Childhood Dystonias

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Opinion statement
Dystonia is a movement disorder caused by diverse etiologies. Its treatment in children is particularly challenging due to the complexity of the development of the nervous system from birth to young adulthood. The treatment options of childhood dystonia include several oral pharmaceutical agents, botulinum toxin injections, and deep brain stimulation (DBS) therapy. The choice of drug therapy relies on the suspected etiology of the dystonia and the adverse effect profile of the drugs. Dystonic syndromes with known etiologies may require specific interventions, but most dystonias are treated by trying serially a handful of medications starting with those with the best risk/benefit profile. In conjunction to drug therapy, botulinum toxin injections may be used to target a problematic group dystonic muscles. The maximal botulinum toxin dose is limited by the weight of the child, therefore limiting the number of the muscles amenable to such treatment. When drugs and botulinum toxin injections fail to control the child’s disabling dystonia, DBS therapy may be offered as a last remedy. Delivering optimal DBS therapy to children with dystonia requires a multidisciplinary team of experienced pediatric neurosurgeons, neurologists, and nurses to select adequate candidates, perform this delicate stereotactic procedure, and optimize DBS delivery. Even in the best hands, the response of childhood dystonia to DBS therapy varies greatly. Future therapy of childhood dystonia will parallel the advancement of knowledge of the pathophysiology of dystonic syndromes and the development of clinical and research tools for their study.

Introduction
Dystonia is defined as a movement disorder manifesting as sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, and/or postures [1••, 2]. This general definition may need to be modified to specifically describe dystonia and dystonic hypertonia in childhood [3••]. Furthermore, unlike dystonia in adults that typically remains focal or spreads only to nearby muscle groups [4], childhood dystonia often generalizes, i.e., spreading from a limb to the trunk as well as at least two other parts of the body [5].

Classification of dystonia has direct implications for narrowing down the differential diagnosis, choosing the diagnostic work-up, predicting the prognosis, and choosing treatment options. Virtually, any lesion of the nervous system can induce dystonia. Indeed, dystonic syndromes have numerous etiologies that used to be
classified traditionally as either primary, also known as idiopathic, or secondary dystonia [6–10] (Table 1). Primary dystonias include neurological disorders where the cause is unknown or where a specific genetic mutation causes a neurological disorder whose primary feature is dystonia. Primary dystonias also include paroxysmal dystonias and dystonia-plus syndromes [11, 12] where the dystonia is associated with other neurological signs, such as myoclonus or parkinsonism. Secondary dystonias are those where a cause of the dystonia can be readily identified.

With advancement in the understanding of the clinical phenotype, genetics, and pathophysiology of dystonias, the traditional classification of dystonia into primary and secondary has become ambiguous. This led to an updated consensus-based classification of dystonia that is aligned along two axes [1••]:

- Axis 1 addresses the clinical characteristics of dystonia, i.e., its phenomenology described in terms of age at onset, body distribution, tempo-rall pattern, and associated features.
- Axis 2 addresses the etiology of dystonia and is subdivided into degenerative and non-degenerative forms at the gross, microscopic, or molecular level; further subdivision includes the distinction between inherited and acquired forms.

The evaluation of a dystonic child starts by witnessing that the patient has indeed dystonic movements and postures. Intermittent dystonias are best recognized on a home video if the neurological exam in the clinic is unremarkable. The age at onset, pattern and progression of the dystonia, the family history, and the associated neurological signs and symptoms (such as parkinsonism or myoclonus) are essential in elucidating the neurological signs and symptoms (such as parkinsonism or myoclonus). Secondary dystonias are those where a cause of the dystonia can be readily identified.

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The treatment of secondary dystonia consists of treating the underlying cause if possible as well as the use of antidystonic drugs. For example, dopamine receptor blocking drugs should be discontinued in tardive dystonia. Copper restriction and chelation must be implemented promptly in dystonic children with Wilson disease. Dopa-responsive dystonia (DRD), also known as Segawa syndrome, is exquisitely responsive to low-dose levodopa [12••, 17], and since its phenomenology may overlap with other forms of progressive generalized dystonia, a trial of levodopa in every child with primary or some of the secondary dystonia may be reasonable.

Status dystonicus, also known as dystonic storm, is defined as frequent and severe episodes of exacerbation of generalized dystonia, requiring hospitalization [21]. Status dystonicus is a life-threatening neurological...
emergency that may occur in the context of primary or secondary dystonia. It often manifests as painful dystonic muscle spasms that may lead to respiratory compromise as well as metabolic complications, such as hyperpyrexia, dehydration, respiratory failure, and rhabdomyolysis that may cause acute renal failure. Although dystonic storms may occur without an obvious trigger, they have been reported to be associated with infections, reduction of lithium dose, tetrabenazine withdrawal, and the introduction of clonazepam, penicillamine, or zinc therapies [22].

Botulinum toxin injections may be used as adjunctive therapy to weaken specific dystonic muscles that are causing pain or motor impairment. The maximal botulinum toxin dose per session is dictated by the weight of the child, hence possibly limiting the number of the muscles that can be injected.

Dystonias are not consistently responsive to DBS therapy [19, 23, 24], and, given the potential complications of DBS surgery/therapy, bilateral globus pallidus internus (GPI) DBS surgery should only be offered to patients who fail medical and botulinum toxin therapy.

