Treatment of dystonia and tics

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Treatment of dystonia and tics continues to evolve. In dystonia, while oral agents such as benzodiazepines, baclofen and anticholinergics remain in use, botulinum toxin (BoNT) continues to be regarded as the treatment of choice for focal and segmental dystonia, but new preparations are being studied. While deep brain stimulation (DBS) has typically focused on targeting the globus pallidus internus (GPI) when treating dystonia, more recent research has expanded the targets to include subthalamic nucleus (STN) and other targets. In addition to DBS, thalamotomies continue to show therapeutic benefit in focal hand dystonias. Treatment of tics includes a growing armamentarium of options besides the three FDA-approved drugs, all dopamine receptor blockers (haloperidol, pimozide and aripiprazole). Because of lower risk of adverse effects, dopamine depleters (e.g. tetrabebazine, deuterabebazine, and valbenazine), along with novel D1 receptor antagonists, are currently studied as treatment alternatives in patients with tics. Practice guidelines for the treatment of tics and Tourette syndrome have been recently updated. Data regarding the use of DBS in treatment of tics remains relatively sparse, but international registries have expanded our understanding of the effect of stimulation at several targets.

1. Introduction

While treatment strategies for dystonia and tics have improved, they continue to rely on symptomatic rather than pathogenesis-targeted or disease-modifying therapies. Although oral medications have previously been used to treat these hyperkinetic movement disorders, additional therapeutic modalities, such as botulinum toxin (BoNT), have had notable impact on the quality of life of patients afflicted with dystonia and tics [1]. In this review, we discuss available therapies for the treatment of dystonia and tics, among the most common hyperkinetic disorders encountered in our movement disorders clinic, with particular emphasis on newer oral agents, BoNT, and deep brain stimulation (DBS).

2. Dystonia

2.1. Oral agents

All oral agents are used off-label for treatment of dystonia, as none have been approved by the United States Food and Drug Administration (FDA)
[1]. A cross-sectional international study recently examined the patterns of medication use in 2026 dystonia patients enrolled in the Dystonia Coalition [2]. In this international biorepository study, 73% of patients used some medication for their dystonia. The oral medications were classified into seven categories: 1) anticholinergics, 2) antidopaminergic medications 3) dopaminergic agents, 4) benzodiazepines, 5) baclofen, 6) non-benzodiazepine hypnotics, and 7) muscle relaxants, with benzodiazepines and muscle relaxants most frequently used. Oral medications were more frequently used by older patients, those with generalized dystonia, shorter duration of disease, and in patients with comorbid anxiety or depression.

Data regarding anticholinergic agents remains largely derived from older, empirical studies. Trihexyphenidyl remains one of the few oral agents assessed by randomized, double-blind, placebo-controlled trials [3]. A high dosage of 30 mg resulted in a clinically meaningful improvement in 22 of 31 (71%) patients with cervical dystonia (CD) in a double-blind, crossover trial, with considerable benefit sustained in 42% of these patients after a mean follow-up of 2.4 years [4]. However, use of trihexyphenidyl is frequently limited by side effects, such as cognitive deficit, urinary retention, dry mouth and blurring of vision, particularly in adults. In the Dystonia Coalition study, only 5% of all patients and 15.7% of those with generalized dystonia used trihexyphenidyl [2]. Diphenhydramine has shown modest benefit in a small series of patients with truncal dystonia [5].

Antidopaminergic agents include vesicular monoamine transporter 2 (VMAT2) inhibitors, which act as dopamine depleters by blocking monoamine neurotransmitter uptake in presynaptic vesicles [6]. While more commonly used in other hyperkinetic conditions such as chorea and tardive dyskinesia (TD), they have been increasingly studied in dystonia and may be particularly useful in tardive dystonia [1]. Tetrabenazine, an older agent in the class, resulted in symptom improvement in 66 of 82 (80.5%) tardive dystonia patients and 68 of 108 (62.9%) idiopathic dystonia patients in one study [7]. Improvement has been noted in other small studies [8,9]. One case report noted improvement in twins with myoclonus-dystonia [8,9]. Tetrabenazine is used as a treatment of dystonia should be discouraged. Olanzapine is a dopamine receptor blocker (DRB) that is commonly used in other hyperkinetic conditions such as chorea and tardive dyskinesia (TD), they have been increasingly studied in dystonia and may be particularly useful in tardive dystonia [1]. Tetrabenazine, an older agent in the class, resulted in symptom improvement in 66 of 82 (80.5%) tardive dystonia patients and 68 of 108 (62.9%) idiopathic dystonia patients in one study [7]. Improvement has been noted in other small studies [8,9]. One case report noted improvement in twins with myoclonus-dystonia [8,9].

