

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



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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.

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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.

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1. Introduction

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

(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 have 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.,

Table 1

Rating scales used as outcome measures in studies of BoNT treatment for blepharospasm. The number of studies is reported for each study type and outcome measure.

Type of clinical trials (number)	Placebo-controlled studies (4)		Active comparator studies (5)		Methodological uncontrolled studies (1)	
Type of efficacy measure	Primary	Secondary	Primary	Secondary	Primary	Secondary
Motor rating						
Jankovic rating scale	3 (Girlanda et al., 1996; Jankovic et al., 2011; Jankovic and Orman, 1987)		1 (Roggenkamper et al., 2006)	1 (Wabbels et al., 2011)		
Blepharospasm rating and disability scales						
Severity rating sub-scale	1 (Jankovic and Orman, 1987)	1 (Truong et al., 2008)	1 (Sampaio et al., 1997)			
Frequency of involuntary movement sub-scale		1* (Truong et al., 2008)	1 (Sampaio et al., 1997)			
Video-rating of dystonia severity on a global scale	1 (Jankovic and Orman, 1987)					
Unified dystonia rating scale			1 (Ochudlo et al., 2007)			
Duration of treatment effect			1 (Nussgens and Roggenkamper, 1997)	1 (Roggenkamper et al., 2006)		
Non-motor and functional rating						
Blepharospasm rating and disability scales (Blepharospasm disability sub-scale)	1* (Truong et al., 2008)		1 (Sampaio et al., 1997)			
Fahn-Marsden dystonia rating scale	1 (Jankovic and Orman, 1987)					
Disability scale	1 (Jankovic and Orman, 1987)					
Blepharospasm disability index		1 (Jankovic et al., 2011)	1 (Wabbels et al., 2011)	1 (Roggenkamper et al., 2006)		
Patient evaluation of global response scale		1* (Jankovic et al., 2011)		1* (Roggenkamper et al., 2006)		
Short form 36 questionnaire			1 (Ochudlo et al., 2007)			
Montgomery-Åsberg depression rating scale			1 (Ochudlo et al., 2007)			
Pain, bruising and redness rating scale					1 (Boyle et al., 2009)	
Motor, non-motor and functional rating						
Patient global assessment scale				1 (Wabbels et al., 2011)		

Abbreviations: *, modified version of the scale.

2006) in two trials; the short form 36 questionnaire (Jenkinson et al., 1993) in one trial; the Montgomery-Åsberg depression rating scale (Montgomery and Asberg, 1979) in one trial; the pain, bruising and redness rating scale in one trial (Boyle et al., 2009). The patient global assessment scale (Brin et al., 1995) was used in one trial to assess both motor and disability features.

The most used scales in the reviewed BoNT trials were the Jankovic rating scale for motor features, the blepharospasm rating and disability scales and the blepharospasm disability index for non-motor and disability features. The Jankovic rating scale was rated as suggested by the MDS task force that recommended the Blepharospasm Disability Index (Albanese et al., 2013). The Blepharospasm Disability Index was used as a secondary measure in one controlled trial (Jankovic et al., 2011), as a primary efficacy measure in one active comparator trial (Wabbels et al., 2011) and as a secondary efficacy measure in another active comparator trial (Roggenkamper et al., 2006). The other recommended scale for rating blepharospasm and cervical dystonia, the Craniocervical Dystonia Questionnaire (Muller et al., 2004), was not used in any of the clinical trials reviewed.

3.2. Oromandibular dystonia

The efficacy of BoNT in the treatment of oromandibular dystonia was evaluated in two placebo-controlled trials (Jankovic and Orman, 1987; Lee et al., 2010).

Six efficacy rating measures were used in these trials, including four rating scales to assess motor features and two scales for rating non-motor and disability features of dystonia. Table 2 provides a detailed description of assessment tools used as primary and secondary outcome measures. The following motor rating scales were used: the Jankovic rating scale; the motor subscale of the blepharospasm rating and disability scales; a video rating of dystonia severity on a global scale; the bruxism symptom questionnaire (Lee et al., 2010). The following non-motor and disability scales were used: the disability subscale of the Fahn-Marsden dystonia rating scale; a subjective disability analog scale (Jankovic and Orman, 1987).

