Botulinum Toxin Therapy of Dystonia

10

Dirk Dressler and Petr Kanovsky

10.1 History

Botulinum toxin (BT) is infamous as the compound with the highest toxic potency of any natural or man-made substance causing the clinical syndrome of botulism in man and animals. At the end of the 1970s, this perception began to change, when BT was first used by Alan B. Scott to treat strabismus in children [1, 2]. It soon became clear that this had established a completely novel therapeutic principle which could be used in various muscle hyperactivity syndromes. Subsequently BT was used in blepharospasm, hemifacial spasm and cervical dystonia, thus reaching neurology [3, 4]. Here its use exploded and soon numerous other medical specialties became involved. With its use in crocodile tears, pioneered by Manuel Meyer in Zurich, exocrine glands became a second principal target tissue for BT. Recently, BT's use for treatment of pain syndromes was established [5]. For most of its indications, BT therapy is the therapy of choice [6]. For some, it has revolutionised therapy altogether. This, together with its exploding use in cosmetics, has generated an industry with annual sales in excess of three billion US dollars. BT's use in dystonia, however, is still one of the most important indications for BT, both with respect to the amount of BT used and with respect to the therapeutic impact generated.

D. Dressler, MD, PhD (✉)
Movement Disorders Section, Department of Neurology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany
e-mail: dressler.dirk@mh-hannover.de

P. Kanovsky
Department of Neurology, Palacky University Medical School, Olomouc, Czech Republic
e-mail: petr.kanovsky@fnol.cz

P. Kanovsky et al. (eds.), *Dystonia and Dystonic Syndromes*,
DOI 10.1007/978-3-7091-1516-9_10

10.2 Pharmacology of Botulinum Toxin Drugs

10.2.1 Structure

As shown in Fig. 10.1, BT drugs consist of the BT component and of excipients. The BT component is formed by botulinum neurotoxin (BNT) and by non-toxic proteins also known as complexing proteins. BNT consists of a heavy amino acid chain with a molecular weight of 100 kD and a light amino acid chain with a molecular weight of 50 kD. BNT and complexing proteins form superstructures of different sizes [7]. In Xeomin®, the complexing proteins are removed during the manufacturing process [8].

10.2.2 Mode of Action

When a BT drug is injected into a target tissue, it is bound to glycoprotein structures located on the cholinergic nerve terminal. Subsequently, BNT's light chain is internalised by using synaptic vesicle proteins and syntagmins of the neuron's acetylcholine vesicle-recycling mechanism [9–12]. Intracellularly, BT cleaves different proteins of the acetylcholine transport protein cascade (**s**oluble **N**-ethylmaleimide-sensitive fusion *a*ttachment protein *re*ceptor or SNARE proteins) transporting the acetylcholine vesicle towards the synaptic cleft [13]. Different BT types target different SNARE proteins. BT interrupts the synaptic transmission only temporarily. Structural neuronal changes or functional neuronal impairment other than the synaptic blockade itself cannot be detected. Recently, we therefore suggested classifying BT not as a neurotoxin but as a temporary neuromodulator [14]. BT can block cholinergic neuromuscular transmission but also the cholinergic autonomic

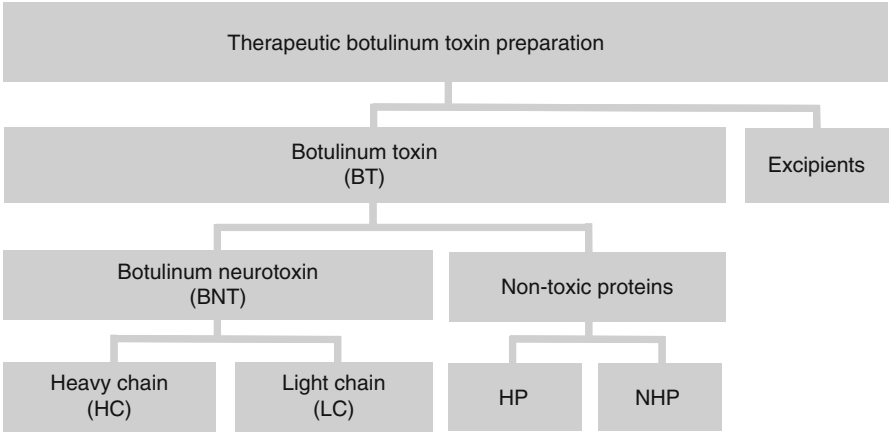

Fig. 10.1 Contents of therapeutic botulinum toxin preparations. *HP* haemagglutinating protein, *NHP* non-haemagglutinating protein

innervation of the sweat glands, the tear glands, the salivary glands and the smooth muscles depending on the target tissue selected.

Apart from a direct action upon the striated muscle, BT can act upon the muscle spindle organ reducing its centripetal information traffic [15–17]. Whether this BT-induced blockade of the muscle spindle's centripetal information is relevant to BT's therapeutic action remains unclear [18, 19].

Although BT can produce numerous indirect central nervous system effects, direct central nervous system effects beyond the alpha motoneuron are a controversial issue [20, 21].

In addition to the blockade of the acetylcholine secretion, animal experiments indicate BT-induced blockade of transmitters involved in pain perception, pain transmission and pain processing [22–28]. This may be the basis of BT's action on pain syndromes.

10.2.3 Time Course of Action

After intramuscular injection, initial BT effects can be detected within 2–3 days depending on the detection method used. BT reaches its maximal effect after about 2 weeks, maintains it and then gradually starts to decline after 2–2.5 months. BT injections into glandular tissue can exert prolonged effects of up to 6 or 9 months. BT's action follows a dose-effect correlation [29]. An additional dose-duration correlation can also be assumed. Both correlations are valid only within certain limits. Although there may be interindividual variability of the duration of action, there is remarkable intraindividual reproducibility of the duration of action throughout years of continued treatment [30, 31].

