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Botulinum neurotoxins for the treatment of focal dystonias: Review of rating tools used in clinical trials

Francesca Del Sorbo [a], Alberto Albanese [b, c, *]

[a] Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
[b] Istituto di Neurologia, Istituto Clinico Humanitas, Rozzano, Milano, Italy
[c] Istituto di Neurologia, Università Cattolica del Sacro Cuore, Milano, Italy

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ABSTRACT

Botulinum neurotoxins (BoNTs) are used to achieve therapeutic benefit in focal dystonia. An expert panel recently reviewed published evidence on the efficacy of BoNTs for the treatment of focal dystonias and produced recommendations for clinical practice. Another panel reviewed the clinimetric properties of rating scales for dystonia and produced recommendations for current usage and future directions. Considering that the strength of evidence derives not only from the quality of the study design, but also from usage of validated outcome measures, we combined the information provided by these two recent reviews and assessed the appropriateness of the rating instruments used in clinical trials on BoNT treatment in focal dystonia.

Data sources included all the publications on BoNT treatment for focal dystonias reviewed by the recent evidence-based analysis. We reviewed all rating instruments used to assess primary and secondary outcome following BoNT treatment. The publications were allocated into five topics according to the focal dystonia type reviewed in the meta-analysis: blepharospasm, oromandibular dystonia, cervical dystonia, upper limb dystonia, and laryngeal dystonia. For each topic, papers were divided, according to the terminology used in the meta-analysis, into placebo-controlled, active comparator and methodological or uncontrolled. For each topic we identified the rating tools used in each study class and annotated which were the mostly used in each focal dystonia type. Outcome measures included tools related to motor and non-motor features, such as pain and depression, and functional as well as health-related quality of life features. Patient- and investigator-reported outcomes were also included. Rating instruments were classified as recommended, suggested, listed or not included, based on recommendations produced by the rating scale task force. Both primary and secondary outcome measures were assessed. As a final step we compared current practice, as summarized by the meta-analysis, with the recommendations of the rating scales panel.

For blepharospasm, three placebo-controlled trials used suggested scales, one active-comparator study used a recommended scale and three active-comparator studies used suggested scales. For oromandibular dystonia, one placebo-controlled study used a suggested scale. For cervical dystonia, six placebo-controlled trials used a recommended scale, four active-comparator trials used a recommended scale and one active-comparator study used a suggested scale. For upper limb and laryngeal dystonia, no trial used validated instruments.

Appropriately designed studies should be based on recommended rating instruments. Therapeutic trials not using clinimetrically tested rating measures do not provide sufficient information on efficacy of BoNT treatment, even if the study design is robust. Further research is needed to develop and validate new tools to assess all types of focal dystonia and to apply them in prospective placebo-controlled clinical trials.

1. Introduction

Treatment possibilities for dystonia have greatly expanded in recent years after the introduction of botulinum neurotoxins

Abbreviations: BoNTs, botulinum neurotoxins; DBS, deep brain stimulation; MOS, medical outcomes study; SF-36, short form 36 questionnaire; TWSTRS, Toronto western spasmodic torticollis rating scale; VAS, visual analog scale.

* Corresponding author. Istituto di Neurologia, Istituto Clinico Humanitas, Via Alessandro Manzoni, 56, 20089, Milano, Rozzano, Italy.
E-mail address: alberto.albanese@unicatt.it (A. Albanese).

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(BoNTs) and functional surgery (Jinnah and Factor, 2015). BoNTs are considered the treatment of choice for most focal and segmental dystonias. Pallidal deep brain stimulation (DBS) is considered a good option, particularly for isolated generalized or cervical dystonia, after medication or BoNT have failed (Albanese et al., 2015).

Adequate tools need are determinant to rate improvement or deterioration after treatment. The evaluation of dystonia requires validated rating scales that take into account its dynamic condition, changes in severity depending on the posture assumed and voluntary action (e.g., task specificity) (Albanese et al., 2011). The variable nature of dystonia makes the development of rating scales with robust clinimetric properties a key issue.

Many scales to rate dystonia have been used in published trials, although they have been validated only in few cases. The clinimetric properties of rating scales for dystonia have been recently reviewed to produce recommendations for clinical usage and future directions (Albanese et al., 2013). Six rating scales haves been recommended, meaning that they have been applied to patients with dystonia, have been used by other groups outside the original developers and have been clinimetrically confirmed. They rate blepharospasm, cervical dystonia and laryngeal dystonia; by contrast, no recommended scales are available for other focal dystonias.

The efficacy of BoNT for the treatment of dystonia has been recently reassessed (Hallett et al., 2013). This evidence-based review ranked the clinical trials of BoNT treatment for dystonia in placebo-controlled, active-controlled and methodological or uncontrolled studies. The quality of a study design is considered a strong indicator of external validity of the collected data, but measurement tools are also an important variable for robustness of the collected data as they contribute significantly to objective outcome assessment, a fundamental feature of high quality clinical trials (Gross and Johnston, 2009).