There was no recommended scale for oromandibular dystonia and one suggested scale (the oromandibular dystonia questionnaire (Merz et al., 2010)) that was not used in any of the clinical trials reviewed.

Table 2
Rating scales used as outcome measures in studies of BoNT treatment for oromandibular dystonia. The number of studies is reported for each study type and outcome measure.

Type of clinical trials (number)	Placebo-controlled (2)	Active comparator (0)	Methodological uncontrolled (0)
Type of efficacy measure	Primary	Secondary	Primary Secondary
Motor rating			
Jankovic rating scale	1 (Jankovic and Orman, 1987)		
Blepharospasm rating and dysability scales (Severity rating sub-scale)	1 (Jankovic and Orman, 1987)		
Video-rating of dystonia severity on a global scale	1 (Jankovic and Orman, 1987)		
Bruxism symptom questionnaire	1 (Lee et al., 2010)		
Non-motor and disability rating			
Fahn-Marsden dystonia rating scale	1 (Jankovic and Orman, 1987)		
Disability scale	1 (Jankovic and Orman, 1987)		

3.3. Cervical dystonia

The efficacy of BoNT for the treatment of cervical dystonia was evaluated in thirteen clinical trials, including eight placebo-controlled studies, one of which is unpublished (Brashear et al., 1999; Brin et al., 1999; Comella et al., 2011; Lew et al., 1997; Poewe et al., 1998; Truong et al., 2005, 2010), and five active comparator studies (Benecke et al., 2005; Brans et al., 1996; Comella et al., 2005; Odegren et al., 1998; Pappert and Germanson, 2008).

Eleven efficacy rating measures were used, including four rating scales to assess motor features, six scales for rating non-motor and disability features of dystonia, and one scale to assess motor, non-motor and disability features altogether. Table 3 provides a detailed description of assessment tools used as primary and secondary outcome measures. The following motor rating scales were used: TWSTRS severity scale (Consky et al., 1990) in six trials; the original Tsui scale (Tsui et al., 1986) in two trials, and the modified version in one trial (Poewe et al., 1998); visual analog scale for symptom severity in six trials; investigator and patient global assessment scales in six trials. The following non-motor and disability scales were used: TWSTRS-disability scale in six trials; TWSTRS-pain scale in seven trials; visual analog scale for pain in nine trials; sickness impact profile (de Bruin et al., 1992) in one trial; short-form 36 questionnaire in one trial; medical outcomes study short-form general health scale (Stewart et al., 1988) in one trial. The TWSTRS total score was used to assess motor, non-motor and disability features altogether in eight trials.

The most used scales in the reviewed BoNT trials were the TWSTRS and a visual analog scale for pain. The TWSTRS was rated as recommended, while the visual analog scale lacked criteria for inclusion. The TWSTRS total score was used as primary measure in six placebo controlled (Brashear et al., 1999; Brin et al., 1999; Comella et al., 2011; Lew et al., 1997; Truong et al., 2005, 2010) and two active comparator studies (Comella et al., 2005; Pappert and Germanson, 2008). The TWSTRS motor score was used as primary measure in one placebo controlled study (Benecke et al., 2005), and as secondary measure in three placebo-controlled (Comella et al., 2011; Lew et al., 1997; Truong et al., 2010) and three active comparator studies (Benecke et al., 2005; Comella et al., 2005; Pappert and Germanson, 2008). The TWSTRS disability score was used as primary measure in one active-comparator study (Brans et al., 1996), and as secondary measure in three placebo-controlled (Comella et al., 2011; Lew et al., 1997; Truong et al., 2010) and two active comparator studies (Comella

et al., 2005; Pappert and Germanson, 2008). The TWSTRS pain score was used as secondary measure in three placebo-controlled (Comella et al., 2011; Lew et al., 1997; Truong et al., 2010) and in four active comparator studies (Benecke et al., 2005; Brans et al., 1996; Comella et al., 2005; Pappert and Germanson, 2008).

