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Strategies for treatment of dystonia

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Abstract Treatment of dystonias is generally symptomatic. To produce sufficient therapy effects, therefore, frequently a multimodal and interdisciplinary therapeutic approach becomes necessary, combining botulinum toxin therapy, deep brain stimulation, oral antidystonic drugs, adjuvant drugs and rehabilitation therapy including physiotherapy, occupational therapy, re-training, speech therapy, psychotherapy and sociotherapy. This review presents the recommendations of the IAB—Interdisciplinary Working Group for Movement Disorders Special Task Force on Interdisciplinary Treatment of Dystonia. It reviews the different therapeutic modalities and outlines a strategy to adapt them to the dystonia localisation and severity of the individual patient. Hints to emerging and future therapies will be given.

Keywords Dystonia · Treatment strategies · Botulinum toxin · Deep brain stimulation · Antidystonic drugs ·

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Rehabilitation therapy · Multimodal therapies · Interdisciplinary approach

Introduction

Dystonias may be classified as idiopathic or symptomatic. In symptomatic dystonias, the aetiology is known, thus offering the occasional chance for causal or near-causal treatment. In idiopathic dystonias, the cause is not yet identified. In this—by far largest—group of dystonias, all treatment has to be symptomatic. Typically, symptomatic treatment is only partially effective. It is therefore wise to consider multimodal treatment options to take advantage of additive treatment effects. The goal of IAB—Interdisciplinary Working Group for Movement Disorders—is to encourage those multimodal therapies. IAB, therefore, formed a Special Task Force on treatment of dystonia. This paper presents the proceedings of this initiative. It describes currently available treatment options for dystonia and will also hint at emerging treatment strategies and future developments. It will not provide details or an exhaustive bibliography. Its aim is to provide a strategic view and emphasise and encourage a multimodal therapeutic approach.

Botulinum toxin therapy

Therapeutic use of botulinum toxin (BT) was pioneered by the ophthalmologist Alan B. Scott in the early 1970s (Scott et al. 1973). In the early 1980s, it was adopted in neurology for the treatment of blepharospasm and cervical dystonia.

Mode of action

BT therapy is based on the fully reversible, well-controllable and strictly local paralysing effect of BT. With this, the dystonic muscle hyperactivity can directly be reduced. Target muscle selection and dosing allow a high degree of individualisation. Muscular pain will respond subsequently. Additional central nervous system effects on dystonia as well as intrinsic analgesic effects are discussed. BT's effect starts within few days after the application and will gradually fade away after 8–12 weeks before BT therapy has to be repeated. Repetition of injections allows adaptation of BT therapy to changes of the dystonic symptomatology over time. Long-term follow-up over more than 25 years demonstrates that this procedure can be repeated without loss of efficacy or additive adverse effects.

Adverse effects

Reduction of the dystonic muscle activity also reduces the target muscle's voluntary muscle activity. This inherent adverse effect can be reduced by dose adjustment and agonistic muscles overtaking the target muscle's function. Other possible adverse effects are local and caused by BT spread into adjacent muscles. Using BT type A drugs, systemic adverse effects are clinically very rarely detectable even when high doses are applied.

Dosing

Therapeutic BT doses used vary enormously, depending on the target muscle size, the degree of their dystonic involvement and the number of target muscles identified.

Injection scheme

Target muscle selection is highly individualised. It depends on the skilful analysis of the dystonic postures or movements. Palpation as well as active and passive manoeuvres can help to identify the target muscle and exclude antagonistic muscle activities and preventive postures. Occasionally, electromyography may improve target muscle selection. Once the injection scheme is developed, the actual BT placement is performed using palpation and anatomical landmarks. For muscles of the forearm and deep leg muscles, ultrasound guidance can be helpful. In those cases, similar results can be produced by recording electromyographic signals from the target muscle through a special injection needle. Additional electrostimulation through the special injection needle can further improve the precision of BT placement.

BT drugs

BT drugs registered in major industrialised countries include onabotulinumtoxinA (Botox®, Allergan, Irvine, CA, USA), abobotulinumtoxinA (Dysport®, Ipsen, Slough, Berks, UK) and incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, Frankfurt/M, Germany). All of these BT drugs are based upon BT type A. They have similar properties, except for Xeomin® which lacks complexing proteins and contains neurotoxin with an improved purity. RimabotulinumtoxinB (Myobloc®, US World Drugs, Louisville, KY, USA; NeuroBloc®, Eisai, Hatfield, Herts, UK) is the only BT type B drug available. Its market share is marginal because of substantial systemic anticholinergic adverse effects and high

antigenicity. It may be used in patients with antibodies against BT type A drugs. Potency labelling is specific for the particular BT drug used. Comparison of the potency labelling is a matter of debate. OnabotulinumtoxinA and incobotulinumtoxinA can be compared using a 1:1 ratio (Dressler et al. 2012, 2014), onabotulinumtoxinA/incobotulinumtoxinA and abobotulinumtoxinA using a 1:2, 1:3 or 1:4 ratio and onabotulinumtoxinA/incobotulinumtoxinA and rimabotulinumtoxinB using a 1:40 ratio.