Dopamine receptor blockers (DRBs) carry the risk of metabolic syndrome, weight gain and other potential side effects, including TD. Therefore, their use as a treatment of dystonia should be discouraged. Olanzapine has been associated with modest improvement in an open label trial of 4 patients, and clozapine has improved symptoms in small series of refractory oromandibular dystonia (OMD) [11] and generalized dystonia [12], but not in another series of patients with CD [13].

Benzodiazepines were the most commonly used medications in an international cohort [2], but there are no randomized controlled trials (RCT) to support their use [3]. Muscle relaxants, such as cyclobenzaprine and tizanidine, may be more helpful for treating pain associated with muscle spasm rather than dystonic posturing or movements [2,4]. Levodopa can provide notable benefit with relatively low doses in dopa-responsive dystonias, such as GTP cyclohydrolase 1 deficiency, tyrosine hydroxylase deficiency, or sepiapterin reductase deficiency [1]. Levodopa can also provide benefit in ataxia-telangiectasia, SCA3, and dystonia associated with Parkinson’s disease and other parkinsonian disorders [1,15]. Oral baclofen use is primarily based on case reports and clinical experience, without much objective evidence [3,5]. It can be helpful in patients with Parkinson’s disease with wearing off dystonia [16]. Intrathecal baclofen has been studied more extensively. In one series, 71 of 77 patients with generalized dystonia, mostly due to cerebral palsy (CP), had sustained benefit with intrathecal baclofen at a median follow-up of 29 months [17]. A recent RCT showed higher achievement of treatment goals with intrathecal baclofen versus placebo in 31 patients with severe dyskinetic CP [18]. Zolpidem, a non-benzodiazepine hypnotic, has been shown to improve various dystonias in an open-label trial [19], with the highest improvement in generalized dystonia but no improvement in CD. In a review of the literature, patients who received zolpidem in three studies had a significant average Burke-Fahn-Marsden Dystonia Rating Scale (BFMRDS) decrease from 7.2 ± 7.9 to 5.5 ± 5.0 [20]. Zolpidem improved dystonic dysarthria in a patient with Wilson’s disease in a case report, and improved dystonia in 3 patients with Lobag in a case series [21,22].

Recent trials have investigated new uses of older agents as treatment options for dystonia. Zonisamide was found to improve both myoclonus and dystonia in 23 patients with myoclonus-dystonia in a crossover RCT [23]. Apraclonidine eye drops, an alpha-2 adrenergic receptor agonist, have been shown to provide a transient benefit in blepharospasm severity, presumably via contraction of the superior tarsal (Muller’s) muscle; this approach is particularly beneficial in patients with premature wearing off following BoNT injection [24]. Sodium oxybate has been used in a small series of patients with myoclonus-dystonia [25] and in a larger open-label trial for spasmodic dysphonia [26]. It is currently being studied in a RCT in patients with spasmodic dysphonia and voice tremor (NCT02292458) [27]. Perampanel, an anti-epileptic medication that acts as an AMPA receptor antagonist, is being studied in a phase I/IIa trial in patients with CD (NCT02131467) [28]. Riluzole, a glutamate antagonist, showed benefit in a small series of patients with CD or cranial dystonia [30].