The other recommended scale for cervical dystonia (the Cervical Dystonia Impact Scale: CDIP-58 (Cano et al., 2004)) was not used in the clinical trials reviewed.

3.4. Upper limb dystonia

The efficacy of BoNT for the treatment of upper limb dystonia was evaluated in six clinical trials, including four placebo-controlled studies (Cole et al., 1995; Kruisdijk et al., 2007; Tsui et al., 1993; Yoshimura et al., 1992) and two methodological or uncontrolled studies (Chen et al., 1999; Geenen et al., 1996).

Ten efficacy-rating measures were used, including nine to assess motor features and one for rating non-motor and disability features of dystonia. Table 4 provides a detailed description of the scales used as primary and secondary outcome measures. The following motor rating instruments were used: patient's choice to continue treatment in one trial (Kruisdijk et al., 2007); visual analog scale for symptom severity in three trials; a symptom severity scale developed for carpal tunnel syndrome (Atroshi et al., 1997) in one trial; the writer's cramp rating scale (Wissel et al., 1996) in one trial; writing speed (Chen et al., 1999) in two trials; custom patient-based ratings in five trials (Chen et al., 1999; Cole et al., 1995; Geenen et al., 1996; Tsui et al., 1993; Yoshimura et al., 1992); custom investigator-based ratings (Chen et al., 1999; Cole et al., 1995; Yoshimura et al., 1992) in three trials; objective writing measurements (Tsui et al., 1993) in one trial; manual muscle testing scale in one trial (Cole et al., 1995). A functional scale developed for carpal tunnel syndrome (Atroshi et al., 1997) was used in one trial.

The most used outcome measures in the reviewed trials were visual analog scales and patient and investigator rating measures to quantify symptom severity. The task force did not include such measures, as they did not fulfill inclusion criteria. Conversely, the task force rated the Arm dystonia disability scale and the Writer's cramp rating scale (Fahn, 1989) as suggested for upper limb dystonia: the Writer's cramp rating scale was used as secondary efficacy measure in one placebo-controlled trial (Kruisdijk et al., 2007), whereas the Arm dystonia disability scale was not used in any of the reviewed trials.

Table 3

Rating scales used as outcome measures in studies of BoNT treatment for cervical dystonia. The number of studies is reported for each study type and outcome measure.

Type of clinical trials (number)	Placebo-controlled (8)		Active comparator (5)		Methodological uncontrolled (0)	
Type of efficacy measure	Primary	Secondary	Primary	Secondary	Primary	Secondary
TWSTRS total score	6 (Brashear et al., 1999; Brin et al., 1999; Comella et al., 2011; Lew et al., 1997; Truong et al., 2005; Truong et al., 2010)		2 (Comella et al., 2005; Pappert and Germanson, 2008)			
Motor rating TWSTRS-Severity scale		3 (Comella et al., 2011; Lew et al., 1997; Truong et al., 2010)	1 (Benecke et al., 2005)	3 (Benecke et al., 2005; Comella et al., 2005; Pappert and Germanson, 2008)		
Tsui scale	1* (Poewe et al., 1998)		1 (Odergren et al., 1998)	1 (Brans et al., 1996)		
VAS for symptom severity		5 (Brashear et al., 1999; Brin et al., 1999; Lew et al., 1997; Truong et al., 2005; Truong et al., 2010)		1 (Pappert and Germanson, 2008)		
Global assessment		3 (Comella et al., 2011; Poewe et al., 1998; Truong et al., 2010)		3 (Benecke et al., 2005; Comella et al., 2005; Odergren et al., 1998)		
Non-motor and disability rating TWSTRS-Disability scale		3 (Comella et al., 2011; Lew et al., 1997; Truong et al., 2010)	1 (Brans et al., 1996)	2 (Comella et al., 2005; Pappert and Germanson, 2008)		
TWSTRS-Pain scale		3 (Comella et al., 2011; Lew et al., 1997; Truong et al., 2010)		4 (Benecke et al., 2005; Brans et al., 1996; Comella et al., 2005; Pappert and Germanson, 2008)		
VAS for pain	1 (Poewe et al., 1998)	5 (Brashear et al., 1999; Brin et al., 1999; Lew et al., 1997; Truong et al., 2005; Truong et al., 2010)		3 (Benecke et al., 2005; Odergren et al., 1998; Pappert and Germanson, 2008)		
Sickness impact profile		1 (Lew et al., 1997)				
SF-36		1 (Truong et al., 2010)				
MOS short-form general health scale				1 (Brans et al., 1996)		