Indications

BT therapy is used to treat cervical dystonia. Overall, about 80 % of patients report a good or very good therapeutic effect. It best works in tonic torticollis. Local adverse effects include dysphagia and reduced neck stability. Adjacent muscles in the shoulder girdle may be included in the injection scheme. Another well-established indication for BT therapy is blepharospasm. The outcome is similar to cervical dystonia. Mandibular muscles are also approachable by BT therapy. In spasmodic dysphonia, perioral or transcutaneous BT injections into the opening or closing muscles of the vocal cord can produce extremely satisfying effects for the patient. Reproducibility of the therapy effects, however, can sometimes be problematic. Writer's cramps are difficult to treat due the complexity of the muscular system in the forearm and the narrowness of the therapeutic window of the forearm muscles. Paretic adverse effects and insufficient therapeutic effects are notoriously difficult to separate by dose adjustments. About half of the patients are satisfied with the therapeutic effect of BT therapy, while the other half quits treatment. Ultrasound and electromyography guidance are crucial to produce satisfactory results. Musician's dystonias, affecting the upper extremity, respond favourably when BT therapy is performed after careful analysis of the movement pattern and when it is applied under guidance (Schuele et al. 2005; van Vugt et al. 2014). In tongue and facial muscles producing embouchure dystonia, the results are less favourable since functional requirements for performing musicians are extreme. Apart from focal dystonias, also more widespread dystonias can be treated effectively with BT therapy. For this, the concept of high-dose therapy was recently introduced (Dressler et al. 2015). Not exaggerating well-established dosing in individual target muscles, this concept is based on lack of systemic toxicity and immunologic acceptance of high doses of Xeomin® (400–1200 MU), thus allowing to address more target muscles than previously believed. Even in generalised dystonia, BT therapy may be used when functional or pain foci can be identified. In widespread, painful and severe dystonias, especially in young patients, deep brain stimulation becomes the therapy of choice.

Reduced response to BT therapy

Reduced response to BT therapy is obtained in special subforms of dystonias, such as antecollis, tremulous forms and alternating activation patterns in cervical dystonia or additional apraxia of eyelid opening in blepharospasm, especially when it occurs in progressive supranuclear palsy. Pretarsal injections and the lid suspension operation can improve the therapeutic outcome. In writer's cramp, predominant involvement of finger muscles as opposed to involvement of wrist muscles reduces the therapeutic benefit. In spasmodic dysphonia, abductor types may have less favourable outcomes than adductor forms. Psychiatric co-morbidity and unsolved social benefit issues may also interfere with the therapy outcome.

In general, most cases of reduced therapy outcome are caused by inadequate injection schemes applying insufficient BT doses, employing insufficient number of target muscles or using inappropriate target muscles. Additionally, the role of some target muscles including the scalenii, the levator scapulae, the deep neck muscles, the pectoralis, the teres major and the latissimus dorsi is not yet generally appreciated. In some patients, the formation of antibodies against botulinum neurotoxin may partially or completely block the biological action of BT, thus reducing the therapeutic effect.

Oral drug treatment

Oral drugs have been used for many years to treat dystonia. Except for few special forms of dystonia, no single one has striking effects. In general, drug treatment of dystonia is disappointing: testing is time consuming, efficacy is limited and adverse effects are common.

Indications

Oral drugs may be used in mild dystonias and in addition to BT therapy or deep brain stimulation when residual symptoms are present or during the end of the BT treatment cycle. Usually, they are introduced sequentially in a special order starting with anticholinergics and followed by benzodiazepines, baclofen, tetrabenazine and clozapine. After anticholinergics, this order has been challenged. There are no robust comparative studies between different antidystonic drugs available. In addition to these drugs, almost every compound reaching the central nervous system has been tried for dystonias—usually without lasting effect.

In severely affected children and in exacerbated generalised dystonia (dystonic storm), a cocktail introduced by C David Marsden and including anticholinergics, benzodiazepines and tetrabenazine has been tried (Marsden et al.