2.2. Botulinum toxin

Currently, serotypes of BoNT-A, including onabotulinumtoxinA (ONA), abobotulinumtoxinA (ABO), incobotulinumtoxinA (INCO), and of BoNT-B, such as riambotulinumtoxinB (RIMA), are in clinical use for treatment of dystonia. While BoNT has become a mainstay of therapy in focal and segmental dystonia, the Dystonia Coalition study found that only 1230 of 2026 (60.7%) dystonia patients received BoNT [2]. In a longitudinal registry of CD patients receiving ONA treatment, 544 of 1046 (52%) of patients had withdrawn from the registry [31]. Of those who withdrew, 23.2% were lost to follow-up, 9.1% withdrew consent, 8.1% had no response at any treatment session, and 3.1% had adverse effects. Other longitudinal studies have noted approximately one third of CD patients discontinue therapy, most commonly due to a presumed lack of benefit [32], although lack of response can often be improved by changes in dosage and better target selection [33].

While the FDA has approved each commercial preparation for various indications (Table 1), BoNT is often used for off-label indications. A practice guideline was released from the American Academy of Neurology (AAN) for the use of BoNT in blepharospasm, CD, adult spasticity, and headache [34] (Table 1). In CD, ABO and RIMA have level A recommendations, while ONA and INCO have received only level B recommendations, largely because of a paucity of RCTs. In blepharospasm, ONA and INCO have level B recommendations, ABO has a level C recommendation, and RIMA has unknown efficacy. In practice, the BoNT-A formulations are often used interchangeably for CD, while RIMA is typically avoided due to greater injection pain and autonomic side effects, such as dry mouth [35]. In contrast to INCO, which has low antigenicity due to its lack of non-toxic accessory proteins, RIMA, although initially effective in patients with neutralizing antibodies against BoNT-A, may be eventually associated with immunoresistance [33]. Evidence is also expanding for non-FDA FDA-approved indications and levels of recommendation for Botulinum formulations [31].

![Table 1](https://example.com/table1.png)

| FDA approved | CD | BSP | ULS | CM | OAB | AH | strabismus |
|-------------|----|-----|-----|----|-----|----|-----------|
| Ona         | B  | B   | A   | A  |     |    |           |
| Abo         | CD | ULS | (adults), ULS (children), GL | 104 | A | C | A | A | |
| Inco        | CD | BSP | ULS | GL | silorhea | 105 | B | B | A | U |
| Rima        | CD | sialorhea | 106 | | A | B | U |

Legend: ONA = onabotulinumtoxinA, ABO = abobotulinumtoxinA, INCO = incobotulinumtoxinA, RIMA = riambotulinumtoxinB, CD = cervical dystonia, BSP = blepharospasm, ULS = upper-limb spasticity, LLS = lower-limb spasticity, CM = chronic migraine, OAB = overactive bladder, AH = axillary hyperhidrosis, GL = glabellar lines.
approved indications, such as OMD and bruxism [36,37]. However, generalized dystonia and specific forms of dystonia, such as anterocollis or abductor spasmotic dysphonia, can be challenging to treat with BoNT [1].

BoNT cannot be administered more frequently than every 12 weeks, due to concerns for immunogenicity [33], but many patients prefer shorter dosing intervals [38]. DaxibotulinumtoxinA (DAXI) is a new BoNT-A formulation, currently in clinical development, designed for an extended duration of benefit [39]. It has no non-toxic accessory proteins, like INCO, but has a proprietary stabilizing excipient peptide composed of two protein transduction domains on a lysine backbone that bonds to the neurotoxin [39]. Preclinical studies showed less diffusion of DAXI [40]. A phase 2, open-label study in 37 CD patients showed an average 38% reduction in TWSTRS scores at 4 weeks and 50% reduction at 6 weeks [39]. Notably, 68% of patients continued to have >20% reduction in symptoms at 24 weeks, and doses were well-tolerated with mostly mild-to-moderate, transient adverse effects. While the duration of benefit is promising, further studies are needed, and a phase 3 RCT, ASPIEN-1 (NCT03608397), and a phase 3 open-label trial, ASPIEN-OLS (NCT03617367), are currently in progress [41,42].