Abbreviations: *, modified version of the scale; MOS, medical outcomes study; SF-36, short form 36 questionnaire; TWSTRS, Toronto western spasmodic torticollis rating scale; VAS, visual analog scale.

3.5. Laryngeal dystonia

The efficacy of BoNT for the treatment of laryngeal dystonia was evaluated in nine clinical trials, including one placebo-controlled study (Truong et al., 1991) and eight methodological or uncontrolled studies (Adams et al., 1995; Adler et al., 2004; Bielamowicz et al., 2001; Bielamowicz and Ludlow, 2000; Finnegan et al., 1999; Ludlow et al., 1988; Warrick et al., 2000; Wong et al., 1995).

Eleven types of efficacy rating measures were used to assess motor features of laryngeal dystonia. Non-motor and disability features were not rated in these trials. Table 5 provides a detailed description of the assessment tools used as primary and secondary outcome measures. The following motor rating tools were used: different sound spectrograms in two trials; different investigator-designed speech rating scales in six trials; different types of patient-rated speech scales in four trials; investigator-rating of abduction impairment on trans-nasal optic fiber examinations in

one trial (Bielamowicz et al., 2001); voice breaks counts (Bielamowicz et al., 2001) in two trials; investigator-rated visual analog scales for assessing acoustic parameters and nasopharyngoscopic parameters were used in one trial each; a patient-rated visual analog scale for speech symptoms was used in two trials; acoustic and aerodynamic measures were used in four trials.

None of these measures met inclusion criteria of the rating scale task force that conversely recommended the Voice handicap Index and the Vocal performance questionnaire as generic voice scales and suggested the Unified spasmodic dysphonia rating scale and the voice related quality of life scale. These instruments were not used in the reviewed studies.

4. Discussion

We analyzed all the rating instruments used by the studies included in a recent meta-analysis on BoNT treatment for focal

Table 4
Rating scales used as outcome measures in studies of BoNT treatment for upper limb dystonia. The number of studies is reported for each study type and outcome measure.

Type of clinical trials (number)	Placebo-controlled (4)		Active comparator (0)		Methodological uncontrolled (2)	
Type of efficacy measure	Primary	Secondary	Primary	Secondary	Primary	Secondary
Motor rating						
Patient's choice to continue treatment	1 (Kruisdijk et al., 2007)					
VAS for symptom severity	1 (Cole et al., 1995)	1 (Kruisdijk et al., 2007)			1 (Chen et al., 1999)	
Symptom severity scale		1 (Kruisdijk et al., 2007)				
Writer's cramp rating scale		1 (Kruisdijk et al., 2007)				
Writing speed		1 (Kruisdijk et al., 2007)			1 (Chen et al., 1999)	
Patient rating	3 (Cole et al., 1995; Tsui et al., 1993; Yoshimura et al., 1992)				2 (Chen et al., 1999; Geenen et al., 1996)	
Videotape investigator rating	2 (Cole et al., 1995; Yoshimura et al., 1992)				1 (Chen et al., 1999)	
Objective writing measurements	1 (Tsui et al., 1993)					
Manual muscle testing scale	1 (Cole et al., 1995)					
Non-motor and disability rating						
Functional status scale		1 (Kruisdijk et al., 2007)				

