

## Therapeutic Advances in Dystonia

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**ABSTRACT:** Knowledge on dystonia has greatly improved recently, because of a renewed effort in understanding its cause, pathophysiology, and clinical characterization. Different drug classes traditionally have been used for the symptomatic treatment of dystonia, more recently surpassed by the introduction of botulinum neurotoxins and deep brain stimulation. No curative or disease-modifying treatments are available. Recent knowledge regarding the pathophysiology of inherited dystonias is highlighting new potential treatment strategies. We review

therapeutic advances in dystonia that have been published over the last 3 years, particularly regarding oral medications, local injections of botulinum neurotoxins, deep brain stimulation, and transcranial or epidural brain stimulations. We discuss evidence of efficacy, highlight recent advances, and focus on key areas under development. © 2015 International Parkinson and Movement Disorder Society

**Key Words:** dystonia; treatment; medication; surgery; botulinum toxins; deep brain stimulation

Knowledge of dystonia has greatly improved recently, because of a renewed effort in understanding its causes, pathophysiology, and clinical characterization. Two research networks have been established in the United States (Dystonia Coalition: [dystoniacoalition.com](http://dystoniacoalition.com)) and Europe (European Network for the Study of Dystonia Syndromes: [euro-dystonia.org](http://euro-dystonia.org)), a new definition and classification of dystonia has been recently developed,<sup>1</sup> and a review of available rating tools has been performed.<sup>2</sup> Mendelian forms of isolated dystonia have been associated with several genes. The most common inherited forms are autosomal dominant and related to the TOR1A (DYT1) and THAP1 (DYT6) genes; recently, mutations in HPCA (DYT2) gene have been reported to cause autosomal-recessive dystonia.<sup>3,4</sup>

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A variety of oral medications provide benefit to patients with dystonia; pharmacological treatment is traditionally based mainly on empirical experience rather than scientific rationale.<sup>5</sup> Different drug classes have been used for the symptomatic treatment of dystonia and more recently surpassed by the introduction of botulinum neurotoxins (BoNTs) and deep brain stimulation (DBS). Dopa-responsive dystonia is the only syndrome in which the underlying mechanisms have been elucidated and a disease-specific treatment is available.<sup>6</sup>

Botulinum neurotoxins are an established treatment for dystonia. Three type A BoNT (BoNT/A) and one type B BoNT (BoNT/B) products are widely available<sup>7</sup>: onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, CA, USA), abobotulinumtoxinA (Dysport®/Reloxin®/Azzalure®, Ipsen Pharma, Boulogne Billancourt, France), incobotulinumtoxinA (Xeomin®/Bocouture® Merz GmbH, Frankfurt, Germany), and rimabotulinumtoxinB (Myobloc®/Neurobloc®, Solstice Neurosciences Inc., Louisville, KY, USA). Other BoNT/A products are available on a few markets or are ready to be marketed. These have not yet received a generic name: Prosigne®/Lantox® (Lanzhou Institute of Biological Products, China), PurTox® (Mentor Worldwide LLC, Santa Barbara, CA, USA), and Neuronox® (Medy-Tox Inc, South Korea).<sup>8</sup> All BoNT

products are licensed for focal dystonias, usually for the most common forms (blepharospasm and cervical dystonia), with appreciable regional differences.

Botulinum neurotoxin treatment is the accepted standard of care for patients with focal dystonias, including cervical dystonia (CD), which is the most prevalent adult-onset focal dystonia. Once the efficacy of BoNT was demonstrated in the 1980s, it rapidly assumed a place as the treatment of choice for this condition, confirmed by evidence derived from meta-analyses and guidelines. Two Cochrane reviews concluded that BoNT/A and BoNT/B are effective and safe for treating CD<sup>9,10</sup> and that BoNT/A is highly effective and safe also for treating blepharospasm<sup>11</sup>; the American Association of Neurology and the European Federation of Neurological Societies assigned level A recommendations to BoNT/A as first-line treatment in CD.<sup>12,13</sup> Recent reviews have supported these positions and showed that BoNT is the most effective treatment for reducing motor symptoms and pain in patients with CD.<sup>14,15</sup>

In recent years DBS has emerged as an effective and safe therapeutic option in patients with severe generalized, segmental, or focal dystonia.<sup>16,17</sup> Globus pallidus internus (GPi) is the preferred target for DBS in isolated idiopathic or inherited early-onset generalized and adult-onset dystonia and acquired dystonia secondary to neuroleptic exposure or perinatal hypoxic encephalopathy. In 2003, the Food and Drug Administration allowed in the United States a humanitarian exemption for the use of DBS in dystonia, whereas in Europe all main producers of DBS devices received the CE marking for use on dystonia patients. Randomized controlled trials on GPi DBS have been performed on different dystonia types, including generalized<sup>18</sup> and cervical.<sup>19</sup> Subthalamic nucleus and thalamic DBS are also under scrutiny as targets for isolated dystonia syndromes.

