: 62 (SD = 11) Female: NR%</td>
<td></td>
<td></td>
<td></td>
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<td>presented.</td>
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<tr>
<td>Nonrandomized Studies</td>
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<tr>
<td>Grosset et al., 2015</td>
<td>United Kingdom</td>
<td>Patient Chart Review 257 charts reviewed of patients on ABO who were switched to INCO. 49% of patients had CD. Remaining patients had indications not relevant to this Rapid Response (including blepharospasm, hemifacial spasm, and segmental or generalized dystonia) Mean (SD) Follow-up: 91 (31) weeks</td>
<td>122 patients with CD from a neurology outpatient clinic in Scotland. Average age: 57.2 (SD = 14) Female: 74%</td>
<td>Switch to INCO Mean dose initially after switch: Approximately 100*</td>
<td>On ABO prior to switch Mean (SD) one year prior to switch: 379 (166) units Last dose prior to switch: 402 (171) units</td>
<td>ABO: INCO 4:1</td>
</tr>
<tr>
<td>Dressler et al., 2014</td>
<td>Germany</td>
<td>Open-label, cross-over trial. Patients on ONA for an average (SD) of 18.4 (12.4) treatment cycles were crossed over to</td>
<td>40 patients with CD previously treated with ONA for at least four injections. Patients were treated at BoNT outpatient</td>
<td>Switch to INCO for at least four injections Mean (SD) dose: 295.7 (96.1) MU</td>
<td>ONA for at least four injections Mean (SD) dose: 295.7 (96.1) MU</td>
<td>1:1 ONA:INCO</td>
</tr>
<tr>
<td>First Author, Publication Year, Country</td>
<td>Study Design</td>
<td>Patient Characteristics, Sample Size (n)</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Conversion Ratio</td>
<td>Clinical Outcomes</td>
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<tr>
<td>INCO and followed for an average (SD) of 9.2 (4.5) cycles post-switch.</td>
<td>clinics.</td>
<td>Average age: 53 (SD = 12) Female: 65%</td>
<td></td>
<td></td>
<td></td>
<td>Injection interval (actual time between injections)</td>
</tr>
</tbody>
</table>

ABO= Abobotulinumtoxin A; BoNT-A= Botulinum neurotoxin A; FDQ=Functional Disability Questionnaire; INCO= Incobotulinumtoxin A; MEI=Movement Energy Index; MU=Million units; ONA= Onabotulinumtoxin A; SD=Standard deviation; SF-36=Short Form 36; TWSTRS=Toronto Western Spasmodic Torticollis Rating Scale

* Read from graph; no standard deviation reported
### Appendix 3: Critical Appraisal of Included Publications