1984). However, deep brain stimulation would nowadays be preferred in those patients.

Anticholinergics

Anticholinergics are the drugs with the best antidystonic effect (Brans et al. 1996; Maltese et al. 2014). The best-studied compound is trihexyphenidyl (Artane®). To reduce adverse effects, the starting doses should be low and dose increases should be slow until sufficient effects are obtained or until adverse effects become intolerable. Typical anticholinergic adverse effects include dryness of mouth, blurred vision on reading, memory impairment, nervousness, drowsiness, urinary retention and constipation. Effectivity usually starts at around 8–10 mg/day. Adverse effects may start at the same doses. If they are tolerated in doses of up to 14 or 16 mg/day, there is a chance of therapeutic benefit for the patient. Interestingly, children tolerate much higher doses and, therefore, have a better chance for therapeutic benefit. Other anticholinergic substances including benztropine, biperiden, ethopropazine and diphenhydramine showed similar effectivity and adverse effect profiles.

Benzodiazepines

GABA-A agonists including clonazepam and diazepam have direct antidystonic properties. Anxiolytic effects and mental relaxation may induce uncontrolled dose expansion which needs to be avoided by controlled prescriptions. Withdrawal may reveal physical dependency. Immediate adverse effects include reduced reaction times leading to driving restrictions, memory impairment, apathy and drowsiness.

Baclofen

Baclofen (Lioresal®), a GABA-B agonist, has antispastic and less powerful antidystonic effects. It also may have some analgesic effects. Its dose is slowly increased until satisfactory effects or intolerable adverse effects occur. The upper dose limit is around 120 mg/day. Adverse effects include drowsiness and nausea. Withdrawal may provoke seizures. In some patients, baclofen given continuously and intrathecally through an implanted radio-controlled pump may procedure some improvement.

Dopaminergics

Occasionally, levodopa can have mild antidystonic effects. This effect has to be distinguished from the often dramatic levodopa effect on true dopa-responsive dystonia. Adverse effects are mild including hypotension and nausea.

Antidopaminergics

D2 receptor blocking agents may have antidystonic effects. Interestingly, they can—at the same time—cause tardive dystonias. For this, they should not be used in idiopathic dystonia except under extraordinary circumstances. In tardive dystonias, they are contraindicated. Clozapine an atypical dopamine receptor blocker does not produce tardive dystonia. Its antidystonic potency is only moderate. It can produce drowsiness. Dopamine levels within the central nervous system can also be reduced by dopamine-depleting agents blocking the re-uptake of dopamine into the presynaptic nerve terminals. Tetrabenazine and reserpine are the best described dopamine depletors. Antidystonic effects are mild und unpredictable. Both frequently produce parkinsonoids and less frequently depression. With reserpine, hypotension is another adverse effect. Tardive dystonia has not been described as an adverse effect yet.

Antidystonic drugs for special indications

In dopa-responsive dystonia (Segawa disease) dystonia and parkinsonism with typical diurnal fluctuations and often remarkable lateralisation of symptoms are caused by lack of dopamine due to various enzyme defects. Levodopa produces dramatic long-term symptom relief. Most patients respond to levodopa at a dose of 5 mg/kg body weight/day. Lack of efficacy to levodopa doses of more than 600 mg/day makes dopa-responsive dystonia unlikely. Dyskinesias may occur, but are mild. Fluctuations do not occur due to intact dopamine storage capacity. Use of dopamine agonists is not sufficiently studied. Paroxysmal kinesigenic dyskinesia responds well to anticonvulsants such as carbamazepine. Paroxysmal non-kinesigenic dyskinesia responds less favourably to carbamazepine, and benzodiazepines may be tried instead. Emotional stress, fatigue, alcohol or caffeine as precipitating factors should be avoided. Paroxysmal exercise-induced dyskinesia may respond only partially to carbamazepine and benzodiazepines. Physical exercise as a precipitating factor should be avoided. Ketogenic diet or modified Atkins diet may be helpful in patients with GLUT1 mutations.

Adjuvant drugs

In more severe dystonias, pain may become the leading symptom. If antidystonic treatment is not sufficient, analgesics may be added at least temporarily. If dystonic tremor does not respond sufficiently, beta-blockers and primidone may sometimes work. In myoclonic dystonias, occasionally anticonvulsants may be helpful. If there is a strong stress induction of the dystonic symptoms, rapid-

onset benzodiazepines such as lorazepam (Tavor 1.0 Expidet®) may offer help.

Surgery

Surgery has long been used to treat dystonias. First, strategies focussed on peripheral interventions, later on central interventions were developed. Today, peripheral interventions are almost entirely abandoned.