## Recent Developments

### Oral Medications

With advances in the knowledge regarding the causes and pathophysiology of dystonia, small-molecule therapies are being developed and studied. Novel treatments may arise from improvement of currently available compounds or development of approaches targeted at the underlying pathophysiology.<sup>20</sup> Well-designed exploratory and confirmatory trials are necessary to evaluate the safety and efficacy of potential new drugs for dystonia.<sup>21</sup> Several clinical trials of drugs designed for the symptomatic treatment of dystonia have been initiated in the last 2 years (Table 1). A pilot trial to evaluate safety and tolerability of ampicillin in patients with DYT1 generalized dystonia is currently underway (NCT01433757). This drug improved significantly torsinA-dependent

secretory function in DYT1 patient fibroblasts.<sup>22</sup> Another ongoing trial is aimed at assessing the symptomatic efficacy of levetiracetam in oromandibular and cranial dystonia (NCT02199509). Levetiracetam is an S-enantiomer pyrrolidone derivate used in the treatment of epilepsy, which has shown anti-dystonic effects in an animal model of paroxysmal dystonia.<sup>23</sup> However, levetiracetam has already been studied in an open trial for segmental and generalized dystonia<sup>24</sup> in 10 patients, with a daily dose of 3 g for 4 weeks: none of the patients showed improvement of dystonia, and mild side effects (nausea, dizziness, somnolence) were reported. The anti-epileptic drugs zonisamide and 1,3-dimethoxymethyl-5,5-diphenyl-barbiturate have been tested on patients with myoclonus dystonia (DYT11; NCT01806805 and NCT00506012). These studies have been completed, but the results are not yet available.

An open-label phase 2 study to evaluate the safety and tolerability of perampanel in CD (*SAFE-Per CD* study; NCT02131467) has been announced. This selective  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist was originally developed for epilepsy and is licensed for this use in the United States and Canada. The CD trial was designed based on earlier encouraging data on the efficacy of the nonselective glutamate antagonist riluzole in CD.

### Botulinum Neurotoxins

A longitudinal observation in a mixed population of patients with different forms of focal dystonia suggested that the efficacy of BoNT/A is sustained for at least 12 years of continuous use.<sup>25</sup> A recent update of the same retrospective series compared the last available injection with the first treatment (average follow-up: 18.5 years) reporting that repeated treatments are associated with sustained symptomatic benefit, decreased latency effect, and prolonged duration of therapeutic response.<sup>26</sup> The risk of developing neutralizing antibodies is quite low (1.2%) with currently marketed BoNT/A products.<sup>27</sup> The most common adverse events consist in unwanted muscle weakness, such as dysphagia in CD patients, or diplopia and ptosis in blepharospasm patients. Overall safety and efficacy also have been repeatedly demonstrated by prospective studies on patients with blepharospasm and CD.<sup>28,29</sup>

Dosing and targeting commonly vary during the first two to three treatment sessions and tend to stabilize afterwards. Recently, the dogma of fixed-dose injection intervals has been challenged: when incobotulinumtoxinA injections were performed with flexible intervals between repeated treatment sessions in patients with blepharospasm or CD, the flexible regimen was well tolerated.<sup>30</sup> Although BoNT is traditionally considered to provide a chemodenervation of motor neurons, it has been recently shown also to act