#### Table 3A: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 Checklist

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Did the review authors explain their selection of the study designs for inclusion in the review?</strong></td>
<td>Did the research questions and inclusion criteria for the review include the components of PICO?</td>
</tr>
<tr>
<td>- There was a rationale provided for the choice of study design and the importance of the research question.</td>
<td>- The inclusion criteria were not well defined and the PICO dimensions were not clearly stated. The selection criteria were only described as ONA versus ABO clinical trials. Non-English language and studies prior to 1991 were excluded.</td>
</tr>
<tr>
<td><strong>Did the review authors perform study selection in duplicate?</strong></td>
<td>Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?</td>
</tr>
<tr>
<td>- Two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include.</td>
<td>- There was no statement that the review methods were established prior to the conduct of the review.</td>
</tr>
<tr>
<td><strong>Did the review authors describe the included studies in adequate detail?</strong></td>
<td><strong>Did the review authors use a comprehensive literature search strategy?</strong></td>
</tr>
<tr>
<td>- The studies were described in very limited detail in the publication but a detailed supplemental table was available online.</td>
<td>- The literature search did not appear to include the grey literature, nor did they search the reference lists of other publications.</td>
</tr>
<tr>
<td></td>
<td>- The timeframe of the search was not stated.</td>
</tr>
<tr>
<td><strong>Did the research questions and inclusion criteria for the review include the components of PICO?</strong></td>
<td><strong>Did the review authors perform data extraction in duplicate?</strong></td>
</tr>
<tr>
<td>- The inclusion criteria were not well defined and the PICO dimensions were not clearly stated. The selection criteria were only described as ONA versus ABO clinical trials. Non-English language and studies prior to 1991 were excluded.</td>
<td>- It was unclear if data extraction was in duplicate.</td>
</tr>
<tr>
<td><strong>Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?</strong></td>
<td><strong>Did the review authors provide a list of excluded studies and justify the exclusions?</strong></td>
</tr>
<tr>
<td>- There was no statement that the review methods were established prior to the conduct of the review.</td>
<td>- A list of excluded studies was not provided.</td>
</tr>
<tr>
<td><strong>Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?</strong></td>
<td><strong>Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?</strong></td>
</tr>
<tr>
<td>- The review authors state that the Cochrane Risk of Bias tool was used to assess the studies, but the results are not reported.</td>
<td>- The RoB was not accounted for when discussing the results.</td>
</tr>
<tr>
<td><strong>Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?</strong></td>
<td><strong>Did the review authors report on the sources of funding for the studies included in the review?</strong></td>
</tr>
<tr>
<td>- The RoB was not accounted for when discussing the results.</td>
<td>- The sources of funding of the studies in the review are not reported.</td>
</tr>
<tr>
<td><strong>Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?</strong></td>
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</tr>
<tr>
<td>- Funding and sources of conflict of interest are reported with one of the manufacturers of BoNT-A.</td>
<td>- Funding and sources of conflict of interest are reported with one of the manufacturers of BoNT-A.</td>
</tr>
</tbody>
</table>

ABO= Abobotulinumtoxin A; BoNT-A= Botulinum neurotoxin A; ONA= Onabotulinumtoxin A; PICO= Population, intervention, comparator, outcome; RoB= Risk of Bias;
Table 4A: Strengths and Limitations of Randomized Controlled Trials using the SIGN 50 Checklist16

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>The study addresses appropriate and clearly focused question.</td>
<td>An adequate concealment method is used.</td>
</tr>
<tr>
<td>- The study question was appropriate.</td>
<td>- The method of allocation concealment was not described.</td>
</tr>
<tr>
<td>All relevant outcomes are measured in a standard, valid and reliable way.</td>
<td>Subjects and investigators are kept blind about allocation.</td>
</tr>
<tr>
<td>- Standardized scale measures such as the Tsui Score and TWSTRS were used to measure outcomes.</td>
<td>- Three physicians prepared prescription cards for the others patients to maintain the blinding.</td>
</tr>
<tr>
<td>The assignment of subjects to treatment groups is randomized.</td>
<td>The only difference between groups is the treatment under investigation.</td>
</tr>
<tr>
<td>- The assignment to the order of treatments was random and the method of randomization was described.</td>
<td>- No information on co-interventions such as pharmacotherapies was provided. Thus, it is unclear if there were differences between groups.</td>
</tr>
<tr>
<td>What percentage of subjects in each treatment arm dropped out before the study was completed?</td>
<td>The treatment and control groups are similar at the start of the trial.</td>
</tr>
<tr>
<td>- Follow-up was complete.</td>
<td>- This is not applicable as the patients were their own controls in the cross-over.</td>
</tr>
<tr>
<td>All subjects are analyzed in the groups to which they were randomly allocated (intention to treat analysis).</td>
<td></td>
</tr>
<tr>
<td>- Both ITT and per protocol analyses were performed and produced similar results.</td>
<td></td>
</tr>
</tbody>
</table>

ITT=Intention to treat; TWSTRS=Toronto Western Spasmodic Torticollis Rating Scale

Table 5A: Strengths and Limitations of Nonrandomized Studies using the Downs and Black Checklist17