<table>
<thead>
<tr>
<th>Table 1. Classification of dystonia</th>
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<tbody>
<tr>
<td><strong>Primary dystonias</strong></td>
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<tr>
<td>Dystonia of unknown cause</td>
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<tr>
<td>Dystonia with DYT gene mutationa</td>
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<tr>
<td>DYT 1: early-onset primary torsion dystonia</td>
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<tr>
<td>DYT 2: early-onset primary dystonia with prominent crano-cervical involvement</td>
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<tr>
<td>DYT 3: adult onset dystonia-parkinsonism (prevalent in the Philippines)</td>
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<td>DYT 4: whispering dystonia (adult onset spasmodic dysphonia) with generalization and “hobby horse” gait</td>
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<tr>
<td>DYT 6: adult-onset torsion dystonia with prominent crano-cervical and laryngeal involvement</td>
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<tr>
<td>DYT 7: adult-onset primary cervical dystonia</td>
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<td>DYT 8: adult-onset mixed dystonia with generalization</td>
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<td>DYT 11: early onset dystonia (in one Italian family)</td>
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<td>DYT 12: rapid onset dystonia parkinsonism and alternating hemiplegia of childhood</td>
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<tr>
<td>DYT 13: early onset torsion dystonia (in one Italian family)</td>
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<td>DYT 15: primary focal dystonia with progression (in one Lebanese family)</td>
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<tr>
<td>DYT 20: adult-onset mixed dystonia with generalization</td>
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<tr>
<td>DYT 21: cranio-cervical dystonia, often tremulous, with/without upper limb tremor</td>
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<tr>
<td><strong>Dystonia-plus syndromes</strong></td>
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<tr>
<td>Dopa-responsive dystonia</td>
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<tr>
<td>Progressive dopa-responsive dystonia with diurnal variation due to DYT 5a gene mutation</td>
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<tr>
<td>Akinetic rigid syndrome with dopa-responsive dystonia or complex encephalopathy due to DYT 5b gene mutation</td>
</tr>
<tr>
<td>Myoclonus-dystonia syndrome due to a DYT 11 and DYT 15 gene mutation</td>
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<tr>
<td>Rapid-onset dystonia parkinsonism syndrome due to DYT-12 gene mutation</td>
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<tr>
<td><strong>Paroxysmal dystonias</strong></td>
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<tr>
<td>Paroxysmal non-kinesigenic dystonia due to DYT 8 and DYT 20 gene mutation</td>
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<tr>
<td>Paroxysmal kinesigenic dystonia due to DYT 10 gene mutation</td>
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<tr>
<td>Paroxysmal exercise-induced dystonia</td>
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<tr>
<td>Paroxysmal exercise-induced dyskinesia with/without epilepsy due to DYT 18 gene mutation</td>
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<tr>
<td><strong>Secondary dystonias</strong></td>
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<tr>
<td>Acquired dystonias</td>
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<tr>
<td>Demyelinating brain diseases</td>
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<tr>
<td>Anoxic brain injury</td>
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<tr>
<td>Acute disseminated encephalomyelitis</td>
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<tr>
<td>Infections</td>
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<tr>
<td>Tumors</td>
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<th>Table 1. (Continued)</th>
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<tr>
<td>Stroke</td>
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<tr>
<td>Drugs, especially dopamine receptor blocking agents and antiepileptic drugs</td>
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<tr>
<td>Heredodegenerative dystonias</td>
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<tr>
<td>Wilson disease</td>
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<td>Huntington disease</td>
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<tr>
<td>Dentatorubralpallidolysisian atrophy</td>
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<tr>
<td>Spino cerebellar ataxias (especially spinocerebellar ataxia type 3)</td>
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<tr>
<td>Errors of metabolism</td>
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<tr>
<td>Glutaric aciduria</td>
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<td>Methyl malonic academia</td>
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<tr>
<td>Lesch–Nyhan syndrome</td>
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<tr>
<td>Lipid storage disorders</td>
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<tr>
<td>Niemann–Pick disease, types C and D</td>
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<tr>
<td>GM1 and GM2 gangliosidoses</td>
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<tr>
<td>Cereoid lipofuscinoses</td>
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<tr>
<td>Mitochondrial disorders</td>
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<tr>
<td>Neuronal degeneration with brain iron accumulation, including pantothenate kinase</td>
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<tr>
<td>Associated neurodegeneration</td>
</tr>
<tr>
<td>Psychogenic dystonia</td>
</tr>
</tbody>
</table>

*DYT 9, DYT 14, and DYT 19 are synonymous with DYT 18, DYT 5a, and DYT 10, respectively. DYT 22 name is reserved but not published.*
Physical and occupational therapies are often prescribed as adjunctive treatment of childhood dystonia to prevent contractures, mobilize joints, and optimize motor function. Speech therapy may improve dysphonia and dysphagia as well as enhance communication skills of the child. The use of assistive devices such as customized braces, electric wheelchairs, and communication devices may also be useful to address specific needs.

**Treatment**

### Pediatric treatment considerations

Just like normal neurological function changes during the development of a child’s nervous system, so does neurological dysfunction [3••]. Childhood dystonia follows this rule, therefore, manifesting in an age-dependent manner in terms of onset, progression, response to treatment, and development of adverse effects to medications. It is essential for the pediatric neurologist to recognize the variety of movement patterns that would be considered normal in a toddler, while they reflect pathology in older children or adults [25, 26]. This makes the development of dystonia rating scales particularly difficult for the assessment of children of all ages in the context of research or clinical care [27].

Childhood dystonia is most commonly treated with trihexyphenidyl, baclofen, and levodopa (in combination with carbidopa) [28, 29]. Clinicians prescribe these drugs “off-label” although none of the antidystonia drugs or botulinum toxin have been approved by the US Food and Drug Administration (FDA) for the treatment of childhood dystonia. Only baclofen has FDA-approved dosing for children for the treatment of spasticity. Dosing of antidystonia medications in children is weight dependent as well as age dependent. Published dosing recommendations are based on small studies or opinions of expert pediatric neurologists. Only trihexyphenidyl was evaluated in a double blind, placebo-controlled trial [30].

The key for safe and effective antidystonic drug therapy is by following a slow titration schedule where the dose of the drug is increased gradually until adequate dystonia control is achieved or until adverse effects appear. Adverse effects would then appear gradually allowing ample time for the clinician to address them. Assessing such adverse effects may be particularly difficult in younger children, since they may not have the verbal skills to report them [3••]. Early studies suggest that children in their mid-teens were less likely to report cognitive adverse effects than young adults in their mid-20s [30]; however, more rigorous observation suggested that dystonic children as young as 8–15 years had a definite decline in their school performance while taking trihexyphenidyl despite their inability to self-report cognitive adverse effects [31•].

Since dystonia improvement on drug therapy may be delayed by weeks, each antidystonic drug should be allowed several weeks after reaching the target dose to manifest its motor benefit before being discarded as an ineffective drug. A drug that fails should be tapered slowly while observing for worsening of dystonia even if no obvious benefit occurred while titrating the dose up. Worsening of dystonia while tapering a drug may suggest that the drug was at least partially effective and could be reinstated prior to adding another antidystonic drug.

Any antidystonic drug may improve dystonia in a child while worsening it in another. While some dystonias improve on dopaminergic drugs and worsen on dopamine blocking agents, other ones conversely improve on dopamine blocking agents.
agents and worsen on dopaminergic drugs. This adds to the heterogeneity of the pathophysiology of dystonia syndromes. Since levodopa is safer in general than dopamine blocking agents, it may be reasonable to try levodopa first.

Unlike adult dystonia, childhood dystonia has unique features impacting DBS therapy. Namely, childhood dystonia is more often secondary than primary, is often associated with motor dysfunction other than dystonia such as spasticity or dystonic hypertonia [32], and has a course that is affected by brain maturation and neuroplasticity. DBS therapy may exert a beneficial effect on the abnormal neuroplasticity in dystonic children. However, the effects of DBS on normal plasticity are unknown and may potentially be detrimental [3••].

Finally, treating childhood dystonia is further complicated by the fact that choosing therapeutic strategies involves the parents and a child, who may or not be able to provide informed consent. This adds a layer of complexity to ethical issues when choosing DBS surgery.

Pharmacologic treatment

The aim of drug therapy is to abolish dystonia and its associated pain while improving disability with the least amount of adverse effects. A combination of antidystonia drugs may be required, although this may potentiate the adverse effects of individual drugs, such as sedation and nausea. Each drug, therefore, should be used at its lowest effective tolerable dose. Dosage and common adverse effects of drugs used in the treatment of childhood dystonia are summarized in Table 2. All antidystonic drugs are relatively cheap with the exception of tetrabenazine and botulinum toxin.

Treatment of primary dystonia

Levodopa

Levodopa is the drug of choice for children with DRD [12••]. Since levodopa may be effective in a minority of patients with other forms of primary dystonia, it is reasonable to try it as the first drug in any child presenting with any form of early-onset dystonia without a known etiology. Indeed, it has a relatively favorable adverse event profile that allows a relatively quick therapeutic trial [12••, 33].