**TABLE 1.** Unpublished and ongoing clinical trials on oral medications in dystonia

| Study       | Compound                                     | Rationale                                                            | Trial Design<br>(AAN Class of Evidence)                               | Dystonia Type                                                                                       | Follow-up<br>Period         | Outcome Measures                                                                                                                                                                                                                                                                                                                        | Results/Status                                                                                                 |
|-------------|----------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| NCT00506012 | 1,3-Dimethoxymethyl-5,5-diphenyl-barbiturate | Barbituric acid derivative                                           | Open-label sequential dose escalation (class III)                     | Myoclonus dystonia                                                                                  | 12 weeks                    | <b>Primary:</b> Myoclonus and dystonia scales, overall functional status<br><b>Secondary:</b> Safety measures                                                                                                                                                                                                                           | Terminated (estimated completion date August 2011); no study results published or posted on ClinicalTrials.gov |
| NCT01806805 | Zonisamide                                   | Antiepileptic drug                                                   | Randomized placebo-controlled, double-blind (class I)                 | Myoclonus dystonia including isolated myoclonus caused by epsilon-sarcoglycans mutation or deletion | 23 weeks                    | <b>Primary:</b> Severity of myoclonus (UMRS)<br><b>Secondary:</b> Severity of dystonia (BFMDRS); severity of myoclonus (EMG)                                                                                                                                                                                                            | Completed (estimated completion date July 2014); no study results published or posted on ClinicalTrials.gov    |
| NCT02199509 | Levetiracetam                                | Efficacious in an animal model of paroxysmal dystonia                | Randomized, double-blind placebo-controlled cross-over (class I)      | Oromandibular or cranial dystonia                                                                   | 15 weeks                    | <b>Primary:</b> Sum of eyes, mouth, speech, and swallowing BFMDRS subscores (% change at weeks 6 and 14)<br><b>Secondary:</b> Sum of eyes, mouth, speech, and swallowing BFMDRS subscores (% change at weeks 3 and 11); sum of eyes and upper face, lower face and jaw and tongue GDS subscores (weeks 3, 6, 11 and 14); adverse events | Recruiting                                                                                                     |
| NCT01433757 | Ampicillin                                   | Improvement of torsin A-dependent secretory function in DYT1 patient | Pilot, randomized, double-blind, placebo-controlled phase I (class I) | DYT-1 dystonia, confirmed by genetic testing                                                        | 70 days                     | <b>Primary:</b> Safety and tolerability of ampicillin<br><b>Secondary:</b> BFMDRS                                                                                                                                                                                                                                                       | Recruiting                                                                                                     |
| NCT02131467 | Perampanel                                   | AMPA antagonist                                                      | Open label (Phase 2A)                                                 | Cervical dystonia                                                                                   | 4 weeks of stable treatment | <b>Primary:</b> Tolerability (number of patients able to remain on drug), safety<br><b>Secondary:</b> TWSTRS, CIDP-58, GIC                                                                                                                                                                                                              | Not yet recruiting (study start date: September 2014, estimated completion date: September 2016)               |

Abbreviations: BFMDRS, Burke-Fahn Marsden Dystonia Rating Scale; GDS, Global Dystonia Severity; GIC, Global Impression of change; TWSTRS, Toronto western spasmodic torticollis rating scale; UMRs, Unified Myoclonus Rating Scale.

at sensory nerve terminals.<sup>31</sup> This is also evident in patients with CD, in which BoNT/A is efficacious not only on the motor features but also on pain.<sup>32</sup>

During the last 3 years, several new trials have investigated potential ways to optimize BoNT therapy, including novel formulations and new ways of delivering and improved muscle targeting (Table 2). The results of a pilot trial of acetyl hexapeptide-8 in 22 patients with blepharospasm were recently reported.<sup>33</sup> Acetyl hexapeptide-8, a competitive SNAP25 inhibitor, is the active ingredient in a number of cosmetic creams used to treat wrinkles and works to weaken the muscles; it is available as a skin cream instead of an injection. In this controlled trial patients received either a topical acetyl hexapeptide-8 (0.005%) cream or a placebo cream containing no active substance. These were applied daily to the eyelids beginning on the day after BoNT injection; the application stopped when the blepharospasm rating scale reverted back to baseline. The topical application was safe and extended the duration of symptomatic control after BoNT.

Another study designed to determine whether amlodipine, a calcium channel blocker, can augment the effect of BoNT/A injections in CD patients. This trial has been recently completed, but the results are not yet available (NCT00015457). The Automatic Subdermal Injector System is a proprietary technology aimed to deliver a variety of products, including BoNTs, in the subdermal bloodless space, between the skin and muscle. This device has been studied to deliver BoNT/A in spasticity and migraine. A clinical trial using onabotulinumtoxinA was designed to test this approach in patients with CD (NCT02074293).

Recently, a novel formulation of liquid abobotulinumtoxinA has been tested in patients with CD.<sup>34</sup> This double-blind study assessed changes in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score and subscores in more than 350 patients randomly assigned to liquid abobotulinumtoxinA, current abobotulinumtoxinA, or placebo. The liquid formulation was rated as efficacious and tolerated as the current formulation.