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the hypothesis/aim/objective of the study clearly described?</td>
<td>Are the main findings of the study clearly described?</td>
</tr>
<tr>
<td>- Yes</td>
<td>- The description of results according to condition are limited and appear to differ in terms of dose to some extent.</td>
</tr>
<tr>
<td>Are the main outcomes to be measured clearly described in the Introduction or Methods section?</td>
<td>Does the study provide estimates of the random variability in the data for the main outcomes?</td>
</tr>
<tr>
<td>- Yes, the conversion ratio and patient rating scales were described</td>
<td>- Some standard deviations are not reported.</td>
</tr>
<tr>
<td>Are the characteristics of the patients included in the study clearly described?</td>
<td>Were the statistical tests used to assess the main outcomes appropriate?</td>
</tr>
<tr>
<td>- Patient characteristics are presented but are limited</td>
<td>- Only descriptive outcomes have been reported.</td>
</tr>
<tr>
<td>Are the interventions of interest clearly described?</td>
<td>Have actual probability values been reported (e.g. 0.035 rather than &lt;0.05) for the main outcomes except where the probability value is less than 0.001?</td>
</tr>
<tr>
<td>- Yes, there is good description of both BoNT-A</td>
<td>- No statistical comparisons are made; the data presentation is descriptive.</td>
</tr>
<tr>
<td>Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?</td>
<td>Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?</td>
</tr>
<tr>
<td>- The patients were seen at a specialty neurology clinic which seems representative of where patients would receive treatment for a condition such as CD.</td>
<td>- There was no statistical models and therefore no adjustment for potential confounders.</td>
</tr>
<tr>
<td>Have the characteristics of patients lost to follow-up been described?</td>
<td>Have all important adverse events that may be a</td>
</tr>
</tbody>
</table>

Grosset et al., 2015

16 SIGN: Surgical, Interventional, and Neurological. Available at: www.sign.ac.uk/publishedguidelines.html

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| - Follow-up was complete given that this was a retrospective chart review. Duration of follow-up was variable. | - consequence of the intervention been reported?  
- Adverse event reporting was limited |
| | Were those subjects who were prepared to participate representative of the entire population from which they were recruited?  
- Unclear; the study was a retrospective chart review. It is not clear if all charts from the time period were assessable. |
| | Were the subjects asked to participate in the study representative of the entire population from which they were recruited?  
- Unclear; but consent was not required. It is not clear if all charts from the time period were assessable. |
| | Were the main outcome measures used accurate (valid and reliable)?  
- Unclear; the switch appeared to be open-label. There is a potential for bias in patient ratings of efficacy and adverse effects. |
| | Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%  
- Not applicable because there were no statistical tests. |
| | Was compliance with the interventions reliable?  
- Compliance was not reported. |
| | Were losses of patients to follow-up taken into account?  
- Duration of follow-up was variable. |
| | Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?  
- The patients were seen at an outpatient clinic, which could potentially be representative of where patients would receive treatment for a condition such as CD, but the type and location of the clinic is not clearly described. |
| | Were the main findings of the study clearly described?  
- The description of results are presented, but more functional outcomes and outcomes on adverse effects would have been more informative to include, in addition to duration of treatment. |
| | Were the main outcome measures used accurate (valid and reliable)?  
- The study was an open-label design and the manner in which treatment duration was assessed was based on patient reported deterioration of effect, but it was not clear how that was measured or ascertained. |
| | Were the statistical tests used to assess the main outcomes appropriate?  
- 95% confidence intervals have been used to compare the therapies to determine an equivalence range of ± 1.5 weeks; however, there is no rationale provided for the selection of this value. |