10.2.4 Botulinum Toxin Drugs

BT drugs are either based upon BT type A, such as Botox® (onabotulinumtoxinA, Allergan Inc, Irvine, CA, USA), Dysport® (abobotulinumtoxinA, Ipsen Ltd, Slough, Berks, UK) and Xeomin® (incobotulinumtoxinA, Merz Pharmaceuticals, Frankfurt/M, Germany), or upon BT type B, such as NeuroBloc®/MYOBLOC® (rimabotulinumtoxinB, Solstice Neurosciences Inc, Malvern, PA, USA). Additional BT drugs are distributed in fringe markets (Fig. 10.2). As shown in Table 10.1, the properties of BT type A drugs are similar. Those of the BT type B drug are considerably different. Differences include antigenicity, adverse effect profiles, adverse effect frequency, injection site pain, storage conditions, mode of preparation, pharmacological stability and potency labelling. Although all BT drugs are based upon BT, they are not generics. They can be compared in principle and they can be interchanged in an ongoing therapy, but comparisons and interchanges have to be performed with caution. Current understanding suggests that Botox® and Xeomin® have identical therapeutic effects and adverse effect profiles [32, 33]. Their potency labelling is identical, making exchanges between both products particularly easy [34].

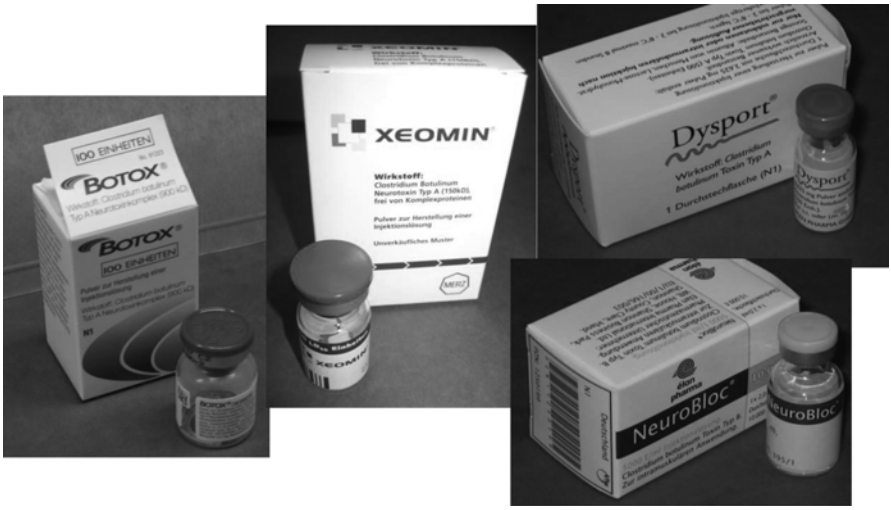

Fig. 10.2 Some of the currently available botulinum toxin drugs

With an improved specific biological activity, Xeomin® should have a reduced antigenicity as compared to conventional BT drugs [8].

Dysport® also has an identical therapeutic profile as Botox®. Its potency labelling is still a matter of debate. Currently, a conversion ratio between the mouse units measured by Allergan for Botox® and the mouse units measured by Ipsen for Dysport® of 1:2.5 must be assumed. NeuroBloc®/MYOBLOC®'s potency labelling can be compared to that of Botox® by using a conversion ratio 1:40. Its disadvantageous adverse effect profile and its problematic antigenicity will be discussed below. It can only be recommended for those dystonia patients with complete secondary therapy failure due to formation of antibodies against BT type A.

10.2.5 Antigenicity

Since BT consists of foreign proteins, antibodies can be formed against BNT and the non-toxic proteins. Antibodies formed against BNT (BNT-AB) block BT's biological activity and, thus, produce antibody-induced therapy failure (ABTF). BNT-AB are therefore called blocking or neutralising antibodies. BNT-AB and BT are in a functional balance [35]. The therapeutic relevance of BNT-AB titres has to be considered. Antibodies formed against the non-toxic proteins do not interfere with BT's biological activity and are called non-neutralising antibodies.

Risk factors for ABTF include the amount of BT applied at each injection series, the interinjection interval [36] and the immunological quality of the BT drug as described by their specific biological activity. The specific biological activity varies between different therapeutic preparations as shown in Table 10.1 [37–40]. A

Table 10.1 Properties of different botulinum toxin drugs

	Botox®	Dysport®	Xeomin®	NeuroBloc® MYOBLOC®
Manufacturer	Allergan Inc	Ipsen Ltd	Merz Pharmaceuticals	Solstice Neurosciences Inc
Pharmaceutical preparation	Powder	Powder	Powder	Ready-to-use solution 5,000MU-E/ml
Storage conditions	Below 8 °C	Below 8 °C	Below 25 °C	Below 8 °C
Shelf life	36 months	24 months	36 months	24 months
Botulinum toxin type	A	A	A	B
SNARE target	SNAP25	SNAP25	SNAP25	VAMP
pH value of the reconstituted preparation	7.4	7.4	7.4	5.6
Stabilisation	Vacuum drying	Freeze-drying (lyophilisate)	Vacuum drying	pH reduction
Excipients	Human serum albumin 500 ug/vial Sodium chloride 900 ug/vial Buffer system	Human serum albumin 125 ug/vial Lactose 2,500 ug/vial Buffer system	Human serum albumin 1 mg/vial Sucrose 4.7 mg/vial Buffer system	Human serum albumin 0.5 mg/ml Disodium succinate 0.01 M Sodium chloride 0.1 M H_2O hydrochloric acid
Biological activity	100 MU-A/vial	500 MU-I/vial	100 MU-M/vial	1.0/2.5/10.0 kMU-E/vial
Biological activity in relation to Botox®	1	1/3	1	1/40
Specific biological activity	60 MU-EV/ngBNT	100 MU-EV/ngBNT	167 MU-EV/ngBNT	5 MU-EV/ngBNT