dystonias and evaluated whether the measures implemented in such studies tallied with recommendations provided by the task force on dystonia rating scale (see Fig. 1). It emerged that the rating scales recommended by the task force were only used in studies on cervical dystonia and blepharospasm. For cervical dystonia, alone

there was a robust fitting of a recommended scale (the TWSTRS scale) with a placebo-controlled study design (six trials). The same scale was used also in four active-comparator studies for cervical dystonia. A less robust fitting was observed in blepharospasm studies, where three placebo-controlled trials used suggested

Table 5
Rating scales used as outcome measures in studies of BoNT treatment for laryngeal dystonia. The number of studies is reported for each study type and outcome measure.

Type of clinical trials (number)	Placebo-controlled (1)		Active comparator (0)		Methodological uncontrolled (8)	
Type of efficacy measure	Primary	Secondary	Primary	Secondary	Primary	Secondary
Motor rating						
Sound spectrograms ratings by investigator	1 (Troung et al., 1991)				1 (Ludlow et al., 1988)	
Speech rating scales by investigator	1 (Troung et al., 1991)				4 (Adams et al., 1995; Bielamowicz et al., 2001; Bielamowicz and Ludlow, 2000; Wong et al., 1995)	1 (Adler et al., 2004)
Speech rating scales by patient	1 (Troung et al., 1991)				2 (Adler et al., 2004; Bielamowicz et al., 2001)	1 (Adler et al., 2004)
Voice analysis of acoustic parameters	1 (Troung et al., 1991)					
Investigator rating of abduction impairment on transnasal fiberoptic examinations					1 (Bielamowicz et al., 2001)	
Voice breaks counts					2 (Bielamowicz et al., 2001; Bielamowicz and Ludlow, 2000)	
VAS for acoustic parameters investigator-rated					1 (Warrick et al., 2000)	
VAS for nasopharyngoscopic parameters investigator-rated					1 (Warrick et al., 2000)	
VAS for speech symptoms patient-rated					1 (Warrick et al., 2000)	1 (Adler et al., 2004)
Acoustic measures					2 (Adams et al., 1995; Wong et al., 1995)	
Aerodynamic measures					2 (Finnegan et al., 1999; Wong et al., 1995)	

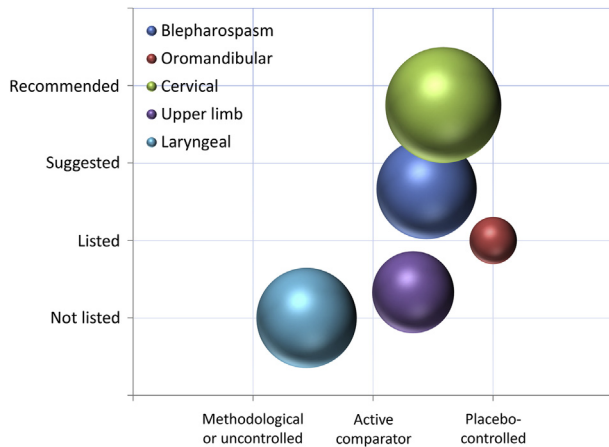


Fig. 1. The strength of studies reviewed is charted against the robustness of the rating instruments adopted in the studies. Each bubble represents a focal dystonia type, with size indicating the number of studies (blepharospasm: 9; oromandibular dystonia: 2; cervical dystonia: 12; upper limb dystonia: 6; laryngeal dystonia: 9). The best combination is provided by cervical dystonia, followed by blepharospasm. Oromandibular dystonia has been the object of high quality trials that have used listed rating scales. The combination is largely insufficient for upper limb and laryngeal dystonia although the number of studies is appreciable.

scales and one active-comparator study used a recommended scale. Furthermore, one placebo-controlled study on oromandibular dystonia used a suggested scale. By contrast, the evidence collected on upper limb and laryngeal dystonia was based on the use of non-recommended outcome measures.