**Standard dosage**

The starting dose of levodopa is 1 mg kg\(^{-1}\) day\(^{-1}\) in three divided doses. The dose may be increased every week aiming at the lowest effective tolerable dose, up to 10 mg kg\(^{-1}\) day\(^{-1}\) to titrate the dystonic symptoms. Most patients rarely require more than 4–5 mg kg\(^{-1}\) day\(^{-1}\). Patients who do not respond to 600 mg/day are very unlikely to have DRD.

**Main side effects**

Levodopa may cause anorexia, nausea, vomiting, constipation, sedation, hallucinations, and dyskinesia.

To prevent gastrointestinal adverse effects, levodopa is available in combination with carbidopa or benzerazide that are aromatic amino acid decarboxylase inhibitors that do not cross the blood–brain barrier. Such adverse effects are typically blocked by 25 mg of carbidopa for each 100 mg of levodopa or by 1–2 mg kg\(^{-1}\) day\(^{-1}\) of benzerazide [34, 35]. For a precise dose titration in small increments, the drug may be dissolved in an acidic solution, such as orange juice, and dispensed over 24 hours as long as the solution is kept refrigerated and away from direct sunlight. In rare instances, nausea may require additional
Table 2. Dosage and common adverse effects of drugs used in the treatment of childhood dystonia

<table>
<thead>
<tr>
<th>Name of the drug</th>
<th>Starting dose</th>
<th>Titration schedule</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>1 mg kg(^{-1}) day(^{-1}) in 3 divided doses</td>
<td>Increase every week, up to 10 mg kg(^{-1}) day(^{-1})</td>
<td>Anorexia, nausea, vomiting, constipation, sedation, hallucinations and dyskinesia</td>
</tr>
<tr>
<td></td>
<td>Use with 25 mg of carbidopa for each 100 mg of levodopa OR with 1–2 mg kg(^{-1}) day(^{-1}) of benzerazide OR domperidone is 0.75 mg/kg in 3 divided doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>0.03–0.06 mg kg(^{-1}) day(^{-1}) in 3 or 4 divided doses (lower end of the range for children&lt;4 years)</td>
<td>Increase by 0.03–0.06 mg/kg every 3–7 days, up to 6–60 mg/day</td>
<td>Dry mouth, constipation, blurred vision, tachycardia, sedation, urinary retention, chorea, decreased concentration, memory loss, and hallucinations</td>
</tr>
<tr>
<td>Baclofen</td>
<td>0.3 mg kg(^{-1}) day(^{-1}) at bedtime</td>
<td>Increase by 0.3 mg/kg every week, up to 10–60 mg/day (occasionally 180 mg/day) in 3 or 4 divided doses</td>
<td>Sedation and nausea Baclofen withdrawal may cause seizures or psychosis</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>For children &lt;10 years or &lt;30 kg: 0.01–0.03 mg kg(^{-1}) day(^{-1}) in 3 divided doses For older or heavier children: 0.5 mg tid</td>
<td>Increase by 0.25–0.5 mg every 3–7 days, up to a maximum of 0.2 mg kg(^{-1}) day(^{-1}) in 3 divided doses</td>
<td>Sedation, imbalance, agitation and restlessness</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>10 mg kg(^{-1}) day(^{-1}) in 2 divided doses</td>
<td>Increase gradually by 5 mg kg(^{-1}) day(^{-1}) every week, up to 35 mg kg(^{-1}) day(^{-1}) in 2 divided doses</td>
<td>Sedation, fatigue and imbalance Not to use with erythromycin</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.025–0.05 mg kg(^{-1}) day(^{-1}) in 2 or 3 divided doses</td>
<td>Increase gradually by 0.5 mg/day every 5–7 days, up to 0.15 mg kg(^{-1}) day(^{-1}) in 2 or 3 divided doses</td>
<td>Sedation, parkinsonism, anticholinergic effects Occasionally restless, neuroleptic malignant syndrome and tardive dyskinesia</td>
</tr>
<tr>
<td>Pimozide</td>
<td>0.05 mg/kg at bedtime</td>
<td>Increase by 0.05 mg/kg every 3–7 days up to 0.2 mg kg(^{-1}) day(^{-1}) in 2 divided doses</td>
<td></td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>0.5 mg/kg mg at bedtime</td>
<td>Increase by 0.5 mg kg(^{-1}) day(^{-1}) every week, up to 4–5 mg kg(^{-1}) day(^{-1}) in 3 divided doses (maximal dose 200 mg/day)</td>
<td>Sedation, hypotension, parkinsonism and suicidal depression</td>
</tr>
<tr>
<td>Reserpine</td>
<td>20 μg kg(^{-1}) day(^{-1}) in 2 divided doses</td>
<td>Increase by 20 μg kg(^{-1}) day(^{-1}) every 2–3 weeks, up to 0.25 mg or higher as tolerated in 2 divided doses</td>
<td></td>
</tr>
</tbody>
</table>
25 mg tablets of carbidopa taken along with the carbidopa/levodopa 25/100 tablets. Alternatively, domperidone, a peripheral dopamine receptor blocking agent that does not cross the blood–brain barrier, may be used to block the peripheral levodopa-induced adverse effects, such as anorexia, nausea, and constipation. In children under 12 years of age or those weighing <35 kg, the recommended maximum dose of domperidone is 0.75 mg/kg in three divided doses. Domperidone is readily available in Canada and Europe but not in the USA.