BNT botulinum neurotoxin, *MU-A* mouse unit in the Allergan mouse lethality assay, *MU-E* mouse unit in the Solstice mouse lethality assay, *MU-I* mouse unit in the Ipsen mouse lethality assay, *MU-M* mouse unit in the Merz mouse lethality assay, *MU-EV* approximate equivalence mouse unit, 1MU-EV = 1MU-A = 1MU-M = 3MU-I = 40MU-E

probable risk factor for ABTF is the reactivity of the immune system of the individual patient [41, 42]. Potential risk factors include the target tissue; the type of injection, i.e. intradermal, intramuscular or intraglandular injections; and female sex. Cumulative dose, treatment time and patient age have been excluded as risk factors. Recent analysis revealed that ABTF usually develops within the first 2–3 years of BT therapy [43]. After a treatment time of more than 5 years, ABTF becomes rare.

10.2.6 Safety Aspects and Adverse Effects

Based upon a broad therapeutic window and strictly local effects avoiding contact with excretion organs, BT excels with a remarkably advantageous adverse effect profile. Adverse effects can be classified as obligate, local or systemic. BT adverse effects occur in a typical time window after BT application. They usually start after 1 week and last for 1–2 weeks. Severity and duration of adverse effects depend on the BT dose applied, the target tissue and the adjacent tissues. Systemic spread of BT becomes clinically relevant only when BT doses applied are very high. BT transport through the blood-brain barrier is excluded by BT's molecular size. The use of BT during pregnancy is contraindicated as a precautionary measure until further experience is gained. Extremely rarely, BT applications may trigger acute autoimmune reactions with brachial plexopathies or with dermatomyositis [44]. Caution is required when using BT in patients with pre-existing pareses, as in amyotrophic lateral sclerosis, myopathies and motor polyneuropathies, or in patients with impaired neuromuscular transmission, such as myasthenia gravis and Lambert-Eaton syndrome [45, 46]. Warnings not to use BT in patients receiving aminoglycoside antibiotics seem theoretical. With large numbers of patients being treated over prolonged periods of time, long-term experience is ample but does not indicate additional adverse effects [47].

Based upon a conversion factor of 1:1, the adverse effect profiles of Xeomin® and of Botox® are identical [32, 33]. The adverse effect profile of BT type B drugs is substantially different from the adverse effect profile of therapeutic BT type A drugs. Whereas even low and intermediate BT-B doses frequently produce systemic autonomic adverse effects, frequency of motor adverse effects is similar after BT type B and BT type A [48]. Whereas BT type A has a relatively strong effect on the motor system and a relatively weak effect on the autonomic nervous system, this correlation is reversed in BT type B [49]. Because of its systemic autonomic adverse effects, BT type B should be used with caution in patients with pre-existing autonomic dysfunction or in connection with anticholinergics.

10.2.7 Therapeutic Profile

With the features described above, BT's therapeutic profile can be summarised as shown in Table 10.2. BT can be used in muscles, exocrine glands and structures associated with pain. BT's therapeutic effect follows a time course, which is remarkably reproducible in the individual patient, but shows some interindividual variability. When BT is injected into muscle tissue, it produces a peripheral paresis. This paresis manifests clinically after a few days, reaches its maximum after 1–2 weeks, is usually stable for 6–12 weeks and then gradually resolves over several weeks. The extent of the therapeutic effect is well controllable by the amount of BT applied. Adverse effects are benign and fully reversible. With BT type B, systemic anticholinergic adverse effects and ABTF are frequent.

Table 10.2 Therapeutic profile of botulinum toxin drugs

Target tissues	Striate and smooth muscles ('neuromuscular junction') Exocrine glands Structures involved in generation, perception or transmission of pain
Therapeutic effect	Localised Predictable time course Fully reversible Extent well controllable Duration controllable within certain limits
Adverse effects	Fully reversible Obligate adverse effects manageable Local adverse effects few Systemic adverse effects BT-A: extremely rare BT-B: frequent anticholinergic adverse effects

Table 10.3 The multilayer concept of comprehensive dystonia therapy

Layer	Description	Modalities
1	Antidystonic treatment	Botulinum toxin therapy Oral drugs Intrathecal baclofen Surgical interventions
2	Adjuvant drugs	Analgesics Anxiolytics
3	Adjuvant treatment	Physiotherapy
4	Adjuvant measures	Social support Providing information Patient support groups

10.3 Basic Principles of Botulinum Toxin Therapy

10.3.1 The Multilayer Concept of Dystonia Treatment

Dystonia is a chronic condition for which no causal therapy exists. In most cases, dystonia treatment therefore has to be multimodal and long term. Co-ordinating the efforts of interdisciplinary treatment teams over prolonged periods of time may be supported by special working groups such as IAB (Interdisziplinärer Arbeitskreis Bewegungsstörungen) [50].

Treatment of dystonia can best be described as a multilayer concept (Table 10.3). The basal layer includes antidystonic therapies. Here, BT therapy is pivotal. It is entirely symptomatic. Nevertheless, its use may change the long-term perspective of patients affected. In children, symptomatic suppression of dystonic muscle activity

may enable certain motor developments otherwise prevented. In adults, it can avoid the development of complications otherwise potentially dominating the clinical picture. The use of BT therapy early in dystonia's course therefore seems advisable. BT's therapeutic effect may involve central mechanisms. Its predominant effects, however, are peripheral. Usually, BT therapy should be complemented by physiotherapy where stretching exercises that can increase and maintain joint mobility, training of antagonistic muscles that can improve functional capabilities and retraining the impaired patient's self-perception in space are the main tasks [51]. BT therapy can easily be combined with other antidystonic treatment options, including oral antidystonic drugs, intrathecal baclofen and peripheral or central surgery including deep brain stimulation.