2.3. Deep brain stimulation

DBS is considered the surgical treatment of choice in patients with segmental or generalized dystonia who continue to be disabled despite optimal medical or BoNT therapy. In the Dystonia Coalition, 51 of 2026 patients (2.52%) had undergone DBS, most of whom were young (<35 years old) and had generalized dystonia. Certain types of genetic dystonia, such as TOR1A, KMT2B, TAF1, and SGCE, typically have better responses to DBS than others, such as THAP1, ATP1A3 and GNAL [6,14,43,44]. CD can also respond to DBS, particularly the phasic variety [45]. In one study involving 19 patients, bilateral Gpi DBS improved TD symptoms, including dystonia subscores [46]. An RCT with 25 patients with TD did not show significant reduction in BFMDRS between active and sham stimulation at 3 months but found an average of 41.5% improvement via blinded evaluation = during the open-label extension [47]. Secondary dystonia is typically less responsive [15].

The two main targets for dystonia treatment with DBS are Gpi and subthalamic nucleus (STN). Gpi has been the typical target, based off studies showing sustained benefit in generalized dystonia such as a 58% reduction in the BFMDRS at 3 years [48] or 57.8% reduction at 5 years [49]. Gpi has been effective in CD as well, such as in a 10 patient study in Canada showing improvement in pain and TWSTRS severity scores [50], or a sham-controlled study in Europe with 62 patients showing 26% reduction in TWSTRS compared to 6% reduction with sham stimulation [51]. Although quite effective, some patients experienced bradykinesia and other parkinsonian side effects with Gpi DBS and, therefore, some investigators have transitioned to targeting. In a crossover study, 12 patients with dystonia were bilaterally implanted with electrodes in both STN and Gpi [52]. Patients were randomly assigned to stimulation of Gpi for 6 months, then STN for 6 months, and had blinded assessments with BFMDRS and TWSTRS (where applicable). Mean improvement in BFMDRS at 6 months was 13.8 points with STN stimulation and 9.1 points with Gpi stimulation. Other longitudinal studies have found sustained benefit with STN stimulation without parkinsonism as an adverse effect (AE) of Gpi DBS. In one series of 27 patients with primary dystonia who underwent STN DBS placement, BFMDRS scores had improved by 55% at 1 month, 77% at 1 year, and 79% at 3 to 10 years [53]. In another study, a group of 20 patients with isolated dystonia underwent STN DBS placement and were blindly assessed by BFMDRS and TWSTRS at 6 and 12 months, followed by an extension with unblinded assessment at 18, 24, and 36 months [54]. All patients had prominent upper body dystonia or CD, and 4 patients had DYT1. BFMDRS decreased by 9.1 points (51.1%) at 6 months and 10.9 points (60.8%) at 12 months in the initial core study, with sustained reduction of 12.3 points (68.5%) at 18 months, 13.6 points (76.1%) at 24 months, and 12.6 points (70.4%) at 36 months. TWSTRS scores showed a similar pattern of reduction of 22.2 (54.2%), 25.4 (61.8%), 27.3 (66.5%), 29.8 (72.6%) and 27.3 (66.6%) points at 6, 12, 18, 24, and 36 months respectively. Only 2 of 20 patients had <25% improvement at 12 months, and these patients had confounding cervical spine disease and bi-branchial dystonia. Only 2 patients continued to require BoNT injections after surgery. Another retrospective study of 14 patients with STN DBS placement for primary dystonia found improvement in BFMDRS scores by 59.0%, 85.0%, and 90.8% at 1 month, 1 year, and 5 years after surgery [55], further supporting STN as a target option.

2.4. Ablation

Pallidotomy and thalamotomy have been largely replaced by DBS [6], although interest in ablation has re-emerged during the past few years with the advent of MRI-guided focused ultrasound [1]. However, recent research has shown particular benefit of ventral-oralis anterior (Voa) and posterior (Vop) thalamotomies in treating focal hand dystonia. The thalamic Voa complex, located in the anterior thalamus, is involved in pallidothermalamic and cerebellothalamic pathways [56]. Several small case series have shown improvement in focal hand dystonia (such as writer’s cramp and musician’s dystonia) with Voa thalamotomies [56–62]. A recent retrospective study reported on the outcomes of 171 patients who underwent Voa-Vop thalamotomy for focal hand dystonia [63]. The primary target for these patients was the Voa-Vop junction using atlas coordinates, where 9 lesions in 3 separate tracks were made by a monopolar radiofrequency probe. Patients were assessed at 1 week, 3 weeks, 12 months, and at last available follow-up by the Task Specific Focal Dystonia (TSFD) scale, which is a 5 point scale ranging from inability to perform task (1) to normal functioning (5). 138 of 172 patients (80.2%) were deemed “good responders”, with TSFD scores of 4 or 5. The mean TSFD score was 4.34 at 1 week, 4.24 at 12 months, and 4.34 at last visit (mean of 25.4 months). Dystonia recurred in 18 of 171 (10.5%) patients, 7 of whom improved with a repeat thalamotomy. Permanent AEs including dysarthria, foot weakness, hand dysesthesias, and verbal recall disturbance occurred in 6 patients (3.5%) [64].