Central surgery

Surgery on the central nervous system for movement disorders was developed in the 1950s (Cooper 1956). It is based on stereotaxy, i.e. a local intervention in the depth of the brain controlled by a three-dimensional geometric coordinate system referring to morphological reference points. Because of mixed results, stereotaxy was previously reserved for severe cases of dystonia only. With the advent of advanced imaging techniques, stereotaxy was revived in the 1980s. Originally, stereotaxy used ablative techniques in the form of thermocoagulation and to a lesser degree of cryocoagulation and chemocoagulation. From the early 1990s, thermocoagulation was more and more replaced by high-frequency stimulation techniques (deep brain stimulation, DBS) probably blocking central nervous system nuclei in a similar way to ablative techniques. With advanced stimulation electrodes, adjustment of the exact stimulation point became possible without moving the stimulation electrode after implantation. Improved imaging techniques allow precise calculation of the target point. Additional neurophysiological recordings of neuronal firing patterns further improve targeting precision.

DBS for dystonia was introduced in 1996 (Iacono et al. 1996). It is usually performed bilaterally, thus improving the therapeutic outcome. The target point with the best antidystonic effect is the globus pallidus internus (GPi-DBS). Thalamic stimulation (VIM-DBS) produces much less robust effects. Stimulation using the subthalamic nucleus (STN-DBS) has been experimental. Therapeutic effects on phasic components of dystonia tend to occur within several days. Therapeutic effects on tonic components can take weeks to months to fully develop. GPi-DBS can produce substantial improvement of idiopathic generalised dystonia (Vidailhet et al. 2007; Volkmann et al. 2012). The extent of this improvement may not be obtained by BT therapy. Whether patients with a DYT1 gene defect show better results than patients with other gene defects remains open. Tardive dystonia also seems to respond to GPi-DBS (Gruber et al. 2009). The presence of structural lesions—as in symptomatic dystonias—seems to reduce the DBS effects. Comparable results can be obtained in segmental dystonia. Here, however, BT therapy can provide similar improvement, especially when high-dose therapy is considered. In focal dystonias, antidystonic effects of DBS and BT therapy are similar.

Reduced results and adverse effects can be caused by suboptimal electrode positions, intraoperative or postoperative infections, intraoperative haemorrhage, electrode displacements, electrode disconnections and potentially patient particularities. Disadvantages of DBS include high costs, need of a highly specialised neurosurgical team, time-consuming postoperative programming and stimulator replacement after battery discharge (usually after 3–5 years). DBS can be combined with BT therapy, oral drugs and adjuvant measures.

Peripheral surgery

Since the nineteenth century, myotomy (muscle dissection) and myectomy (muscle resection) were used to treat dystonia. When electric stimulation became available, techniques for denervation of dystonic muscles were developed. For blepharospasm, denervation and myectomy alone or in combination may be performed. Results are problematic, since therapeutic effects are difficult to control and insufficient therapeutic effects or paretic adverse effects can easily occur. When denervation is used, long-lasting pain syndromes may become a major problem. Both operations are now largely abandoned. Denervation surgery may be used in spasmodic dysphonia. However, chemical denervation using BT has almost entirely replaced this operation. In young patients with dystonia in isolated muscles, myectomy or denervation may be preferred to prolonged BT therapy. Also to avoid prolonged BT therapy spastic-dystonic conditions of the lower limb can be treated by selective fasciculotomy. For cervical dystonia, a combination of myectomy, peripheral denervation and anterior ramisectomy was developed by Claude Bertrand of Montreal in the 1980s (Bertrand et al. 1982; Bertrand 1993). In rotational cervical dystonias, the results are comparable to BT therapy. Currently, it is considered in patients with antibody-induced failure of BT therapy and hesitancy to undergo DBS. The adverse effects include often substantial muscle hypotrophy.

Adjuvant measures

Adjuvant measures may be summarized under the term rehabilitation therapy. Physiotherapy can help to activate antidystonic muscles, re-adjust impaired body posture and stretch target muscles of BT therapy, thus preventing contractures. In most cases BT therapy should only be

Table 1 Algorithm for treatment of dystonia

Dystonia severity	Dystonia localisation	Primary treatment	Additional treatment	Comments
Mild	Focal	ADD/none		Inform patient about diagnosis and prognosis. ADD may be tried. If no success treatment may be postponed
	Widespread	ADD/none		
Moderate	Focal	BTT	RT (optional)	In antecollis and alternating torticollis consider DBS
	Widespread	BTT	RT (optional)	
Severe	Focal	BTT	RT ADD (optional) AD (optional)	In case of insufficient effect consider DBS
	Widespread	BTT	RT ADD (optional) AD (optional)	Either test BTT first or recommend DBS straight away
		DBS	RT BTT (optional) ADD (optional) AD (optional)	