Changes in muscle pattern or difficulty in targeting the involved muscles are a common cause of secondary unresponsiveness that is typically encountered in patients with CD. Traditionally, BoNT injections have been performed by using inspection/palpation. Electromyography (EMG)-guided injections provide better outcome because of more precise muscle selection and fine targeting of the motor endplate zone.<sup>35</sup> A recent study evaluated the feasibility of motor endplate zone location with high-density surface EMG of relevant cervical muscles and showed that endplate-targeted, half-dosed BoNT injections resulted in a similar treatment effect to injecting the full dose in the standard technique.<sup>36</sup> Ultrasound-guided BoNT injections pro-

vide the most recent technique, which allows visualization of muscles, provides an atlas-like observation, and also visualizes the diffusion of BoNT-containing fluid out of the needle tip.<sup>37</sup> Ultrasound-guided injections are just beginning to be used in patients with CD or in pediatric patients.<sup>38,39</sup> The combination of ultrasound and EMG is also possible, and dedicated probes are becoming available. This combined approach eliminated recurrent dysphagia observed after EMG-guided BoNT injections in CD.<sup>40</sup>

## Deep Brain Stimulation

After pivot trials reporting the efficacy of GPi DBS in generalized dystonia, recent evidence has supported the long-term efficacy and safety of this procedure (Table 3). The target of choice in most studies is the posteroventral lateral GPi. Large series on generalized dystonia published before 2013 are limited to 3 years,<sup>41,42</sup> with two open-label studies attempting to analyze longer-term outcome.<sup>43,44</sup> Two recent open-label studies reported long-term outcome in isolated generalized dystonia.<sup>45,46</sup> They encompass 15 DYT1 and 8 DYT6 mutation carriers, showing that long-term GPi-DBS is effective, although an early postoperative beneficial response to DBS is less likely in DYT6 dystonia. Recent data on patients with DYT1 dystonia also confirmed that GPi-DBS has no adverse effects on the main domains of cognitive function.<sup>47</sup> Although only based on class II-III evidence, efficacy and safety of GPi DBS have been well documented in isolated generalized dystonia: The treatment is overall safe and efficacious and should not be delayed. Patients with DYT11 myoclonus dystonia have been treated with DBS of the GPi or the ventral intermediate thalamic nucleus.<sup>48</sup> Improvement of myoclonus scores has been reported as equal with either target; dystonia scores, instead, show greater improvement after GPi implants.

Studies on monogenic dystonias suggest that disease duration before implant predicts outcome: Patients with shorter disease duration have better postoperative control of dystonia. This is particularly evident with DYT1 mutation carriers. Probably, an earlier DBS contributes to prevent secondary complications such as fixed musculoskeletal abnormalities and cervical myelopathy, which influence the stimulation efficacy.<sup>45,46,49</sup>

In addition to generalized dystonia, interest in the use of DBS has recently extended to patients with isolated CD (Table 3). This is the most prevalent dystonia syndrome that can be effectively treated with BoNT; therefore, the indication for DBS is limited to CD cases not responding adequately to BoNT treatment. Globus pallidus internus is the target of choice in most studies on CD.<sup>19,50,51</sup> A prospective study with rater-blinded comparisons of preoperative and postoperative assessments has reported efficacy of bilateral GPi-DBS after 5 or more years, with 49% total TWSTRS score improvement at 1

**TABLE 2.** Clinical trials on botulinum neurotoxins in dystonia (2013-2015)

| Study                              | Type of Treatment                                           | Trial Design (AAN Class of Evidence)                                  | Dystonia Type                    | Follow-up Period | Outcome Measures                                                                                                                              | Results/Status                                                                                                                          |
|------------------------------------|-------------------------------------------------------------|-----------------------------------------------------------------------|----------------------------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Lungu et al., 2013 <sup>33</sup>   | Topical acetyl hexapeptide-8 (AH8) plus BoNT injections     | Pilot, randomized, double-blind, placebo-controlled phase I (class I) | Blepharospasm (24 patients)      | 3 months         | <b>Primary:</b> Time to return to baseline JBRS after a BoNT injection and initiation of AH8                                                  | No significant adverse events, trend for longer time until return to baseline JBRS in the active group                                  |
| Delnooz et al., 2014 <sup>36</sup> | Endplate-targeted BoNT injections                           | Open-label study (class III)                                          | Cervical dystonia (18 patients)  | 1 month          | <b>Primary:</b> TWSTRS severity subscore                                                                                                      | Endplate-targeted, half-dosed BoNT injection resulted in a similar treatment effect to injecting the full dose using standard technique |
| Poewe et al., 2015 <sup>34</sup>   | Liquid abobotulinumtoxinA formulation                       | Double-blind and open-label phase III study (class II)                | Cervical dystonia (369 patients) | 3 months         | <b>Primary:</b> TWSTRS total and subscores                                                                                                    | Liquid abobotulinumtoxinA was as efficacious as current abobotulinumtoxinA                                                              |
| NCT02074293                        | OnabotulinumtoxinA plus automatic subdermal injector system | Randomized, double-blind, placebo-controlled phase I (class I)        | Cervical dystonia (60 patients)  | 12 months        | <b>Primary:</b> 6-month administration of gadolinium<br><b>Secondary:</b> 12-month administration of onabotulinumtoxinA instead of Gadolinium | Not yet recruiting                                                                                                                      |
| NCT00015457                        | Amlodipine plus BoNT                                        | Randomized, double-blind, placebo-controlled phase I (class I)        | Cervical dystonia (16 patients)  | 3 months         | <b>Primary:</b> TWSTRS severity, disability and pain scores<br><b>Secondary:</b> Duration of response; self-reported duration of effect       | Completed                                                                                                                               |