We reviewed the primary and secondary outcome measures implemented by the recently reviewed studies (Hallett et al., 2013) and verified whether they corresponded with recommendations set forth by the rating scales task force (Albanese et al., 2013). Implementation of recommended rating instruments by high quality studies would provide the strongest possible evidence of efficacy of BoNTs in focal dystonias. By contrast, implementation of non-recommended rating tools would weaken even studies with a methodologically strong design.

2. Materials and methods

We analyzed all the studies reviewed by Hallett and colleagues (Hallett et al., 2013) for primary and secondary outcome rating measures of efficacy of BoNT treatment. The publications were allocated into five topics according to the type of focal dystonia addressed in the meta-analysis: blepharospasm, oromandibular dystonia, cervical dystonia, upper limb dystonia, and laryngeal dystonia. For each topic, papers were divided, according to the meta-analysis terminology, into placebo-controlled, active comparator and methodological or uncontrolled. For each topic we identified the rating instruments used in each study class and annotated which were the mostly used for each specific dystonia type.

The scales recommended by the task force are: the Blepharospasm Disability Index, the Cervical dystonia Impact Scale, the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), the Craniocervical Dystonia Questionnaire (blepharospasm and cervical dystonia), the Voice Handicap Index and the Vocal Performance Questionnaire (laryngeal dystonia). The suggested rating scales are: the Jankovic Rating Scale (blepharospasm), the Blepharospasm Disability Scale, the Functional Disability Questionnaire (cervical dystonia), the Tsui Scale (cervical dystonia), the Body Concept Scale (cervical dystonia), the Oromandibular Dystonia Questionnaire, the Unified Spasmodic Dysphonia Rating Scale, the Voice Handicap Index 10, the Voice-Related Quality of Life Scale, the Arm Dystonia Disability Scale, the Tubiana-Chamagne Score (task-specific dystonia), the Writer's Cramp Rating Scale, the Global Dystonia Rating Scale and the Unified Dystonia Rating Scale (generalized dystonia). Other scales were either listed or not included in the recommendation (Albanese et al., 2013).

From the studies reviewed, all outcome rating measures were identified as potential measures of efficacy for each focal dystonia considered. Outcome measures could include tools related to motor function, non-motor features (such as pain and depression), or functional as well as health-related quality of life features. Patient and investigator reported outcomes were included. Both primary and secondary outcome measures were included in the analysis. Studies not allowing a full analysis of the outcome measures used or not using a rating instrument to evaluate BoNT efficacy were excluded.

As a final step we compared the current practice, as evidenced by the meta-analysis with the recommendations set forth by the rating scale task force.

3. Results

The meta-analysis included a total of 42 clinical trials: twenty placebo-controlled, ten active comparator, and twelve methodological or uncontrolled studies (Hallett et al., 2013). Three studies that used neurophysiological parameters as efficacy measures were excluded (Chen et al., 1999; Contarino et al., 2007; Molloy et al., 2002). All the reviewed studies referred to focal dystonias: ten dealt with blepharospasm, two with oromandibular dystonia, thirteen with cervical dystonia, six with limb dystonia, and nine with laryngeal dystonia.

3.1. Blepharospasm

The efficacy of BoNT for the treatment of blepharospasm was evaluated in ten clinical trials, including four placebo-controlled (Girlanda et al., 1996; Jankovic et al., 2011; Jankovic and Orman, 1987; Truong et al., 2008), five active comparator (Nussgens and Roggenkamper, 1997; Ochudlo et al., 2007; Roggenkamper et al., 2006; Sampaio et al., 1997; Wabbels et al., 2011) and one methodological study (Boyle et al., 2009).

These trials used fourteen efficacy assessments, including five rating scales for motor features, eight rating scales for non-motor and disability features of blepharospasm, and one scale that evaluated motor and functional status altogether. Table 1 provides a detailed description of assessment tools used as primary and secondary outcome measures. The following motor rating scales were used: Jankovic rating scale (Jankovic and Orman, 1987) (five clinical trials); motor subscales of the blepharospasm rating and disability scales (Lindeboom et al., 1995) (three trials), and a modified version in one trial (Truong et al., 2008); video rating of dystonia severity on a global scale in one trial (Jankovic and Orman, 1987); the Unified dystonia rating scale (Comella et al., 2003) in one trial; and duration of treatment effect in two trials (Nussgens and Roggenkamper, 1997). The following non-motor and disability scales were used: disability subscale of the blepharospasm rating and disability scale (Lindeboom et al., 1995) in one trial, and a modified version in another trial (Truong et al., 2008); disability subscale of the Fahn-Marsden dystonia rating scale (Burke et al., 1985) in one trial; a subjective disability analog scale in one trial (Jankovic and Orman, 1987); the blepharospasm disability index (Jankovic et al., 2009) in three trials; a modified version of the patient evaluation of global response scale (Roggenkamper et al.,