<table>
<thead>
<tr>
<th>Name of the drug</th>
<th>Starting dose</th>
<th>Titration schedule</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjunct drugs to levodopa for the treatment of dopa-responsive dystonia</td>
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<tr>
<td>Selegiline</td>
<td>0.5–1.1 mg kg(^{-1}) day(^{-1})</td>
<td>Do not exceed 10 mg/day</td>
<td>Hypertension, encephalopathy and insomnia</td>
</tr>
<tr>
<td>Tetrahydrobiopterin</td>
<td>5–10 mg kg(^{-1}) day(^{-1})</td>
<td>Maximal dose not established</td>
<td>Unknown</td>
</tr>
<tr>
<td>5-Hydroxytryptophan</td>
<td>In young children: 6 mg kg(^{-1}) day(^{-1}) in 3 or 4 divided doses</td>
<td>Maximal dose not established</td>
<td>In adults: nausea, bloating and heartburn</td>
</tr>
<tr>
<td></td>
<td>In adolescents: up to 10 mg kg(^{-1}) day(^{-1}) in 3 or 4 divided doses</td>
<td></td>
<td>Rare adverse effects: serotonin syndrome and eosinophilic myalgia syndrome</td>
</tr>
<tr>
<td>Use with carbidopa or benserazide</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>For treatment of acute dystonic reaction induced by dopamine receptor blocking agents</td>
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<tr>
<td>Benztropine</td>
<td>0.02–0.05 mg/kg im or iv</td>
<td>0.02 to 0.05 mg/kg orally twice per day for 1 to 3 days (maximum 2 mg per dose)</td>
<td>Dry mouth, constipation, blurred vision, tachycardia, sedation, urinary retention, chorea, decreased concentration, memory loss, and hallucinations</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>1–1.25 mg/kg im or iv</td>
<td>1–1.25 mg/kg orally every 6–8 h for 1–3 days without exceeding 50 mg per dose</td>
<td></td>
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<tr>
<td>For acute treatment of status dystonicus (dystonic storm)</td>
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<tr>
<td>Midazolam</td>
<td>0.05 mg/kg iv injection over 2–3 min, followed by 0.03 mg kg(^{-1}) h(^{-1}) (0.5 mcg kg(^{-1}) min(^{-1})) iv drip</td>
<td>Increase every 5 min by 25% of the current infusion rate, up to 0.12 mg kg(^{-1}) h(^{-1}) (2 mcg kg(^{-1}) min(^{-1}))</td>
<td>Similar to those of benzodiazepine in addition to respiratory depression, hypotension, hiccups and seizure-like activity</td>
</tr>
<tr>
<td>Propofol</td>
<td>0.3 mg kg(^{-1}) h(^{-1}) iv drip after initiating mechanical ventilation</td>
<td>Increase by 0.3 mg kg(^{-1}) h(^{-1}) every 5–10 min, up to 0.5–3 mg kg(^{-1}) h(^{-1})</td>
<td>Hypotension and bradycardia</td>
</tr>
<tr>
<td>Botulinum toxins</td>
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<tr>
<td>OnabotulinumtoxinA (Botox™)</td>
<td>Starting dose varies based on the number and size of muscles involved. See text for details</td>
<td>25 U/kg up to a total dose of 400 U</td>
<td>Dysphagia, decreased gastrointestinal motility, excessive muscle weakness and respiratory muscle compromise</td>
</tr>
<tr>
<td>IncobotulinumtoxinA (Xeomin™)</td>
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<td>25 U/kg up to a total dose of 400 U</td>
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<tr>
<td>AbobotulinumtoxinA (Dysport™)</td>
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<td>30 U/kg up to a total dose of 1500 U</td>
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<tr>
<td>RimabotulinumtoxinB (Myobloc™ in the USA, NeuroBloc™ in other countries)</td>
<td></td>
<td>400 U/kg up to a total dose of 10,000 U</td>
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</tbody>
</table>
Levodopa-induced choreiform dyskinesia is typically dose dependent and can be improved by reducing the levodopa dose. Although a rapid increase in the levodopa dose may trigger dyskinesia, a dose reduction then followed by a slow increase in the dose may not result in the return of the dyskinesia. Tapering levodopa over a few days is preferred over abrupt discontinuation. This is based on the theoretical consideration that abrupt discontinuation of levodopa may lead to neuroleptic malignant syndrome as described in adult patients with Parkinson disease. There are, however, no reports of such severe reaction to abrupt levodopa withdrawal in dystonic children.

**Special considerations**

Patients with DRD have characteristically a sustained excellent control of their dystonia for life [36]. They may even be able to decrease their dose of levodopa as their symptoms improve spontaneously in the third decade. They do not develop motor fluctuations similar to those seen in Parkinson disease patients, such as a gradual reduction of the duration of motor benefits after each dose of levodopa.

The most common type of DRD is due to mutations in the GCH1 gene on chromosome 14 resulting in guanosine triphosphate (GTP) cyclohydrolase I deficiency. Over 100 different mutations have been identified in this gene [12••, 17]. GTP-cyclohydrolase I, 6-pyruvoyl-tetrahydropterin synthase, and sepiapterin reductase are involved in the synthesis of tetrahydrobiopterin (Fig. 1). The latter is a cofactor for phenylalanine hydroxylase, the enzyme that converts phenylalanine to tyrosine, for tyrosine hydroxylase that converts tyrosine to levodopa, and for tryptophan hydroxylase that converts tryptophan to 5-hydroxytryptophan (5-HTP). Aromatic L-amino acid decarboxylase converts levodopa to dopamine as well as 5-HTP to serotonin. Oral tetrahydrobiopterin at 5–10 mg kg$^{-1}$ day$^{-1}$ may be occasionally necessary for complete recovery [37, 38]. Unfortunately, this drug is not readily available for clinical use, and its safety and effectiveness are not established. This may be particularly relevant as tetrahydrobiopterin poorly penetrates the blood–brain barrier.

Other rarer metabolic disorders that may manifest as DRD include the following:

(a) Tyrosine hydroxylase deficiency due to TH gene mutations has a widely variable response to levodopa [39]. Patients with encephalopathy do not respond to levodopa [40]. In patients who do not respond to levodopa or who develop intolerable levodopa-induced dyskinesia, low-dose levodopa with selegiline, a monoamine oxidase type B inhibitor at a dose of 0.5–1.1 mg kg$^{-1}$ day$^{-1}$ may be useful [41] not exceeding 10 mg/day. Potential adverse effects of selegiline include hypertension, encephalopathy, and insomnia due to its amphetamine-like metabolites [42].

(b) Sepiapterine reductase deficiency, due to mutations in the SPR gene [43, 44], results in dopamine as well as serotonin deficiency [45]. In addition to levodopa, 5-HTP may be used at 6 mg kg$^{-1}$ day$^{-1}$ in young children and up to 10 mg kg$^{-1}$ day$^{-1}$ in adolescents in three or four divided doses [38, 46]. 5-HTP crosses the blood–brain barrier readily and is rapidly decarboxylated to serotonin. The adverse effects of 5-HTP in adults are usually mild including nausea, bloating, and heartburn. Nevertheless, the safety and efficacy of high-dose 5-HTP have not been established in children, and therefore, 5-HTP should be used with great caution as it may cause serotonin syndrome and, rarely, eosinophilic myalgia syndrome, a potentially fatal illness. This is despite the fact that 5-HTP does not require a prescription from a physician in the USA because it is considered a food
supplement covered under the Dietary Supplement Act. The conversion of 5-HTP to serotonin in the liver may increase the risk of serotonin-induced heart valve disease [47]. 5-HTP is therefore best taken with an aromatic L-amino acid decarboxylase inhibitor, such as carbidopa or benserazide, which are already offered in combination with levodopa, to limit the peripheral adverse effects of 5-HTP and enhance its bioavailability to the brain.

(c) 6-Pyruvoyl-tetrahydropterin synthase deficiency [48] is best treated with the combination of levodopa, tetrahydrobiopterin, and 5-HTP at doses described above to control dystonia and prevent cognitive deficits [49].

(d) Aromatic L-amino acid decarboxylase deficiency, usually responds well to levodopa [50]. Patients who do not respond to or tolerate levodopa may be tried on selegiline at a dose of 0.5–1.1 mg/kg every morning [51].

It cannot be overemphasized that the potential benefits of the use of tetrahydrobiopterin, 5-HTP, and selegiline for the treatment of DRD are not established as only a small number of patient trials have been published in case reports or series. The safety of such drugs in children cannot be ascertained at the stated doses. Tryptophan should not be used in children because it may cause eosinophilia–myalgia syndrome. An outbreak of this illness in the USA in 1989 was attributed to an

Fig. 1. Metabolism of dopamine and serotonin. Tetrahydrobiopterin is a cofactor for phenylalanine hydroxylase, tyrosine hydroxylase, and tryptophan hydroxylase. The asterisk marks enzymes whose deficiency have been described to manifest as dopa-responsive dystonia.
imported poorly manufactured batch of tryptophan [52] raising the importance of monitoring the quality of biotechnology-derived products, even those classified as dietary supplements.