3. Tics

Treatment of tics is most often studied in the context of Tourette syndrome (TS). Treatment strategies have expanded to include options such as BoNT and DBS, but often rely on a tiered oral medication approach (Fig. 1).

3.1. Oral medications

Alpha-2 agonists clonidine and guanfacine are often tried first in mild cases of TS. These agents have a modest effect on tic control, but because of relatively low risk of AEs (mainly drowsiness, low blood pressure and dry mouth) they are quite helpful, particularly in patients with comorbid ADHD and impulse control disorder [65,66]. In one RCT 34 children with chronic tic disorder (CTD) were treated with extended-release guanfacine or placebo [67]. There was no significant change between treatment and placebo in the Yale Global Tic Severity Scale Total tic score (YGTSS-TTS). Topiramate is sometimes used in mild cases of TS. It has shown efficacy in a small RCT and one retrospective study [68,69]. A meta-analysis found a mean reduction of 7.74 in YGTSS scores in 207 patients treated with topiramate in 3 trials [70].

The second tier of medications usually includes antiparkinsonian drugs, including DRBs (e.g. risperidone, fluphenazine, haloperidol, pimozide, and aripiprazole), or dopamine-depleting drugs (e.g. tetrabenazine, deutetrabenazine, and valbenazine). Currently, only haloperidol, pimozide, and aripiprazole are approved by the FDA for the treatment of TS. In a phase 3 RCT, 119 patients showed a 45.9% and 54.2% decrease in YGTSS-TTS with low and high doses of aripiprazole respectively compared to placebo [71]. Only 16.7% of placebo-treated patients had a >50% reduction in their YGTSS-TTS, as compared to 40.5% and 57.1% of the
low-dose and high-dose cohorts, respectively. Sedation and fatigue were the most common AEs.

The AAN recently performed a systematic review of the literature [72] and issued updated practice guideline recommendations for the treatment of tics in TS and CTD [73]. The only statement able to be made with “high confidence”, based on two Class I studies, was that patients with tics receiving Comprehensive Behavioral Intervention for Tics (CBIT) were more likely to have reduced tic severity than those receiving only supportive psychotherapy [72, 74, 75]. CBIT is composed of habit reversal training, relaxation techniques, and functional intervention, and is typically conducted over 8 sessions [73]. CBIT appears to have a similar effect size as anti-psychotic (DRB) medications [73]. Consequently, the AAN panel gave a Level B recommendation to offering CBIT as an initial treatment option relative to medication [73]. Among their review of oral agents, there was a moderate level of confidence in the treatment effect of haloperidol, risperidone, aripiprazole, tiapride, clonidine, nindong granule (as formulated by Zhao), and 5-ling granule [72], and low confidence in the effect of pimozide, ziprasidone, metoclopramide, guanfacine, topiramate, and tetrahydrocannabinil (THC) [72].