Dressler et al., 1

- Is the hypothesis/aim/objective of the study clearly described?  
  - Yes |
- Are the main outcomes to be measured clearly described in the Introduction or Methods section?  
  - Yes, the conversion ratio and outcomes defined. |
- Are the characteristics of the patients included in the study clearly described?  
  - Patient characteristics are presented but are limited |
- Are the interventions of interest clearly described?  
  - Yes, there is good description of both BoNT-A |
- Does the study provide estimates of the random variability in the data for the main outcomes?  
  - Yes, standard deviations and standard errors are reported |
- Have the characteristics of patients lost to follow-up been described?  
  - Follow-up was complete and there are data presented on the average number of cycles of treatment received by patients. |
### Strengths

Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

- No statistical comparisons are made; the data presentation is to determine equivalence with no rationale for the criteria for equivalence.

### Limitations

**Have all important adverse events that may be a consequence of the intervention been reported?**

- There was no adverse event reporting

**Were those subjects who were prepared to participate representative of the entire population from which they were recruited?**

- Unclear; the authors state that participants were randomly included until the sample size of 40 was reached but there is no description of this process.

**Were the subjects asked to participate in the study representative of the entire population from which they were recruited?**

- Unclear; the authors state that participants were randomly included until the sample size of 40 was reached but there is no description of this process.

**Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%**

- There was no sample size calculation.

**Was compliance with the interventions reliable?**

- Compliance was not reported.

**Were losses of patients to follow-up taken into account?**

- Duration of follow-up was variable. An average duration was reported and was a minimum of four cycles. It is unclear if patients were excluded from the analysis if they did not reach four cycles.

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BoNT-A = Botulinum neurotoxin A; CD = Cervical dystonia;
Appendix 4: Main Study Findings and Author’s Conclusions

Table 6A: Summary of Findings of Included Systematic Reviews

<table>
<thead>
<tr>
<th>Main Study Findings</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dashtipour et al. 2016</strong>&lt;sup&gt;<strong>†</strong>&lt;/sup&gt;</td>
<td>“In summary, data extracted from randomized, clinical studies suggest that a dose conversion of 2.5 to no more than 3 U of ABO for each unit of ONA provides an appropriate balance of safety and efficacy. However, the most appropriate dose ratio when switching from one BoNT to another depends on multiple factors, including the severity of patients’ symptoms, any comorbid conditions, and previous response to BoNT treatment.” p.113</td>
</tr>
</tbody>
</table>

**Two cross-over RCTs were relevant to this Rapid Response:**

**Ranoux et al.**<sup>21</sup>

Double-blind, randomized, cross-over study comparing the efficacy and safety of ONA with ABO at two different conversion ratios (1:3 and 1:4) in CD.

Patients were initially on ONA and then in a random order, patients received

ONA at their usually effective dose (n=51)
ABO at 1:3 conversion ratio (n=51)
ABO at 1:4 conversion ratio (n=52)

**Primary outcomes**

Mean improvement of Tsui score between baseline and 1 month after each injection:

**ONA** – 3.22
ABO (1:3) – 4.32 ($P = 0.02$ vs ONA)
ABO (1:4) – 4.89 ($P = 0.01$ vs ONA)

**Secondary outcomes**

Mean improvement of the TWSTRS pain score between baseline and 1 month after each injection:

**ONA** – 2.59
ABO (1:3) – 4.41 ($P = 0.04$ vs ONA)
ABO (1:4) – 5.37 ($P = 0.02$ vs ONA)

Mean duration of action (interval between day of treatment and day the patient reported a waning of effect):

7 days longer for ABO 1:3 than for ONA ($P = 0.58$)
25 days longer for ABO 1:4 than for ONA ($P = 0.02$)

Mean pain score at injection on a 6-point scale

**ONA** – 1.20
ABO (1:3) – 1.06
ABO (1:4) – 1.04 ($P = NR$)

Treatment-related AEs per arm – n (%)

ONA – 9 (17.6%)
ABO (1:3) – 17 (33%)
ABO (1:4) – 19 (36%)

Most frequent adverse event was dysphagia

ONA – 3%
ABO 1:3 – 15.6%
ABO 1:4 – 17.3%
Main Study Findings

Yun et al.  
Double-blind, randomized, cross-over study Compared ONA with ABO at a dose conversion ratio of 1:2.5 in 103 patients with CD. Patients could not have been on BoNT-A within 16 weeks of study enrollment.