**Anticholinergic agents**

Primary dystonias are most consistently responsive to anticholinergic agents [30, 53, 54], although such drugs are also used for the treatment of secondary dystonias. Trihexyphenidyl is the only antidystonic drug that was evaluated in a double blind, placebo-controlled, albeit small trial for the treatment of childhood dystonia, but its tolerability in children remains poorly studied [31].

Although effective as adjunctive therapy to levodopa, anticholinergic drugs should not be used as first-line therapy for DRD, as such drugs do not provide complete resolution of the dystonia [55]. This is probably because anticholinergic drugs do not correct the specific biochemical abnormality of a decrease in dopamine synthesis inherent to this illness.

**Standard dosage**

The starting dose of trihexyphenidyl is 0.03–0.06 mg kg\(^{-1}\) day\(^{-1}\) in three or four divided doses, with the lower end of the range being more appropriate for children under the age of 4 years. The dose may be increased by 0.03–0.06 mg/kg every 3–7 days until adequate dystonia control is achieved or until adverse effects appear. The slower titration rate, the lower the risk of developing adverse effects. The therapeutic dose of trihexyphenidyl varies greatly among patients from 6 to 60 mg/day, although some children may tolerate higher doses.

**Main adverse effects**

The most common adverse effects of anticholinergic drugs are dry mouth, constipation, blurred vision, tachycardia, sedation, urinary retention, decreased concentration, memory loss, and hallucinations. High doses may induce chorea that is readily reversible by reducing the dose. Anticholinergic drugs should not be discontinued abruptly, as this may cause withdrawal symptoms manifesting as acute mental changes.

**Baclofen**

Baclofen, a modulator of gamma-aminobutyric acid-B receptors, may improve the pain associated with childhood dystonia, although it is overall less effective than trihexyphenidyl in treating dystonia [56].

**Standard dosage**

The starting dose of baclofen is 0.3 mg kg\(^{-1}\) day\(^{-1}\) at bedtime and may be increased gradually by 0.3 mg/kg every week aiming for the lowest effective tolerable dose. The usual therapeutic dose of baclofen ranges from 10 to 60 mg/day in three or four divided doses although occasionally a maximal dose of 180 mg/day may be optimal for some children.

**Main adverse effects**

The most common adverse effects of baclofen are sedation and nausea. Baclofen should not be discontinued abruptly as this may cause withdrawal seizures or psychosis.

**Special points**

Intrathecal baclofen may be used in patients whose dystonia responds to oral baclofen at the expense of bothersome adverse effects, yet the usefulness of such therapy in primary dystonia remains poorly established [57, 58] especially in view of its potentially severe adverse effects such as pump malfunction/infection, CSF leaks, and severe withdrawal reaction such as seizures or status epilepticus [59].
Other medications for primary dystonia

Other medications may be beneficial in a minority of patients with primary dystonia despite the lack of controlled studies to support their effectiveness. They include:

- Long-acting benzodiazepines, such as clonazepam [54, 60]: For children under the age of 10 years or those weighing <30 kg, the starting dose of clonazepam is 0.01–0.03 mg kg\(^{-1}\) day\(^{-1}\) in three divided doses that may be increased gradually by 0.25–0.5 mg every 3–7 days, up to a maximum of 0.2 mg kg\(^{-1}\) day\(^{-1}\) in three divided doses. For older or heavier children, the starting dose of clonazepam is 0.5 mg tid that may be increased gradually by 0.5–1 mg every 3–7 days, up to 12 mg/day. The most common adverse effects of benzodiazepines are sedation and imbalance, but paradoxically, it may also cause agitation and restlessness in some children.

- Carbamazepine (antiepileptic drug): the starting dose of carbamazepine is 10 mg kg\(^{-1}\) day\(^{-1}\) in two divided doses, which may be increased gradually by 5 mg kg\(^{-1}\) day\(^{-1}\) every week, up to 35 mg kg\(^{-1}\) day\(^{-1}\) in two divided doses [61]. The most common adverse effects of carbamazepine are sedation, fatigue, and imbalance. It should never be used concomitantly with the antibiotic erythromycin, as it may result in toxic levels of carbamazepine.

- Dopamine receptor antagonists, such as haloperidol [54, 62]: the starting dose of haloperidol is 0.025–0.05 mg kg\(^{-1}\) day\(^{-1}\) in two or three divided doses, to be increased gradually by 0.5 mg/day every 5–7 days, up to 0.15 mg kg\(^{-1}\) day\(^{-1}\) in two or three divided doses. Alternatively, pimozide may be started at 0.05 mg/kg at bedtime and may be increased by 0.05 mg/kg every 3–7 days up to 0.2 mg kg\(^{-1}\) day\(^{-1}\) in two divided doses. The most common adverse events of dopamine receptor antagonists are sedation, parkinsonism, and anticholinergic effects, as well as occasionally restlessness, neuroleptic malignant syndrome, and tardive dyskinesia.

- Tetrabenazine may improve primary generalized dystonia [63, 64], but it is rarely used in children due to its poor safety profile, its cost, and its lack of popularity due to its relatively limited availability in the USA [65]. Tetrabenazine has the advantage over dopamine receptor antagonists in that it does not cause tardive dyskinesia/dystonia. Indeed, tetrabenazine is actually an established treatment of tardive dystonia as described below [64, 66]. Long-term tolerability of tetrabenazine for the treatment of dystonia has not been studied in children [67].

Treatment of secondary dystonia

The treatment of secondary dystonia relies on the treatment of the underlying pathologic process when possible. Otherwise, medications used for the treatment of primary dystonia as described above may also be used for the treatment of secondary dystonia. Trihexyphenidyl, baclofen, levodopa, carbamazepine, or a combination of these drugs is often tried despite little available data that addresses their efficacy in specific secondary dystonias. Since levodopa may be effective in a minority of patients with secondary dystonia [68], and given its
relatively favorable adverse effect profile, it may be reasonable to try it as the first-line drug in any child with any form of secondary dystonia, with the exception of tardive dystonia and acute dystonic reaction induced by dopamine receptor blocking agents.

For the treatment of tardive dystonia, inhibitors of the vesicular monoamine transporter 2 that act as dopamine depleters, such as reserpine or tetrabenazine, may be effective [64, 66]. The starting dose of reserpine is 20 μg kg⁻¹ day⁻¹ in two divided doses, to be increased by 20 μg kg⁻¹ day⁻¹ every 2–3 weeks, up to 0.25 mg or higher as tolerated in two divided doses. The starting dose of tetrabenazine is 0.5 mg/kg mg at bedtime, to be increased by 0.5 mg kg⁻¹ day⁻¹ every week, up to 4–5 mg kg⁻¹ day⁻¹ in three divided doses with a maximal dose 200 mg/day. The usual effective/tolerable dose varies greatly from 25 to 200 mg/day with an average therapeutic dose of 3.7 mg kg⁻¹ day⁻¹ [69]. Reserpine and tetrabenazine must be administered under very close supervision, as adverse effects, even at moderate doses, are common and may be quite serious. These include sedation, hypotension, parkinsonism, and depression that may be severe enough to lead to suicide. Such adverse effects may be in part due to the depletion of norepinephrine and serotonin that is induced by inhibition of the vesicular monoamine transporter 2 [65]. Nevertheless, reserpine and tetrabenazine do not carry the risk of tardive dyskinesia/dystonia that dopamine receptor antagonists may cause.