The second layer includes adjuvant drugs such as analgesics and anxiolytics. They can become necessary when the effects of the antidystonic drugs are unsatisfactory. Relaxation exercises can break the vicious circle of motor induction in dystonia.

The third layer consists of adjuvant measures including adequate information for the patient and his/her family about the BT therapy as well as about the treated condition. Sharing a solid information base is a prerequisite for a stable patient-physician relationship, which seems particularly important since dystonia is a chronic condition. Patient support groups have a role to play here. Social support gives advice to the patient about available social benefits.

10.3.2 Dosing

BT therapy is a local therapy. Dosing, therefore, depends on two elements, i.e. the number of dystonic muscles requiring treatment (target muscles) and the degree of their dystonic involvement. Given the enormous variability of dystonia with respect to localisation and intensity, communication of total doses per patient is only relevant with respect to systemic adverse effects. Recently, it has been demonstrated that Xeomin® in total doses of up to 840 MU is free of motor or autonomic systemic adverse effects [33]. Indirect evidence suggests the similar safety margins for Botox® [33]. Frequently this dose range is not exploited. Within the individual target muscles, broad consensus emerged amongst physicians over the last years about appropriate dose ranges. Within these dose ranges, the individual dose has to be selected according to the degree of dystonic involvement. Additionally, some general dose modifiers (Table 10.4) should be used to adapt BT doses to the individual strength of the patient's target muscles. When neuromuscular transmission is impaired or when underlying paresis is present, BT dosages may need to be reduced.

10.3.3 Planning of Botulinum Toxin Therapy

Planning of BT therapy is based upon identification of target muscles and their degree of dystonic involvement. This information may be obtained clinically by

Table 10.4 Factors predicting the individual strength of the patient's target muscles. These factors, when present, modify the botulinum toxin dose within the recommended dose ranges

Sex	Male	Dose increase
	Female	Dose reduction
Age	Young age	Dose increase
	Old age	Dose reduction
Body weight	High	Dose increase
	Low	Dose reduction
Proportional muscle mass	High	Dose increase
	Low	Dose reduction

analysing the dystonic movements or postures. Based upon physiological activation patterns, dystonic muscles can be deduced. However, with unphysiological co-activation of antagonistic muscles as a key feature of dystonia, this clinical approach has limitations. An additional problem is compensatory muscle activity and preventive postures may be difficult to identify. The clinical approach does not allow determination of the degree of dystonic involvement. A superior way of planning of BT therapy is based upon electromyography [52]. Needle electromyography allows precise target muscle identification. It also allows comparison between maximal voluntary muscle activation and dystonic muscle activity for calculation of the dystonic involvement. Still, identification of compensatory muscle activation may be a problem. However, recordings of prolonged periods of electromyographic activity often allow distinction between dystonic and compensatory muscle activity. Target muscle selection by estimation of muscle hypertrophy using tomographic imaging techniques is inadequate, since muscle hypertrophy is not a necessary feature of dystonia and precise measurement of hypertrophy would require muscle relaxation which dystonia patients usually cannot maintain. At the end of the planning process stands the injection scheme describing the target muscles with their respective BT doses. This injection scheme is a prediction of the patient's therapeutic response. Subsequent injection series will usually improve the injection scheme. Recommendations not to exceed certain initial total doses and to very gradually build them up are counterproductive and risk the patient's compliance. Once the optimal injection scheme is established, it should be adhered to unless there is evidence of major changes of the treated symptomatology.

10.3.4 Intramuscular Placement of Botulinum Toxin Drugs

Placement of the BT drug into the target muscle can be done clinically by palpation (ideally under voluntary activation of the target muscle), by using surface landmarks or by back-tracing the muscle tendons. To identify individual finger muscles, repetitive active or passive finger movements may allow improved palpation of the target muscles. In target muscles, in which this is difficult, such as the iliopsoas or the piriformis muscles, or when selective injection of individual finger muscles is required, electromyographic guidance using a special injection needle may become necessary.

Simultaneous electric stimulation may be of additional help. General use of electromyography to place BT drugs is not necessary. Whether electromyography-guided BT placement would allow a dose reduction needs to be demonstrated. Tomographic imaging has also been suggested to improve drug placement. Since magnetic imaging may be disturbed by the presence of the injection needle, x-ray tomography has been applied. However, application of substantial radiation doses is problematic for chronic treatment. Ultrasound techniques seem to be more helpful, especially in children who may be uncooperative and particularly pain sensitive [53].

The effects of dilution and number of injection sites within a given target muscle have not been well studied so far. It is believed that increased dilution increases diffusion. The injection volumes at each injection site should be manageable. In our experience, injection volumes of 0.5–1.0 ml and 0.1–0.3 ml in facial muscles seem reasonable.

10.3.5 Monitoring of the Therapeutic Effect

Usually the therapeutic effect of BT therapy is evaluated punctually at 2–4 weeks after application. Apart from subjective scores reflecting overall outcome or dystonic pain, various objective dystonia rating scales, such as the Tsui Scale [54], the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [55] or the Burke-Fahn-Marsden Scale [56], have been introduced. The disadvantage of these scales is that they do not describe the dynamics of BT therapy, i.e. the time it takes for the therapeutic effect to build up and the time when it is waning. In order to construct the integral of the therapeutic effect, a new treatment calendar was recently introduced [57], (Fig. 10.3).