Because of paucity of controlled studies in TS, the VMAT2 inhibitors received relatively little attention from the AAN guidelines. These drugs, however, are increasingly used to treat a large variety of hyperkinetic disorders, including chorea, TD, and tics [76]. One of the chief advantages of these drugs over DRBs is that they do not cause TD. Tetrabenazine was found to have a moderate-to-marked improvement in TS-related symptoms in a majority of patients in a retrospective, open-label study of 77 patients [77]. More recent research has focused on deutetrabenazine and valbenazine due to their lower side-effect profile and easier dosing schedules. In an open-label trial of deutetrabenazine with 23 patients with TS from ages 12 to 18, there was a mean 37.6% reduction in YGTSS-TTS after 8 weeks of treatment, with 61.9% of patients having a >25% reduction in their YGTSS-TTS [78]. Ongoing trials examining deutetrabenazine in TS include ARTISTS1, a 12-week phase 2/3 RCT with a 28 week extension (NCT03452943) [79], and ARTISTS2, an 8-week phase 3 RCT with low-dose and high-dose cohorts (NCT03571256) [80]. Studies with valbenazine have unfortunately not been promising. T-Force GREEN, a pediatric phase 2 study, did not show a significant difference between valbenazine and placebo in reduction of baseline YGTSS [81]. A subsequent pediatric phase 2b study, T-Force GOLD, also did not meet its primary endpoint of reduction of baseline YGTSS compared to placebo [82]. T-Forward, an adult phase 2 study, failed to show a significant change in YGTSS at week 8 of treatment compared to placebo (p = 0.18) [83]. The reasons for these failures are not well understood but may be related to inclusion of relatively mild cases and underdosing.

Additional trials of other classes of medications are currently ongoing (Table 2). While current DRBs target the D2 receptor, ecopipam is a high-affinity D1 receptor antagonist [84]. An open-label trial of ecopipam in 18 adults with TS showed a significant mean reduction in YGTSS-TTS from 30.6 to 25.3 over 8 weeks [85]. A subsequent RCT in 40 children showed a significant mean reduction in YGTSS-TTS of 3.7 and 3.2 points at 16 and 30 days respectively [84]. The proportion of patients with moderate, marked, or severe symptoms per CGI-S significantly dropped from 97.5% to 55% on ecopipam versus 80% on placebo. Building on this, DIAMOND is an actively recruiting phase 2b RCT examining ecopipam in patients from 6 to 17 years old with a primary outcome of reduction in YGTSS (NCT04007991) [86].

Beside dopamine, other neurotransmitters have been implicated in the pathogenesis of TS [86]. Serotonergic abnormality has been proposed in the generation of tics and behavioral comorbidities associated with TS, particularly OCD. Therefore, pimavanserin, a selective serotonin inverse agonist approved by the FDA for the treatment of psychosis associated with Parkinson’s disease, is being studied for use in adults with TS in a pilot, open-label trial [87].

ABX-1431 inhibits monoacylglycerol lipase, an enzyme that regulates 2-arachidonylglycerol which is an endogenous agonist of cannabinoid CB1 and CB2 receptors [86]. Inhibition of MGLL has shown anti-nociceptive, anxiolytic, and anti-inflammatory effects, and exerted neuroprotective effects in animal models of Parkinson’s disease and Alzheimer’s disease [88]. A double-blind crossover single-dose RCT with 19 adult TS patients showed a significant 10% reduction in YGTSS-TTS at 8 h after dosing [89]. A subsequent phase 2 RCT at two dosing levels is ongoing in adult TS patients (NCT03625453) [90].

3.2. Botulinum toxin

BoNT has been examined in several, mostly open-label trials for the treatment of TS. In an open-label series, 29 of 35 patients had improvement.
in tics over a mean of 3.3 injections [91], and 23 patients demonstrated at least markedly improved function. Additionally, 21 of 25 patients with premonitory sensations reported marked relief of those symptoms. Another open-label series examining vocal cord injections with BoNT for treatment of phonic tics in 30 patients demonstrated improvement in tics in 93% and resolution in 50% of patients [92]. In a separate crossover RCT, 18 patients were treated with BoNT or placebo, and targeted tics-per-minute were measured 2 weeks after injection [93]. A 39% reduction in tic frequency was noted in the treatment group versus a 5.8% increase in the placebo group, where there was significantly greater reduction with placebo (24 weeks).

4. Conclusions

Treatment options for dystonia and tics have continued to evolve. In addition to novel oral agents, new preparations of BoNT hold promise for improving symptoms in patients with dystonia and TS. In tics, new oral agents, new preparations of BoNT, and cannabinoid agents are under study. Exploration of new DBS targets, coupled with improvements in DBS technology, will undoubtedly translate into better outcomes for patients with dystonia and tics.

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