Abbreviations: ASIS, Automatic Subdermal Injector System; JBRS, Jankovic Blepharospasm Rating Scale; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

year and 47% improvement at 5 years.<sup>50</sup> The severity, pain, and disability TWSTRS subscales all improved to a similar degree. This study, based on 20 patients referred from a vast geographical area to a single neurosurgical unit, needs confirmation by controlled trials. In another retrospective observation on 28 patient with CD, no predictive outcomes of postimplantation status were identified, including age of onset, disease duration, baseline disease severity, age at surgery, lead tip coordinates, and DBS programming parameters.<sup>52</sup> Another retrospective study on eight CD patients with bilateral GPi DBS instead reported that disease duration influences severity, as assessed by the TWSTRS score ( $P < 0.05$ ).<sup>53</sup>

A recent short-term controlled study in 62 patients with isolated CD reported that GPi DBS is more effective than sham stimulation. Assessment 3 months post-implantation showed a reduction of approximately 26% in the TWSTRS severity subscore.<sup>19</sup> Only a negligible 3% further improvement was recorded 6 months after implantation. This is the first sham-controlled trial and the largest recruited patient cohort that provides definitive proof of efficacy for GPi DBS on CD. The

study raises a number of questions related to the practical management of patients with CD,<sup>54</sup> particularly the definition of cervical dystonia refractory to BoNT treatment. The recent evolution of BoNT targeting strategies using EMG and ultrasound will improve outcome of CD patients receiving BoNT treatment, which will in turn make it necessary to identify clinical algorithms for addressing these patients to GPi DBS after unsuccessful attempts with BoNT.

Less experience has been documented regarding the effects of GPi DBS on acquired dystonia. Recent studies have confirmed the earlier observation that patients with a substantial preservation of the pyramidal tract, of the DBS target region, and of motor output pathways have better outcome. In dystonic (hyperkinetic) cerebral palsy patients, with normal magnetic resonance imaging scan or mild static brain abnormalities, the average BFMDRS motor improvement was 35.9% for adults and 47.5% for children.<sup>55,56</sup> Follow-up for more than 2 years indicated a significant improvement of speech and swallowing. Another recent study showed that response to GPi DBS declines in children with severe idiopathic,