10.4 Specific Indications for Botulinum Toxin Therapy in Dystonia

10.4.1 Cranial Dystonias

Cranial dystonias can affect periocular muscles, mandibular muscles and perioral muscles. Rarely, scalp muscles or periauricular muscles are affected [58]. BT therapy can be used in all of these conditions successfully, either when they occur in isolation or when they occur in various combinations. Cranial target muscles with their recommended doses are shown in Tables 10.5 and 10.6. In periocular dystonia producing the classical clinical picture of blepharospasm, BT is injected into the orbicularis oculi muscle responsible for eyelid closure [3, 59]. Additional target muscles include the procerus and the corrugator supercilii muscles which form the horizontal and vertical nasal root folds and narrow the eyebrows. They may produce tension but do not have much influence on eyelid function. The nasalis muscle forms the longitudinal nasal dorsum fold and can be injected when the patient complains of irritation especially when wearing glasses. The frontalis muscle is an accessory eyelid-opening muscle and, therefore, should not be injected in blepharospasm contrary to occasional belief.

Patient Diary

Dear Patient,

Dystonia describes a group of very different and usually chronic conditions that include spasmodic torticollis (cervical dystonia), blepharospasm, and writer's cramp. In the past, the treatment of dystonia was usually frustrating for both the patient and the physician.

This situation has changed with the introduction of the botulinum toxin therapy. This therapy is now the most successful treatment for many types of dystonia.

To achieve optimal treatment results, the botulinum toxin therapy has to be individualised to match your particular symptoms. For this reason, it is necessary to exactly describe your dystonia, to meticulously monitor your response to the botulinum toxin therapy and to identify additional factors influencing your condition. Your personal experience with your dystonia is the most valuable source of information for all of this. This patient diary is designed to record your experience.

The patient diary can of course also be used to record other therapies.

Dirk Dressler, MD, PhD

Department of Neurology, Rostock University
Gehlsheimer Str. 20, D-18147 Rostock, Germany, dirk.dressler@med.uni-rostock.de

How to use this Patient Diary

1. Please fill in the Patient Diary every night before you go to bed.
2. Please circle the percentage which best describes the severity of all of your dystonia symptoms for that day. 0% describes the situation when you feel no dystonia symptoms at all, 100% when your dystonia is at its worst without any treatment.

   Please see examples A and B for assistance.
3. At first you will find it difficult to describe your dystonia symptoms to an accuracy of 5%. The fine gradation will however help you to accurately record changes in your dystonia symptoms from one day to the next.
4. Use the "Remarks" column to record all special observations of the day.

   Please see example C for assistance.
5. Please have your Patient Diary with you when you see your physician.
6. You can obtain additional copies of the patient diary from your physician.

Examples

A A woman is diagnosed as having cervical dystonia and has not yet been treated. Her dystonia symptoms are 100%. After initiation of a botulinum toxin therapy her dystonic symptoms are reduced to 20% on most days. After about three months the effect of the botulinum toxin therapy gradually fades and her dystonic symptoms are again 60%. About a week after repeating the botulinum toxin injections her dystonic symptoms are again reduced to 20% on most days.

B A man has dystonic symptoms of 50% from 7 am to 3 pm. By the time he goes to bed they have increased to 70%. Considering the entire day, his dystonic symptoms are probably best described by 60%.

C A woman plays tennis for 2 hours twice a week. She records that fact in her Patient Diary and realises that her dystonic symptoms on those days are twice as severe as on days without tennis. As a result of this, she reduces her playing time to 45 minutes and her dystonic symptoms are no longer worse on those days.

Fig. 10.3 Patient diary to monitor the effects of botulinum toxin therapy over time

DAY	DYSTONIA-SYMPTOMS (in percent of maximal untreated dystonia symptoms)	REMARKS
1	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
2	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
3	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
4	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
5	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
6	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
7	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
8	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
9	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
10	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
11	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
12	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
13	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
14	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
15	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
16	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
17	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
18	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
19	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
20	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
21	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
22	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
23	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
24	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
25	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
26	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
27	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
28	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
29	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
30	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	
31	0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	

Fig. 10.3 (Continued)

Table 10.5 Recommended botulinum toxin doses in cranial muscles

Muscle	Function	Recommended dose [MU-A Botox®]
Orbicularis oculi	Eyelid closure	12–64
Procerus	Formation of horizontal nasal root fold	4–12
Corrugator supercilii	Eyebrow adduction	8–16
Nasalis (transversal part)	Formation of longitudinal nasal dorsum fold	8–12
Risorius	Corner of mouth abduction	4–8
Depressor anguli oris	Corner of mouth depression	4–12
Depressor labii inferioris	Stabilisation of lower lip	4–8
Mentalis	Formation of chin dimples	8–12

MU-A mouse unit of the mouse bioassay of Allergan Inc
Dilution: 100 MU-A in 2.5 ml 0.9 % Sodium chloride/H_2O

Table 10.6 Recommended botulinum toxin doses in mandibular muscles

Muscle	Function	Recommended dose [MU-A Botox®]
Masseter	Jaw closing	20–60
Temporalis	Jaw closing	40–80
Pterygoidei (per side)	Jaw protrusion Jaw lateralisation Jaw opening Jaw closing	20–40
Supra- and infrahyoid muscles (per side)	Jaw opening	20–60

MU-A mouse unit of the mouse bioassay of Allergan Inc
Dilution: 100 MU-A in 2.5 ml 0.9 % Sodium chloride/H_2O)

Doses, dilutions and injection points for the treatment of blepharospasm vary considerably, whereas results and adverse effects are surprisingly similar. Adverse effects include ptosis, double vision, lagophthalmus and hematoma. They are rare and transient. Ptosis can almost certainly be avoided by sparing the medial part of the upper eyelid. Some patients with blepharospasm, especially those with progressive supranuclear palsy, have a varying degree of additional apraxia of eyelid opening [60], i.e. a supranuclear impairment of the eyelid-opening mechanism. In those patients, additional BT injections close to the rim of the eyelid are helpful [61]. If this strategy does not produce satisfactory results, a bilateral suspension operation connecting the upper eyelid to the frontalis muscle by a subcutaneous non-resorbable thread is helpful [62]. In mild cases, a wire spring attached to a spectacle frame can produce similar effects.