Probably the most common form of secondary dystonia is acute dystonic reaction induced by dopamine receptor blocking agents, such as neuroleptics and antiemetic drugs. Parenteral anticholinergic drugs, such as benztropine and diphenhydramine, are the treatment of choice [70]. The initial dose of benztropine is 0.02–0.05 mg/kg im or iv, followed by 0.02–0.05 mg/kg orally twice per day for 1–3 days never exceeding 2 mg per dose. The initial dose of diphenhydramine is 1–1.25 mg/kg im or iv, followed by 1–1.25 mg/kg orally every 6–8 h for 1–3 days without exceeding 50 mg per dose. Children who experience acute dystonic reaction should not be rechallenged with dopamine receptor blocking agents.

### Treatment of status dystonicus (dystonic storm)

The treatment of status dystonicus starts by prompt recognition of its symptoms and differentiating it from neuroleptic malignant syndrome and malignant hyperthermia [21]. Treatment is initiated in the emergency room and should be closely monitored in a pediatric intensive care unit where the metabolic and respiratory complications as well as hypotension, which may be induced by treatment, can be addressed [22]. A short-acting parenteral benzodiazepine such as midazolam by intravenous drip may be started at 0.05 mg/kg injection over 2–3 min, followed by 0.03 mg kg⁻¹ h⁻¹ (0.5 mcg kg⁻¹ min⁻¹) that may be increased every 5 min by 25 % of the current infusion rate, up to 0.12 mg kg⁻¹ h⁻¹ (2 mcg kg⁻¹ min⁻¹). Common adverse effects of midazolam are similar to those of benzodiazepine in addition to respiratory depression, hypotension, hiccups, and seizure-like activity.

For children who require deeper sedation, an intravenous propofol drip, a selective modulator of gamma-aminobutyric acid-A receptors, may be added starting at 0.3 mg kg⁻¹ h⁻¹ after initiating mechanical ventilation. The dose of propofol may be increased by 0.3 mg kg⁻¹ h⁻¹ every 5–10 min, up to 0.5–3 mg kg⁻¹ h⁻¹. Common adverse effects of propofol are hypotension and
bradycardia. In extreme instances, barbiturate anesthesia may be required, and continuous EEG monitoring may be used to titrate sedation to an electrographic burst suppression pattern [71].

Other standard oral antidystonia drugs may be added as described above, while the patient is reassessed in therapeutic windows a few minutes after briefly withholding the intravenous sedative(s) drip. Pimozide doses up to 15 mg/day have been used for the treatment of status dystonicus [21, 22]. Intrathecal baclofen [22, 72, 73] or GPi DBS therapy [74, 75] has been reported anecdotally to be useful in selected children with medically intractable status dystonicus.

### Treatment of paroxysmal dystonia

Paroxysmal kinesigenic dyskinesia (PKD) is typically responsive to anticonvulsants, particularly phenytoin, carbamazepine, and valproate. The required doses for the control of the paroxysms are generally lower than those required for the treatment of seizures [76].

Paroxysmal non-kinesigenic dyskinesia (PNKD) is poorly responsive to drug therapy and, unlike paroxysmal kinesigenic dyskinesia, usually does not respond to anticonvulsants [70]. A limited response may be reached using anticholinergic drugs, levodopa, acetazolamide, carbamazepine, haloperidol, gabapentin, and benzodiazepines, particularly clonazepam.

### Botulinum toxin

Botulinum toxin injections may be used to target a problematic group of dystonic muscles, especially those causing pain. The maximal botulinum toxin dose is dictated by the weight of the child, therefore limiting the number of the muscles amenable to such treatment. Out of seven types of naturally occurring types of botulinum toxins (type A through G), two types of botulinum toxins are currently available for clinical use:

- Botulinum toxin type A, onabotulinumtoxinA (Botox™), incobotulinumtoxinA (Xeomin™), and abobotulinumtoxinA (Dysport™). These formulations come as a vacuum-dried powder in a glass vial. The toxin should be mixed with preservative-free 0.9 % normal saline at the desired concentration. The toxin should be used within 4 hours (for Dysport™) to 24 hours (for Botox™ and Xeomin™) of reconstitution while keeping the mixture refrigerated at 2–8 °C between usages.

- Botulinum toxin type B, rimabotulinumtoxinB, brand named Myobloc™ in the USA (also known as NeuroBloc™ in other countries). The toxin is provided in a pre-mixed solution at a concentration of 5,000 U/ml of 0.05 % human serum albumin, 0.01 M sodium succinate, and 0.1 M sodium chloride at approximately pH 5.6.

To date, none of these toxin formulations has been FDA-approved for spasticity in patients under 18 years, let alone for limb or trunk dystonia in children. Dosing and potency between different botulinum toxin formulations have not been compared formally [77]. Therefore, switching among different botulinum toxin formulations is based on expert opinion consensus as follows [78, 79]:

One unit of Botox™ is equivalent in potency to 1 U of Xeomin™, 3–4 U of Dysport™, and 50 U of Myobloc™/NeuroBloc™.
**Standard dosage**

The effect of botulinum toxin injections typically appears within 1–2 weeks, peaks at around 4–6 weeks, and starts wearing off around 2.5–3 months. Consequently, most patients undergo botulinum toxin injections every 3–4 months. The recommended maximal dose of botulinum toxin type A per session is 25 U/kg up to a total dose of 400 U of onabotulinumtoxinA or incobotulinumtoxinA [80] and 30 U/kg up to a total dose of 1500 U for abobotulinumtoxinA [81]. The recommended maximal dose of rimabotulinumtoxinB per session is 400 U/kg up to a total dose of 10,000 U [81]. Using doses higher than the recommended dose in children may cause dysphagia, decreased gastrointestinal motility, and respiratory muscle compromise that may prove fatal. The risk of development of resistance to the toxin, i.e., immunoresistance, is dependent on the dosing interval and on the total dose of toxin administered per session. There is little risk of developing immunoresistance if the injections are performed not more often than every 3 months at doses not exceeding 300–400 U of onabotulinumtoxinA or incobotulinumtoxinA [82]. 1500 U for abobotulinumtoxinA or 10,000 U of rimabotulinumtoxinB. Should this occur, the patient will likely become resistant to the toxin for life. Such resistance may not necessarily be due to the generation of neutralizing antibodies [83]. There are no studies that compare different toxin formulations for their proneness to induce immunoresistance.

For non-palpable muscles, optimal injections are best delivered under electromyographic guidance at the expense of additional pain. Injecting a smaller volume of fluid in the muscles may decrease the unwanted spread of toxin into neighboring muscles. Therefore, it may be best to dissolve the toxin at a high concentration of 100 U per 1 ml of preservative-free normal saline.

In general, the starting dose of onabotulinumtoxinA or incobotulinumtoxinA for specific muscle types is as follows [84]:

- Intrinsic hand muscles: 0.5–1 U/kg
- Arm muscles: 1–2 U/kg (start at the higher end of the range for larger, proximal muscles)
- Proximal leg muscles: 3–6 U/kg
- Distal leg muscles: 1–2 U/kg (3–6 U/kg for gastrocnemius).