AD adjuvant drugs, *ADD* antidystonic drugs, *BTT* botulinum toxin therapy, *DBS* deep brain stimulation, *RT* rehabilitation therapy: physiotherapy, re-training, occupational therapy, speech therapy, sociotherapy, psychotherapy, patient groups

performed in combination with physiotherapy. Scientific evidence for the efficacy of physiotherapy on dystonia, however, is scarce. Self relaxation techniques can help to overcome crisis situations and vicious circles. In musician's dystonia re-training utilising slow-down exercises, self-awareness and tactile discrimination training can be beneficial (van Vugt et al. 2014). Occupational therapy can improve impaired functioning. Speech therapy can improve pharyngo-laryngeal and oromandibular dystonia. Adequate information of the patient and his family helps to understand the nature and prognosis of dystonia and its treatment options. Psychotherapy can improve coping with a chronic disease with all its private and professional consequences. In severe cases, psychotherapy should include the caregivers. Sociotherapy helps the patient to claim social benefits. Introduction to a dystonia patient group is welcome by many, but not all patients.

New potential treatments

Experimental occupational therapies including constraint use and feedback elements may produce mild and temporary effects best studied in writer's cramps and in some musician's cramps (Berque et al. 2010; Candia et al. 2003; O'Neill et al. 1997; Zeuner and Molloy 2008). Transcranial magnetic brain stimulation also may produce mild and temporary effects (Kieslinger et al. 2013; Borich et al. 2009). Transcranial direct current stimulation does not seem to be effective in writer's cramp and with unipolar electrode montages (Benninger et al. 2011; Buttkus et al. 2011); however, bipolar montages over the sensory–motor cortices with accompanying finger exercises seem to produce sustained benefit in musician's dystonia (Furuya et al. 2014). Tetrahydrocannabinol is currently been tested for treatment of dystonia (Jabusch et al. 2004).

Treatment algorithm

For therapeutic purposes, dystonia can best be classified by its severity and localisation. Based upon these features, Table 1 gives some general recommendations to approach the treatment of dystonia. However, various individual aspects of the patient have to be taken into account to optimise dystonia treatment. They include the patient's age, the presence of pain, his compliance, employment situation, personal preferences and his logistical situation. In the end, the treatment scheme will be highly personalised. The best results will be obtained when multiple treatment options can be combined.

In mild forms of dystonia when there is no functional impairment, no pain and no stigmatisation, treatment may be postponed. Counselling of the patient and his family about the nature of dystonia and its prognosis, however, should be performed.

In moderate forms of dystonia, when treatment is required, the treatment of choice is BT therapy. This applies to focal forms, but also to more widespread forms. Rehabilitation therapy is optional.

When there are severe forms of dystonia, BT therapy will still be the first treatment to try. Physiotherapy to enhance BT effects will usually be needed. Other forms of rehabilitation therapy can be added. Antidystonic drugs may be necessary to enhance BT effects and to counterbalance the waning of BT therapy at the end of the treatment cycle. Also, adjuvant drugs may become necessary. In focal forms, this will usually produce satisfactory results. In widespread forms, BT therapy may also be tried first, especially when foci with high symptomatic relevance can be identified. If not, or when BT doses are exhausted, DBS should be used. Alternatively, DBS may be offered as primary treatment. Its effects can be enhanced by combinations with physiotherapy, BT therapy, antidystonic drugs and adjuvant drugs.

In conditions with reduced responses to BT therapy or in antibody-induced failure of BT therapy, DBS or antidystonic drugs may be tried. In tremulous dystonias, beta-blockers and primidone can be effective, in myoclonic forms anticonvulsants. Apraxia of eyelid opening responds well to the eyelid suspension operation.

If pain is a leading symptom, analgesics should be added. If there is a strong stress induction of symptoms, lorazepam should be used when stressful situations are anticipated.

Outlook

In symptomatic dystonias, the challenge will be to develop more and improved causal treatments. In idiopathic dystonias, the underlying causes will first have to be understood better to be able to develop new causal treatments. Alternatively, reparative or at least disease-modifying treatments may be used for those subtypes of dystonia where neurodegeneration occurs following strategies being developed for other neurodegenerative diseases. For many years to come, symptomatic treatments will remain the mainstay of treatment. Best results will be obtained my multidisciplinary approaches.

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