Primary outcome
Mean (SD) change in the Tsui scale from baseline to 1 month after injection:
ABO, 3.98 (3.89)
ONA, 4.77 (4.10)
(P = 0.09)

Secondary outcomes (4 weeks from baseline)
Mean (SD) change from baseline in Total TWSTRS
ABO -9.76 (10.25)
ONA -8.78 (10.11)
(P = 0.429)

Percent of patients scoring 1-3 on CGI scale (CGI-I)
ABO 57.4
ONA 60.6
(P=0.648)

Percent of patients scoring 1-3 on PGI scale (PGI-I)
ABO 79.8
ONA 83.0
(P=0.690)

Adverse Effects
Muscle weakness and dysphagia most common with both treatments; no significant differences between treatments.

Table 7A: Summary of Findings of Included Clinical Studies

<table>
<thead>
<tr>
<th>Main Study Findings</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWSTRS Total – Median (Range)</td>
<td>*In conclusion, the primary analysis showed that the estimated median TWSTRS total score was 1.96 points higher for Botox (1:3) compared with Dysport at week 4; however, the difference was not statistically significant. No significant differences were seen between Botox (1:1.7) and Dysport. At week 12, a statistically significant difference in</td>
</tr>
<tr>
<td>Pretreatment 43.75 (16.00–62.75)</td>
<td></td>
</tr>
<tr>
<td>ONA (1:3)</td>
<td></td>
</tr>
<tr>
<td>Week 4 – 34.25 (11.00–65.00)</td>
<td></td>
</tr>
<tr>
<td>Week 12 – 38.38 (14.00–71.75)</td>
<td></td>
</tr>
</tbody>
</table>
## Main Study Findings

<table>
<thead>
<tr>
<th>ONA (1:1.7)</th>
<th>ABO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4 – 34.25 (0.00–61.75)</td>
<td>Week 4 – 34.50 (6.00–63.75)</td>
</tr>
<tr>
<td>Week 12 – 38.00 (0.00–64.50)</td>
<td>Week 12 – 38.88 (9.00–66.25)</td>
</tr>
</tbody>
</table>

**Median differences to ABO at week 4:**

ONA (1:3) = 1.96, \( P=0.0799 \)

ONA (1:1.7) = 2.67, \( P=0.1612 \)

### Tsui Score – Median (Range)

**Pretreatment – 10.0 (2–21)**

<table>
<thead>
<tr>
<th>ONA (1:3)</th>
<th>ABO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4 – 8.0 (2–18)</td>
<td>Week 4 – 7.0 (1–17)</td>
</tr>
<tr>
<td>Week 12 – 10.0 (1–20)</td>
<td>Week 12 – 8.0 (1–20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ONA (1:1.7)</th>
<th>ABO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4 – 8.0 (0–16)</td>
<td>Week 4 – 0.24 (0.12–2.38)</td>
</tr>
<tr>
<td>Week 12 – 8.0 (0–18)</td>
<td>Week 12 – 0.27 (0.12–5.30)</td>
</tr>
</tbody>
</table>

### MEI – Median (Range)

**Pretreatment – 0.43 (0.15–7.68)**

<table>
<thead>
<tr>
<th>ONA (1:3)</th>
<th>ABO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4 – 0.30 (0.11–4.39)</td>
<td>Week 4 – 0.24 (0.12–2.38)</td>
</tr>
<tr>
<td>Week 12 – 0.27 (0.12–5.91)</td>
<td>Week 12 – 0.27 (0.12–5.30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ONA (1:1.7)</th>
<th>ABO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4 – 0.26 (0.11–3.29)</td>
<td>Week 4 – 0.24 (0.098–8.63)</td>
</tr>
<tr>
<td>Week 12 – 0.24 (0.098–8.63)</td>
<td>Week 12 – 0.27 (0.12–8.63)</td>
</tr>
</tbody>
</table>

### Patient Assessment of Treatment Effect

Larger proportion found the effect of ONA (1:3) to be worse than ABO and ONA at 12 weeks, but this was a post-hoc analysis.