Strength of evidence derives not only from the quality of a study design, but also from usage of validated outcomes. Class I studies are randomized trials of the intervention of interest with pre-defined masked or objective outcome assessment in a representative population (Gross and Johnston, 2009). The methodology of randomized clinical trials has been studied extensively, and guidelines on performing and reporting of these trials are available. The widely used CONSORT checklist requires clearly defined primary and secondary outcome measures, but does not consider whether the rating tools are clinimetrically validated and recommended (Moher et al., 2001). The study methodology is less well formalized for observational studies that are considered to provide weaker evidence. For the implementation of treatment strategies, not only the type of study (randomized controlled or observational) but also the methodological development of the rating instrument should be considered.

Identification of a suitable measure of a clinical outcome for an efficacy study is a process in which various aspects of the nature of the disease or condition under study should be considered along with sources of information by which the required evidence may be feasibly and reliably obtained. The choice of an outcome measure may follow directly from the expected biological mechanism of action of the intervention under study and its impact on the specific medical condition. In all the studies reviewed BoNT treatment was considered to provide only a symptomatic relief of dystonia, although – particularly when treatments are repeated – BoNT may as well influence the pathophysiology of dystonia (Kanovsky and Rosales, 2011).

The selection of clinical outcome measures may be challenging when there are many clinical aspects that could be of interest, and a single measure or scale may not adequately capture the perspective of the clinician and patient. For example, in evaluating BoNT treatment for patients with upper limb dystonia, writing speed, rather than dystonia rating, was measured in two studies (Chen et al., 1999; Kruisdijk et al., 2007). The clinical value of this

measure may be intuitive, although it is not necessarily an indicator of dystonia improvement following treatment. In addition, we also observed the implementation of many subjective clinical assessments, particularly for rating upper limb and laryngeal dystonia, which are a significant source of unwanted variability.

Precise and meaningful measures of improvement or deterioration in symptoms are important in order to evaluate the patient's disease state and the effects of a treatment. In order to be useful rating instruments should meet rigorous scientific standards, including clinimetric evaluations of reliability, validity, and responsiveness (Aronson et al., 2002). Reliability is an important property of a rating scale, essential to establish that any changes observed in patient groups are due to the treatment and not to problems in the scale (Fitzpatrick et al., 1998). Validity is the extent to which a scale measures what it intends to measure (Messick, 1995). Finally, if a scale is used to evaluate the effects of an intervention (e.g., BoNT treatment), responsiveness, i.e. the ability of a measure to detect significant change over time, needs to be evaluated (Deyo et al., 1991). If appropriately designed studies do not use adequate rating instruments, they fail to provide significant information on efficacy of the treatment tested.

Assessment of dystonia is not easy. Rating scales developed for different focal forms show remarkable differences. Recommended scales are available for cervical dystonia, blepharospasms and laryngeal dystonia. By contrast, only suggested (not fully clinimetrically validated) scales are available for oromandibular and arm dystonia (Albanese et al., 2013). Additionally, the available scales do not allow to assess all motor and non-motor (including functional and patient-centered) features of focal dystonia, and no adequate rating tools are available for lower limb and trunk dystonia. This means that investigators need additional validated rating measures to assess all focal dystonia types. Future research will need to develop and validate new tools to fill these needs. These rating instruments should be developed and assessed before new clinical trials are performed.

We discourage the observed practice to develop ad hoc rating instruments, or variants of already developed scales, without appropriate validation, as observed in a number of the studies reviewed. For example, a variety of rating scales to assess speech have been developed and used in clinical trials on laryngeal dystonia. New trials should also address emerging treatment issues. For example, in cervical dystonia there is adequate evidence of BoNT efficacy, but new treatment possibilities (namely DBS) are becoming available (Volkman et al., 2014). Head-to-head trials between BoNT and DBS are needed for cervical dystonia (Albanese, 2014).

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