**TABLE 3.** Main clinical trials on DBS in dystonia (2013-2015)

| Study                                | Target      | Trial Design (AAN Class of Evidence)          | Dystonia Type                                                             | Follow-up Period | Outcome Measures                                                                                                           | Results                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------|-------------|-----------------------------------------------|---------------------------------------------------------------------------|------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cif et al, 2013 <sup>49</sup>        | GPi         | Open (class III)                              | DYT1 (11 patients)                                                        | NA               | Primary: BFMDRS ON-DBS, immediately after switch-off (OFF-DBS1) and 48 h after DBS termination (OFF-DBS2).                 | Significant between ON-DBS and OFF-DBS1. No relapse to preoperative severity at OFF-DBS2.                                                                                                                                                                                                                                         |
| Schjerling et al, 2013 <sup>61</sup> | GPi vs. STN | Prospective double-blind crossover (class II) | Focal, multifocal, or generalized dystonia (12 patients)                  | 12 months        | Primary: BFMDRS and video recordings or TWSTRS for patients with cervical dystonia                                         | Improved of BFMDRS: 13.8 points 6 months after STN stimulation ( $P < 0.05$ ), 9.1 points after GPi stimulation ( $P = 0.08$ )                                                                                                                                                                                                    |
| Walsh et al, 2013 <sup>50</sup>      | GPi         | Prospective (class III)                       | Cervical dystonia (10 patients)                                           | 5 years          | Primary: TWSTRS                                                                                                            | $47.4 \pm 26.4\%$ ( $P < 0.01$ ) mean improvement at 5 years compared with baseline. Maintained at a mean of 7.8 y after surgery.                                                                                                                                                                                                 |
| Witt et al, 2013 <sup>51</sup>       | GPi         | Retrospective (class III)                     | Cervical dystonia (28 patients)                                           | NA               | Primary: TWSTRS                                                                                                            | Patients with lateral shift at baseline had less improvement in TWSTRS severity subscores ( $P = 0.02$ ). No correlations between outcomes and disease duration, age at dystonia onset or surgery, baseline scores, or other variables.                                                                                           |
| Jahanshahi et al, 2014 <sup>47</sup> | GPi         | Prospective (class III)                       | DYT1 (14 patients)                                                        | 12 months        | Primary: IQ, memory for words and faces, working memory, language, executive functions, sustained attention                | Deterioration in sustained attention was only change after surgery                                                                                                                                                                                                                                                                |
| Keen et al, 2014 <sup>56</sup>       | GPi         | Retrospective (class III)                     | Children with cerebral palsy (5 patients)                                 | Up to 42 months  | Primary: Change in BADS and BFMDRS                                                                                         | Mean preoperative and postoperative BFMDRS motor scores were $73.3 \pm 26.6$ and $52.4 \pm 21.5$ with a mean improvement of 28.5% ( $P = 0.10$ ).                                                                                                                                                                                 |
| Sobstyl et al, 2014 <sup>45</sup>    | GPi         | Open (class III)                              | Isolated generalized dystonia, DYT carriers and noncarriers (12 patients) | 5 years          | Primary: Change in the BFMDRS                                                                                              | DYT1 carriers: Mean functional and motor BFMDRS scores decreased from 14.0 and 63.75 to 5.75 ( $P = 0.068$ ) and 22.0 ( $P = 0.066$ ) postoperatively. Non-carriers: scores decreased from 13.0 and 46.5 to 5.25 ( $P = 0.066$ ) and 22.75 ( $P = 0.068$ ) postoperatively.                                                       |
| Volkman et al, 2014 <sup>19</sup>    | GPi         | Randomized, sham-controlled (class I)         | Cervical dystonia (60 patients)                                           | 6 months         | Primary: TWSTRS severity score at baseline and 3 months, assessed by two masked dystonia experts using standardised videos | At 3 months, dystonia severity was significantly reduced in the neurostimulation group (-5.1 points).                                                                                                                                                                                                                             |
| Brüggemann et al, 2015 <sup>46</sup> | GPi         | Retrospective (class III)                     | Isolated DYT1, DYT6, and idiopathic (53 patients)                         | 92 months        | Primary: BFMDRS                                                                                                            | Early follow-up: Greater reduction of dystonia severity in DYT1 carriers (BFMDRS score: -60%) compared with idiopathic (-52%) and DYT6 carriers (-32%; $P = 0.046$ ). Late follow-up: Comparable improvement in the 3 groups (DYT6: -42%; DYT1: -44; idiopathic: -61%). Better outcome in patients with shorter disease duration. |

(Continued)

TABLE 3. Continued

| Study                           | Target | Trial Design (AAN Class of Evidence) | Dystonia Type                  | Follow-up Period | Outcome Measures                                                                                                                                                       | Results                                                                                                                                                                           |
|---------------------------------|--------|--------------------------------------|--------------------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mills et al, 2015 <sup>62</sup> | STN    | Prospective (class III)              | Cervical dystonia (8 patients) | NA               | <b>Primary:</b> Montreal Cognitive Assessment score, completed working memory (n-back) and motor (forced-maintenance) tests under single-task and dual-task conditions | No effect of stimulation on working memory or motor function under single-task conditions; worse performance in working memory tasks in the stimulation group with more difficult |

Abbreviations: BADS, Barry-Albright Dystonia Scale; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; GPi, globus pallidus internus; IQ, intelligence quotient; NA, Not available; SF-36, Short Form General Health Survey scale; STN, Subthalamic nucleus; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

inherited, or acquired dystonia, according to the life span lived with dystonia,<sup>57</sup> suggesting that DBS should be considered as an early option for these patients as well.