Sedation is rarely necessary to perform these injections, but the child needs to be physically restrained by an assistant while allowing the parent to stand near the child’s head. Distracting activity, such as music and toys, are also helpful to alleviate the anxiety of the child during the procedure. It may be best to target the most challenging muscles first and leave the most painful muscle injections, such as those for the intrinsic hand muscles, for last.

**Contraindications**

Botulinum toxin injections should be used with caution in children with neuromuscular disorders.

**Main adverse effects**

Botulinum toxin injections may cause bleeding, excessive muscle weakness that may compromise motor function, local irritation, and burning sensation. Allergic reactions and infections are quite rare if proper sterile technique is followed.
The cost of different types of toxin as well as the price of the procedure for injecting the toxin varies from country to country as well as from center to center within the same country. In the USA, a 100-u vial of Botox™ costs around $550, while Xeomin™ is about $100 cheaper. A dose-equivalent vial of 5000 U of Myobloc™/Neurobloc™ is priced similarly at about $550. In many countries, the equivalent dose of Dysport™ is about 20% cheaper than Botox™ [85]. These estimates do not include the professional fees of the physician administering the toxin.

For comparison purposes, the cost of botulinum toxin injections should be compared to 3- or 4-month supply of an oral antidystonic drug since the injections are administered only once every 3 or 4 months. Even so, oral drug therapy remains much cheaper than botulinum toxin injections.

### Surgical treatment for childhood dystonia

GPI DBS is thought to improve dystonia by modulating abnormal firing patterns in the internal segment of the globus pallidus [86, 87]. The safety and efficacy of GPI DBS therapy on generalized [88] and segmental [89, 90] primary dystonia as well as its long-term benefits are well established [16, 91–93]. This includes a randomized 3-month sham-controlled study done on adult patients, six of whom had DYT-1 gene mutations, which provides class A evidence of the benefit of bilateral GPI DBS in primary generalized and segmental dystonia [89]. GPI DBS has also been reported in small case series to be effective for the treatment of dystonia plus syndromes, such as myoclonus-dystonia syndrome [94, 95] and X-linked dystonia parkinsonism [96], but rapid-onset dystonia parkinsonism may not be consistently responsive to DBS [97, 98].

The benefit of GPI DBS in the treatment secondary dystonias is still debatable, although GPI DBS has been reported in mostly small open-label case series of one to ten patients to benefit several patients with secondary dystonia substantially [99••]. These include cases with tardive dystonia in adults [100, 101], pantothenate kinase associated neurodegeneration [102–106], dystonia/dyskinesia due to GM1 gangliosidosis [107], homocystinuria [108], mitochondrial disorder with striatal necrosis [109], Cockayne syndrome [110], and Lesch–Nyhan syndrome [111–113]. DBS therapy may also be used to treat status dystonicus as reported in ten case series of one to three patients [74, 75, 114, 115]. Although secondary dystonias tend to be less responsive to DBS therapy than primary dystonias [19, 116], generalization should be avoided as further studies are needed to establish the effectiveness of DBS therapy in various specific types of primary as well as secondary dystonias.

The posteroventral area of the GPI is currently the most commonly targeted nucleus for DBS for the treatment of dystonia [99••]. Alternative targets for DBS such as the ventral intermediate nucleus of the thalamus [117–119], the subthalamic nucleus [99••, 120, 121], and the antero-ventral GPI [96, 112] will require further investigation to replace the posteroventral GPI as the prime target for dystonia treatment.

GPI DBS surgery has largely replaced pallidotomy and thalamotomy, as such ablative surgeries, when performed bilaterally often cause dysarthria and dysphagia as well as gait and cognitive impairment. Still, pallidotomy may
rarely be considered in dystonic children who suffer from recurrent DBS lead fractures due to severe neck dystonia or dystonic neck movements.

**Standard procedure**

GPi DBS surgery consists of implanting electrodes in the posteroventral area of the internal segment of the globus pallidus. This is performed under MRI guidance using a stereotactic frame anchored to the child’s head with microelectrode recordings to ascertain the location of the target nucleus and prevent injury to the optic tract. The surgery is usually performed under general anesthesia for children under 16 years. In older children who can tolerate the procedure while awake, intraoperative stimulation can be performed. GPi DBS surgery is usually performed bilaterally since most dystonias in childhood are generalized. The accuracy of the DBS electrode placement procedure cannot be overemphasized as the location of the electrode in the GPi has a major bearing on the response to DBS and on the development of dose-limiting DBS-induced adverse effects [122, 123]. Stimulating the external segment of the globus pallidus, for instance, may even worsen dystonia [124].

Many patients who undergo GPi DBS surgery note an improvement of their dystonia, after implantation of the intracranial electrodes, which is <1.5 mm in diameter, even prior to turning on their stimulators [125]. This motor benefit, referred to as microlesion effect or micropallidotomy, reaches its peak at 3 days after surgery and may last for up to 3 weeks. It is attributed to the small GPi injury caused by the electrodes that mimics a small pallidotomy. Since the microlesion effect may mask the effect of DBS in the early postoperative days, several centers prefer to delay initiating DBS programming for up to 4 weeks after surgery.

Postoperative DBS programming aims at providing dystonia control while minimizing DBS-induced adverse effects. The programming technique varies greatly among centers since evidence-based guidelines for optimal DBS programming in children with dystonia are not well established [126••]. Programming sessions are performed every 3–6 weeks in the first few months after surgery, then every 3–6 months. Usual DBS parameters range between frequencies from 60 to 130 Hz [127], pulse width from 90 to 450 μsec [128], and voltages from 2 to 5 volts [88, 89, 124, 126••, 129]. Most centers opt for stimulating a large area of the GPi, therefore requiring monopolar stimulation pattern using the case of the pulse generator as the anode or positive contact and one or two active or negative contacts at the intracranial end of the DBS electrode [130]. Secondary dystonias, such as dystonia due to Huntington chorea [131] and neuroacanthocytosis [132], may require different DBS parameters than primary generalized dystonias. Although DBS-induced adverse effects may appear immediately after increasing the DBS parameters, dystonia improvement as a result of DBS appears gradually over days to weeks [133]. There also seem to be a cumulative effect of sustained DBS therapy as the dystonia may continue to improve over several weeks or months even without increasing the DBS parameters [88, 128, 134, 135]. This led some authors to suggest that the mechanism of action of DBS on dystonia may be at least in part due to DBS-induced neuroplasticity.
Delivering optimal DBS therapy to children with dystonia requires a multi-disciplinary team of experienced pediatric neurosurgeons, neurologists and nurses to select adequate candidates, perform this delicate stereotactic procedure and optimize DBS parameters. Even in the best of hands, there is great variability in the response of childhood dystonia to DBS therapy [88, 105, 136].

**Indications**

In 2003, the FDA-approved DBS of the GPi or subthalamic nucleus for the treatment of medically intractable primary generalized and segmental dystonia, hemidystonia, and cervical dystonia for patients 7 years of age and older. The approval was under a Humanitarian Device Exemption implying that the effectiveness of DBS had not been demonstrated in large clinical studies, although the safety of the procedure was tolerable enough that the potential benefits of DBS may overweigh its potential risks. Accordingly, performing DBS surgery requires securing the approval and supervision of the Institutional Review Board of the medical center where it will be performed. DBS is not currently FDA-approved for secondary dystonias.