In perioral dystonia, muscles above the oral orifice should generally be injected with special caution in order to avoid drooping of the mouth. BT injections into the upper lip may produce paraesthesias for unknown reasons. The risorius muscle can be injected safely 2 cm lateral to the corner of the mouth, whereas injections into the depressor labii inferioris bear the risk of instability of the lower lip.

In mandibular dystonia, jaw-opening and jaw-closing forms can be distinguished [63]. Combined activation of opening and closing muscles, however, is not infrequent. Additional jaw movements include jaw protrusion and lateral shifts of the jaw. Jaw closing is caused by activation of the masseter, the temporalis and – to a minor extent – the medial pterygoid muscles. Jaw opening is the result of activation of the lateral pterygoid muscle and the suprahyoid muscles forming the muscular floor of the cavity of the mouth. Protrusion and lateral shifts are caused by the pterygoid muscles, mainly the lateral ones. Whereas treatment of the jaw-closing type produces excellent results with only rare adverse effects, treatment of the jaw-opening type is less rewarding. Our experience indicates that BT injections into the

pterygoid muscles through the incisura mandibulae together with injections of the suprahyoid muscles seem to work best in this situation. Attempts to inject the lateral and the medial pterygoid muscles individually would cause major technical problems and discomfort for the patient. Local spread and frequent co-activation of both muscles question the logic of this approach.

10.4.2 Pharyngolaryngeal Dystonia

Tonic or clonic dystonia of the pharynx can produce dysphagia and dyspnea [64]. They can occur spontaneously or in an action-induced fashion. BT injections into the posterior pharynx can easily be placed transorally and are effective. Doses range between 20 and 40 MU of Botox®. Laryngeal dystonia produces the clinical picture of spasmodic dysphonia, either in the adductor form with a strained-strangled voice or in the much less frequent abductor form with hypophonia [65]. In adductor forms, 2.5–10 MU of Botox® is administered into the thyroarytenoid (vocalis) muscle. Unilateral application appears to produce less adverse effects than when the same amount is distributed over both sides. In abductor forms, 2.5–10 MU of Botox® is administered into the posterior cricoarytenoid muscle unilaterally in order to avoid dyspnea. BT application can be performed perorally or transcutaneously using electromyographic guidance. The transoral approach allows detection of additional dystonic muscle activities in the pharynx or the larynx and, therefore, seems to be the superior method.

For the patient and for the physician, BT therapy of spasmodic dysphonia represents a highly satisfying indication [66]. Practically all patients benefit from BT therapy and the degree of improvement is astonishing. In many cases, almost normal speech patterns can be regained. In patients with abductor forms, the treatment results are less favourable. Adverse effects include difficulties with swallowing liquids or solid food. BT therapy can also induce weakness of coughing and some pain at the injection side. In treatment of adductor forms, hoarseness, breathiness of voice and hypophonia can occur, while in treatment of abductor forms, dyspnea may result.

Spasmodic laryngeal dyspnea describes spontaneously occurring or respiration-induced muscle hyperactivity of laryngeal muscles [67]. This condition is very rare and may influence both glottic and supraglottic muscles and can also be treated with BT therapy.

10.4.3 Cervical Dystonia

Cervical dystonia induces deviation of the neck and the head. Frequently shoulder elevation occurs. Whereas the neck can only be flexed and extended on a sagittal plane or frontal plane and rotated on a horizontal plane throughout its entire structure employing numerous interspinal joints, the head is flexed and extended on a sagittal plane, tilted on a frontal plane and rotated on a horizontal plane by using the singular atlanto-occipital joint with the dens as an additional stabilisator. Head and neck deviations can best be described by the scheme shown in Table 10.7. The

Table 10.7 Description of head and neck deviation in cervical dystonia

Head deviation	Neck deviation	Conventional description
Rotation		Torticollis
Flexion	Nil	Antecaput
	Flexion	Antecaput + retrocollis
	Extension	Antecaput + antecollis = posterior shift/retrusion
Extension	Nil	Retrocaput
	Flexion	Retrocaput + antecollis = anterior shift/protrusion
	Extension	Retrocaput + retrocollis
Lateral flexion	Nil	Laterocaput
	Flexion ipsilateral	Laterocaput + laterocollis
	Flexion contralateral	Lateral shift

I 0–30°
II 30–60°
III 60–90°

scheme allows an easy and semiquantitative, although comprehensive, description of the head and neck deviations elicited by cervical dystonia.

Isolated occurrence of head or neck deviations is rare. Most patients suffer from complex combinations of head deviations.

Head rotation occurs always together with *neck rotation*. It is caused by activation of the ipsilateral splenius capitis, the contralateral sternocleidomastoid muscle and the ipsilateral trapezius/semispinalis capitis muscle complex. Deep posterior neck muscles arising from the atlas and the axis including the obliquus capitis inferior, the rectus capitis posterior major and the rectus capitis posterior minor muscles are strong ipsilateral head rotators. The levator scapulae muscle is an additional but weaker ipsilateral head rotator. In head and neck rotation, the role of the sternocleidomastoid is often overestimated, whereas the role of the splenius capitis and the deep posterior neck muscles is often underestimated.