### Adverse Events

Dysphagia, dry mouth and neck weakness were most common and similar across treatments, except dry mouth was highest with ONA (1:3).

**Author’s Conclusion**

*effect between Botox (1:3) and Dysport was observed, suggesting a shorter duration of effect for Botox when this ratio (low dose) was used. Furthermore, the patients’ assessments showed that ratio 1:3 resulted in suboptimal efficacy of Botox. These secondary outcome observations indicate that the dose conversion ratio between Dysport 100 U/mL and Botox 100 U/mL may be lower than 1:3, but this must be further validated in a larger patient material.*
### Main Study Findings

<table>
<thead>
<tr>
<th>Nonrandomized Studies</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grosset et al., 2015&lt;sup&gt;19&lt;/sup&gt;</td>
<td>“In conclusion, switching from abobotulinumtoxin A to incobotulinumtoxin A at a 4:1 unit ratio resulted in good therapeutic effectiveness in terms of treatment efficacy, duration of treatment effect and adverse events profile, and reduced treatment costs for patients with a range of conditions commonly treated in our dystonia clinic.” p.47</td>
</tr>
</tbody>
</table>

**Mean (SD) Dosing Ratio**<sup>*</sup>

3.89 (0.58) 52 to 219 weeks after switching

**Injection Intervals – mean (SD) weeks**

Overall Population
- One year before switching – 12.9 (2.7)
- End of follow-up after switching – 12.9 (3.3)

Injection intervals were reported to be similar across diagnoses and appeared to be similar based upon graphical data.

**Patient Rating of Efficacy** – n (%)

- Excellent – 10 (4)
- Very Good – 201 (78)
- Good – 29 (11)
- Fairly good – 11 (4)
- Fair – 0 (0)
- Poor – 0 (0)
- Negligible – 0 (0)

**Adverse Effects** – n (%)

- Pain at the injection site – 45 (18)
- Bruising – 4 (2)

### Dressler et al., 2014<sup>*</sup>

**Treatment Duration – Mean (SD) Weeks**

- ONA 11.2 (1.1)
- INCO 11.4 (1.3)

Mean difference - 0.3 weeks (95% CI: -0.34 to 0.9); therefore within the therapeutic equivalence range of ±1.5 weeks

**Injection Interval – Mean (SD) Weeks**

- ONA 14.7 (1.6)
- INCO 15.0 (2.2)

Mean difference - 0.5 weeks (95% CI: -0.4 to 1.4); therefore within the therapeutic equivalence range of ±1.5 weeks

“With two-sided 95% confidence intervals of both parameters falling within the therapeutic equivalence range set to ±1.5 weeks, similar efficacy of both BT drugs is indicated. Having based the switch from Botox to Xeomin on a conversion factor of 1:1 confirms previous findings of an identical potency labelling of both products (Benecke et al. 2005; Dressler 2009; Dressler et al. 2012), thus allowing comparisons of efficacy, adverse effects and costs.” p. 31

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<sup>ABO= Abobotulinumtoxin A; BoNT-A= Botulinum neurotoxin A; CI=Confidence interval; INCO= Incobotulinumtoxin A; MEI= Movement Energy Index; MU= Million units; ONA= Onabotulinumtoxin A; SD= Standard deviation; TWSTRS= Toronto Western Spasmodic Torticollis Rating Scale</sup>

<sup>* No results specific to the CD population were presented</sup>