Although there are several suggested guidelines for the indications of DBS for dystonia in adults [7], there are no such guidelines for childhood dystonia due to the lack of controlled studies. In general, DBS therapy is indicated for primary generalized and segmental dystonia refractory to drug and botulinum toxin therapy in patients over the age of 7 years. Primary generalized dystonia, especially that associated with DYT-1 gene mutations, has been singled out as particularly responsive to GPi DBS therapy [137, 138] and pallidotomy [139]. Aside from this exception that some authors also questioned [140], the selection of the ideal candidates for DBS therapy remains a subject of debate mostly due to the lack of prospective, adequately controlled studies with sufficiently large numbers of subjects [141]. By consensus among experts, DBS is unlikely to benefit children with secondary dystonia due to extensive brain injury caused by postanoxic, postencephalitic, perinatal, or poststroke dystonia [135, 136, 142, 143]. Nevertheless, DBS therapy has been reported to benefit substantially several patients with secondary dystonia and status dystonicus as described above, albeit anecdotally in small uncontrolled case series. GPi DBS therefore may be considered in patients with tardive dystonia, pantothenate kinase associated neurodegeneration, dystonia/dyskinesia due to GM1 gangliosidosis, homocystinuria, mitochondrial disorder with striatal necrosis, Cockayne syndrome, and Lesch–Nyhan syndrome, as well as status dystonicus. GPi DBS may also be considered for the treatment of dystonia plus syndromes, such as myoclonus-dystonia syndrome and X-linked dystonia parkinsonism, but it may or may not improve dystonia due to rapid-onset dystonia parkinsonism.

DBS therapy remains a treatment option of last resort due to the potential surgical complications and the inconsistent response of dystonia to DBS therapy [144, 145], irrespective of the pattern of the dystonia [146] and the adequacy of DBS electrode placement [91]. Some authors suggest that early DBS may carry a favorable outcome specifically in patients younger than 21 years with a duration of dystonia of <15 years [147] and without fixed orthopedic deformities [16, 60, 133, 148, 149]. This, however, has not yet been proven in a convincing manner [141].
Contraindications

Patients with bleeding diathesis or on oral anticoagulation or antiplatelet therapy that cannot be withheld for several weeks should not be operated on. Preoperative neuropsychological screening should be performed to establish baseline cognitive function and identify depression, both of which may potentially be worsened by DBS [150••].

Complications

Complications related to DBS therapy may be divided into three categories [133]:

(a) Surgical complications of DBS surgery include infections, intracranial hemorrhage, subcutaneous, and optic tract injury, which may result in irreversible homonymous hemianopsia.

(b) Hardware-related problems include erosion of the skin overlying the hardware, electrode fracture, and rarely pulse generator malfunction.

(c) DBS-induced adverse effects reflect the inadvertent electrical stimulation of structures around the target nucleus. DBS may cause cognitive and mood changes [150••] (which rarely lead to suicide [151]), dysarthria, dysphagia, and phosphenes [152]. The latter is due to stimulation of the optic tract, which is located a few millimeters inferior to the posterior GPi. DBS may also induce bradykinesia, tonic movements, dyskinesia, and even worsening of the dystonia due to electrical stimulation of the internal capsule or various areas within the internal or external segment of the globus pallidus involved in motor control [89, 127, 153]. Such effects are reversible by decreasing DBS parameters but may be dose limiting, compromising the potential benefit of DBS on dystonia control.

The rate of complications related to DBS surgery and the outcome of DBS programming vary greatly among centers. Surgical and hardware-related complications occur more commonly in patients undergoing DBS surgery for dystonia as compared to patients who undergo DBS surgery for Parkinson disease possibly due to the dystonia contributing to additional mechanical stress on the hardware [23, 89, 149, 154].

Cost effectiveness

There is no study that addresses the cost-effectiveness of DBS therapy. Bilateral GPi DBS surgery in the USA currently costs upward of $120,000. Each DBS programming session costs on average between $150 and $350 depending on the duration of the session.

Future therapies

It is essential to recognize that dystonia is a manifestation of multiple diseases of various etiologies. Novel therapies will rely on further understanding the pathophysiology of dystonia [155••]. The discovery of multiple DYT genes [14••] and the development of several animal models including primate models of dystonia [156, 157] are encouraging first steps.
Current treatment options for dystonia are for the most part purely symptomatic. Since most dystonias in childhood spread starting from a group of muscles, one approach would be to develop disease-modifying drugs that may slow down or stop the progression of the illness [158•]. This would require a deep understanding of the specific etiology of the dystonic syndrome and the development of reliable tools to measure the progression of these dystonic syndromes.

The paucity of clinical trials addressing childhood dystonia may be accounted for by the low prevalence of dystonia and by safety concerns that are legitimate to a certain extent. Thus, multicenter trials and more objective means of monitoring adverse effects are paramount [3••, 158•].

**Conclusion**

The treatment of childhood dystonia relies on accurately identifying the type and etiology of the illness. Pharmacological therapy requires trials of multiple medications using a slow titration schedule to achieve the lowest effective dose while minimizing adverse effects. Botulinum toxin injections and DBS therapy were major breakthroughs in the last two decades and may be quite useful in carefully selected patients. Further research will open the way to more effective, safe, and specific therapy for the various types of childhood dystonias.

**Compliance with Ethics Guidelines**

**Conflict of Interest**

Samer D. Tabbal declares no conflicts of interest.

**Human and Animal Rights and Informed Consent**

This article does not contain any studies with animal subjects performed by the author. With regard to the authors’ research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

**References and Recommended Reading**

Papers of particular interest, published recently, have been highlighted as:
- Of importance
- Of major importance


This is an excellent review of an updated consensus-based classification of dystonia and the underlying rationale behind such consensus, including the need for a standardized classification and the shortfalls of previous classification schemes.

This is an outstanding in-depth comprehensive review of the literature of Wilson’s disease including its phenomenology, biochemical pathophysiology, imaging findings and ever-changing treatment.


This study underlines the rigor required when studying the treatment of dystonia in children.


This is a comprehensive introduction to the pharmacologic properties and clinical uses of tetrabenazine.


86. Discussion 70–3.


This is a thorough review of the efficacy of DBS for different types of dystonias. It includes tables of all the reported cases of DBS for each type of dystonia.


This is an excellent review of the literature that pertains to GPi DBS therapy; world-renowned authorities in the field of DBS provide a consensus-based approach to post-operative handling of DBS patients, addressing specific relevant practical issues and DBS programming.


This evidence-based review addresses in great detail the available data to suggest inclusion and exclusion criteria for DBS surgery for dystonia.


This review addresses in great details the effects of DBS on cognition, mood and quality of life of patients with dystonia.


154. Yianni J, Nandi D, Shad A, et al. Increased risk of lead fracture and migration in dystonia compared with


This is an excellent review of 3 common molecular pathways that lead to primary dystonia, namely: 1) cell-cycle and transcriptional regulation in the nucleus, 2) endoplasmic reticulum and nuclear envelope function, and 3) control of synaptic function.


This review addressed the approach for designing effective clinical trials for dystonia.