Head flexion is caused by activation of the supra- and infrahyoid muscles. *Neck flexion* is produced by the scaleni and deep anterior neck muscles including the longus colli, the longus capitis and the rectus capitis anterior muscles. *Head extension* originates from bilateral activation splenius capitis and the deep posterior neck muscles, and *neck extension* from bilateral activation of the trapezius/semispinalis capitis muscle complex. *Lateral head flexion* originates from ipsilateral activation of the sternocleidomastoid and the splenius capitis, and *lateral neck flexion* from ipsilateral activation of the scaleni, the levator scapulae and the trapezius/semispinalis capitis muscle complex. *Protrusion* is the consequence of neck flexion together with head extension, and *retrusion* of neck extension together with head flexion.

Planning of BT therapy for cervical dystonia includes careful examination of the spontaneous head position, the head position under motor and stress activation, the slow active head movement and passive head mobility. When dystonia occurs in waves or when it can be suppressed by gestes antagonistes, the time course of a

Table 10.8 Recommended botulinum toxin doses for cervical muscles

Muscle	Function	Recommended dose [MU-A Botox®]
Sternocleidomastoid	Contralateral horizontal head rotation Sagittal head flexion Frontal head flexion	20–60
Splenius capitis	Ipsilateral horizontal Head rotation	20–100
Scaleni	Frontal head flexion Sagittal head flexion	20–60
Levator scapulae	Shoulder elevation Ipsilateral head rotation Frontal head extension	20–60
Trapezius/semispinalis capitis complex	Sagittal head extension Ipsilateral head rotation	20–80
Trapezius, horizontal part	Shoulder elevation Frontal head flexion	40–80

MU-A mouse unit of the mouse bioassay of Allergan Inc
Dilution: 100 MU-A in 2.5 ml 0.9 % Sodium chloride/H_2O)

dystonic build-up helps to identify compensatory muscle activity. Slow active movements can identify trigger postures and therefore potential preventive postures. Testing for pre-existent dysphagia identifies patients in which BT application into anterior neck muscles should be performed with caution.

Target muscles and recommended BT doses for cervical muscles are shown in Table 10.8.

Dystonic pain as the leading complaint in most patients with cervical dystonia can almost always be markedly reduced by BT therapy. Residual pain may be caused by secondary degenerative processes or by radicular irritation. Head posture can also be improved substantially. Often, patients report the effects of the first BT applications enthusiastically, most likely due to the contrast to the sometimes prolonged period of insufficient treatment. Especially in the treatment of cervical dystonia, additional *physiotherapy* following the above-discussed guidelines is necessary [51]. Certain forms of cervical dystonia respond less favourably to BT therapy. Especially head flexion and neck flexion is difficult to treat when deep anterior neck muscles are involved, but also, alternating types of cervical dystonia may present a therapeutic challenge. In tremor types, sometimes reduced BT doses seem to be helpful.

The most common *adverse effect* of BT therapy of cervical dystonia is dysphagia. Depending on the definition of dysphagia and the effort to search for it, their incidence varies greatly. Applying current treatment standards, certainly less than 5 % of patients experience dysphagia constantly after each injection series. Mild dysphagia may be more frequent. Another adverse effect is head instability, especially due

to impaired head and neck extension. When these adverse effects occur, their duration is usually limited to 1 or 2 weeks. Injection of the scaleni muscles can produce needle contacts with brachial plexus nerve fibres eliciting short-lasting electric sensations especially when injections are placed too close to Erb's point.

10.4.4 Arm Dystonia

Arm dystonia can be divided into *action-induced forms* and *spontaneous forms*. Action-induced forms occur only during certain activities which can sometimes be highly specific. Spontaneous forms are not associated with specific activities, although they may be increased by unspecific physical activity. Writer's cramp is the most common action-induced dystonia [68]. Other highly specific and sometimes peculiar activities can also trigger dystonia, such as playing musical instruments or performing sports. Especially, when these activities are performed under professional conditions, dystonia can result, thus explaining the term occupational cramp.

In *writer's cramp*, a wrist flexor and a wrist extensor type can be distinguished. Additionally, elbow and shoulder muscles may be involved. However, abnormal elbow and shoulder postures may be compensatory in order to change the writing position and to reduce dystonia. Planning of BT therapy for writer's cramp is based on careful examination of the clinical symptomatology. Electromyography is rarely contributory, since normal writing usually generates widespread muscle activation which can hardly be distinguished from dystonic muscle activity. Sometimes, asking the patient to write with the contralateral hand produces the dystonic pattern in the dominant hand without contamination of normal or compensatory muscle activity.

Target muscles and recommended BT doses for arm dystonia are shown in Table 10.9. Results of BT therapy of writer's cramp are limited, because of narrow therapeutic windows of the potential target muscles [69]. This is a problem especially in the finger extensors. Apart from this, writer's cramp frequently affects a large number of forearm muscles. BT therapy targeting all of these muscles would induce major paretic adverse effects. Additionally, distinction between physiological and dystonic muscle activity and identification of compensatory muscle activity may be difficult. Our experience indicates that even after several modifications of the injection scheme, only about half of the patients benefit from BT therapy and continue treatment. Results are better when the finger muscles are not involved, i.e. when the symptomatology is restricted to the wrist or elbow muscles. When finger muscles are involved, the outcome is better when individual finger muscles and when finger flexors rather than finger extensors are dystonic. If the symptomatology is restricted to individual finger muscles, electromyography possibly with additional electric stimulation may facilitate BT placement. If BT therapy is not successful in treatment of writer's cramp, the patient can shift writing to the contralateral hand. About half of the patients can permanently use the contralateral hand for writing, whereas the other half develops writer's cramp in this hand as well within 1 or 2 years. Increased use of keyboards is also one option to circumvent writer's cramp. Retraining exercises may also become a therapeutic option in the future [70].