Globus pallidus internus DBS is not without side effects. In addition to possible surgical complications, motor complications, such as hypokinetic gait or bradykinesia with slowing of finger taps in unaffected limbs, have been reported.<sup>58,59</sup> Small studies of subthalamic nucleus (STN) DBS for dystonia, either generalized or focal, have reported large effect sizes and a comparatively different adverse effect profile, with lower incidence of bradykinesia and a higher incidence of dyskinesia.<sup>60,61</sup> Cognition was not significantly influenced by STN DBS in dystonia patients.<sup>62</sup> In a prospective double-blind crossover study, electrodes were bilaterally implanted in the STN and GPi of 12 patients with focal, multifocal, or generalized dystonia<sup>61</sup>; in most patients, STN stimulation appeared to be superior to GPi stimulation. Further work directly comparing the two targets is required before definitive conclusions can be drawn.

Thalamic ablations have historically been performed in patients with generalized dystonia. Recently, DBS of the motor thalamus has been proposed for selected cases of severe dystonic head tremor.<sup>63</sup> In addition, DBS of the thalamic ventral lateral anterior nucleus was reported to provide a sustained motor benefit in patients with DYT6 dystonia.<sup>64</sup>

### Transcranial and Epidural Stimulation

The rationale for the use of repetitive transcranial magnetic stimulation (rTMS) is based on abnormal inhibitory motor circuits in the brain, brainstem, and spinal cord of patients with dystonia. Use of rTMS has been postulated to reduce abnormal cortical excitability, consequently improving dystonia.

Recent studies reported clinical, neurophysiologic, and imaging improvements after rTMS in patients with focal hand dystonia,<sup>65</sup> axial dystonia,<sup>66</sup> or CD.<sup>67,68</sup> After evidence that the cerebellum is involved in the pathophysiology of dystonia, a recent study pro-

vided novel evidence that rTMS of the cerebellum is a potential target in patients with CD.<sup>69</sup> These data are all preliminary and require confirmation. Preliminary results of an rTMS trial on focal hand dystonia (NCT01884064) reported no significant changes in cortical excitability or handwriting after 5 days of rTMS. An additional study is underway on rTMS for focal hand dystonia (NCT01792336): it is designed to better understand the role of gamma frequency oscillations in cortical facilitation and to determine whether abnormal gamma frequency facilitation might become a potential diagnostic tool for dystonia. Similarly, another study is underway to test the efficacy of rTMS on dystonia in Wilson disease (NCT01980433).

Although cathodal transcranial direct current stimulation has been previously reported to be inefficacious in patients with focal hand dystonia, recent studies found that transcranial direct current stimulation of the motor cortex may improve hand motor control in musicians or children with dystonia.<sup>70,71</sup> The study on musicians, in particular, postulated that fine motor control of the dystonic hand could be improved by simultaneously facilitating the neural crosstalk into the affected cortex, increasing activation in the unaffected motor cortex with anodal stimulation and suppressing abnormal hyperactivity in the affected motor cortex with cathodal stimulation.<sup>70</sup> The observed improvement of the pianists' finger movements encourages further trials.

At variance to rTMS, extradural cortical stimulation through implanted electrodes generates a continuous field over the surface of the brain. Scattered data exist on the efficacy of premotor and motor cortical stimulation; however, a recent small double-blind, crossover, multicenter study on five patients with dystonia secondary to focal basal ganglia lesions reported lack of efficacy for epidural motor cortex stimulation.<sup>72</sup>

### Clinical Implications

Robust proof of efficacy exists for symptomatic treatments of dystonia. However, deciding which patients are

ideal candidates for medication, BoNT, or DBS needs to be further established. Different treatment options may be variably efficacious on dystonic movements (eg, dystonic tremor) or on dystonic postures. A schematic view is that DBS may be particularly beneficial on movements,<sup>73</sup> whereas BoNTs are more efficacious on the postural component. Dystonia has many phenotypic variants and may change phenomenology over time<sup>3</sup>; focal treatment with BoNTs needs to take into account this changing nature of dystonia, whereas DBS may require fine tuning variations over time. Deep brain stimulation is a first-line option in DYT1 mutation carriers and in patients with a potential to develop skeletal deformities or secondary myelopathy, who should be addressed early in surgery. The BoNTs instead stand as a first-line treatment in most forms of focal isolated dystonia.

How to define adequate motor improvement after BoNT treatment needs solid definitions, particularly at a time when DBS is offered to patients with focal dystonia syndromes. For example, a long-term moderate-to-marked improvement has been reported in patients with focal dystonia treated for 20 years with inspection-guided injections of BoNT.<sup>26</sup> A better outcome may be warranted when muscle activity is identified by EMG and ultrasound. Definition of a standard improvement threshold after BoNT treatment of different dystonia types is instrumental for designing treatment algorithms that consider DBS as an option. Complete disappearance of dystonia is unlikely after BoNT treatment, and medical decisions should be based on both motor and functional measures.

The timing of DBS surgery in patients with dystonia remains controversial. Surgery should be considered when oral medication and BoNT have failed and before the development of fixed skeletal deformities or cervical myelopathy. Insufficient evidence exists to recommend early DBS in all forms of dystonia, although recent data suggest that earlier surgery has a better outcome, particularly in DYT1 patients. Age should not be used as an inclusion or exclusion criterion for GPi DBS, and no data are available for children younger than 7 years. Regarding the time course of improvement, some months after DBS may be required before initial clinical improvement and 1 year or longer before full improvement are observed. Furthermore, spontaneous remissions of dystonia may occur in all patients, including those who received DBS implants.

Physical treatments are commonly performed in patients with dystonia either as a standalone protocol or in combination with BoNT and other treatments. Currently insufficient evidence exists to incorporate rehabilitation into dystonia treatment algorithms.<sup>74</sup> Dedicated research is needed to define the role of physical medicine and its relation to medical and surgical treatments for dystonia patients.

## Future Directions

Future clinical therapeutic research in dystonia will need to address two main areas: improving symptomatic control, independence and well-being of patients by symptomatic interventions, and finding disease-specific treatments for genetically determined dystonias. As in other movement disorders, the study of monogenic forms paves the way to innovative treatment approaches. After the recent identification of GNAL mutations in DYT25,<sup>75</sup> a link between dopamine signaling and isolated dystonia provided a specific target of investigation. GNAL encodes the protein G $\alpha$ olf involved in transducing signals downstream of D1 dopamine receptors in striatonigral projecting gamma aminobutyric acid-ergic neurons: its role could be a key for dystonia pathogenesis and treatment. The connection between dopamine signaling dysregulation and dystonia, considered a classic, still requires full understanding, and new developments in this field are expected.<sup>76</sup>

The practical management of dystonia is still too empirical. The recent classification will foster better patient management and improved comparability of clinical trials. Symptomatic treatment strategies need to be assembled into a coherent management workflow, to optimize choice and timing of each intervention in different dystonia syndromes. Outcome, which is currently mainly based on motor features, should be balanced between motor and functional goals.

The identification of biological markers to monitor the progression and remission of isolated dystonia syndromes over time is a still unmet need. Imaging and neurophysiological markers have proved unsuccessful. Imaging is typically normal in such cases, and follow-up is based on motor and functional clinical rating scales. Because dystonia is a network disorder, the underlying dysfunctional unbalance can vary with time, although it always involves the neostriatum. Medium spiny neurons are key players in striatal networks. Recent attention has been paid to the involvement of Rhes in dysfunction of striatal medium spiny neurons.<sup>77</sup> Rhes is a guanosine triphosphate-binding protein found in human and mouse striatum that is emerging as an important player in striatal physiology and pathology. Lack of Rhes causes an aberrant excitatory response to dopamine D2 receptors and activation in cholinergic interneurons, again suggesting a potential new target for dystonia treatment.<sup>78</sup>

Exploratory and proof-of-concept controlled trials are warranted in monogenic and isolated dystonias, where pathogenic hypotheses can lead to innovative treatment approaches. Neurobiological knowledge is indeed progressing. TorsinA, the mutated protein in DYT1 dystonia, is a natural target for treatment. Specific molecules that enhance torsinA activity represent

a promising new approach toward therapeutic development for DYT1 dystonia. Dystonia research consortia are instrumental for performing small well-designed clinical studies on rarer monogenic forms: their activity deserves support from funding agencies. The recent attention to funding rare diseases networks is of high interest. The fallout of this approach also would influence other genetic and nongenetic dystonia types. The observation that selective M1 muscarinic receptor antagonists offset synaptic plasticity deficits in the striatum of DYT1 knock-in mice<sup>79</sup> provides a rationale for designing improved antimuscarinic molecules to be used also in non-DYT1 dystonias.

Although innovative drugs are the expected development in isolated dystonia syndromes, neurorestorative approaches based on grafting (eg, neural stem cell-derived striatal interneurons) could be of potential use in degenerative combined dystonia syndromes, such as X-linked dystonia parkinsonism.<sup>80</sup> For Parkinson's disease, this approach has provided promising results in animal models, but mixed outcome in clinical trials. In the case of dystonia, restoration of small, locally projecting neurons, rather than the long-projecting nigrostriatal pathway, may provide an attainable goal. ■

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