Table 10.9 Recommended botulinum toxin doses for arm muscles

Muscle	Function	Recommended dose [MU-A Botox®]
Deltoideus	Shoulder abduction	40–120
Biceps brachii	Elbow flexion	40–100
Triceps brachii	Elbow extension	40–100
Brachialis	Elbow flexion	40–80
Brachioradialis	Elbow flexion	40–80
Flexor digitorum profundus et superficialis	Finger flexion	40–120
Flexor carpi radialis	Wrist flexion	40–80
Extensor digitorum profundus et superficialis	Finger extension	20–60
Extensor carpi radialis	Wrist extension	20–40
Interosseous	Metacarpophalangeal adduction Metacarpophalangeal abduction	20
Abductor digiti quinti	Little finger metacarpophalangeal abduction	20–40
Flexor pollicis longus	Thumb flexion	20–60

MU-A mouse unit of the mouse bioassay of Allergan Inc
Dilution: 100 MU-A in 2.5 ml 0.9 % Sodium chloride/H_2O)

Treatment of other action-induced arm dystonias, especially when they are occupational, is even more problematic, since the motor performance expected by the patient is usually so high that it cannot be met, either due to dystonic residues or due to therapy-induced paresis [71].

Spontaneous induced arm dystonia usually occurs as part of a spasticity-dystonia syndrome or as idiopathic dystonia. Typical postures include finger flexion, thumb flexion, wrist flexion, elbow flexion and shoulder adduction or shoulder abduction. In spasticity-dystonia syndrome, treatment is focused on pain, prevention of contractures and eased care. Functional improvement may result but is often restricted by the underlying paresis.

10.4.5 Leg Dystonia

Leg dystonia can occur in idiopathic as well as in symptomatic dystonia, mostly as part of a spasticity-dystonia syndrome due to stroke or cerebral palsy. Action-induced forms would be extremely rare. Typical postures include hip adduction; knee flexion; equinovarus posture, i.e. the combination of ankle plantar flexion, foot supination and toe flexion; ankle plantar flexion; and toe flexion. Hip adduction is caused by activation of the adductor muscle group (adductor magnus, minimus, longus, brevis and gracilis muscles), knee flexion by activation of the hamstrings (semimembranosus, semitendinosus, biceps femoris muscles) and

Table 10.10 Recommended botulinum toxin doses for leg muscles

Muscle	Function	Recommended dose [MU-A Botox®]
Adductor muscle group	Hip adduction	100–300
Quadriceps femoris	Knee extension	100–300
Hamstring muscles	Knee flexion	100–300
Triceps surae	Ankle plantar flexion	100–200
Tibialis posterior	Foot supination	60–100
Flexor hallucis longus	Great toe flexion Ankle plantar flexion	60–100
Tibialis anterior	Ankle dorsiflexion	40–100
Extensor digitorum longus	Toe extension Ankle dorsiflexion	40–100
Extensor hallucis longus	Great toe extension Ankle dorsiflexion	40–60

MU-A mouse unit of the mouse bioassay of Allergan Inc
Dilution: 100 MU-A in 2.5 ml 0.9 % Sodium chloride/H_2O)

equinovarus posture by activation of the tibialis posterior, triceps surae, flexor hallucis and digitorum longus muscles. Ankle plantar flexion is the result of activation of triceps surae, peroneus longus and brevis and flexor digitorum longus muscles, and toe flexion of the activation of the flexor digitorum longus and brevis muscles.

Target muscles and recommended BT doses for leg dystonia are shown in Table 10.10.

Hip adduction, ankle plantar flexion and equinovarus postures respond well to BT therapy. BT doses, however, may be high, especially when bilateral injections are necessary. BT therapy for knee extension bears the risk of knee weakness, especially in patients with additional paresis as in spasticity-dystonia syndrome after stroke. Toe and great toe flexion often requires combined treatment of short and long toe and great toe flexors.

10.4.6 Segmental Dystonia and Generalised Dystonia

BT therapy of extended dystonic symptomatologies usually requires selection of those target muscles which play a major role in functional impairment, pain and prevention of complications. Less relevant target muscles may need to be left untreated in order not to exceed total BT doses which are safe with respect to toxicological and immunological adverse effects. Paravertebral muscles require 40–60 MU Botox® per segment per side, the rectus abdominis 40–80 MU Botox® per segment per side and the abdominal wall muscle complex (obliquus internus abdominis, obliquus externus abdominis and transversus abdominis muscles) 80–200 MU Botox® per side.

Toxicological and immunological safety margins have been discussed above. When safety margins are exploited to their full extent, BT therapy can improve even extended symptomatologies substantially. In patients requiring excess BT doses, deep brain stimulation may offer a treatment alternative. Combinations of BT therapy and deep brain therapy or intrathecal baclofen are possible.

10.5 Outlook

BT therapy presents a novel therapeutic concept. It has revolutionised many medical fields. In dystonia, for the first time, it offers help to a large numbers of patients with focal dystonia [72]. In segmental and generalised dystonia, high BT doses are necessary. Emerging experience demonstrates that high BT doses are immunologically and toxicologically safe [73–75]. The recent introduction of low-antigenicity BT drugs may allow booster injections for rapid dose adaptation, reduced interinjection intervals for an improved dynamic adjustment and increased BT dose for treatment of extended BT symptomatologies [76, 77]. High-affinity BT drugs may improve antigenicity even further. They may reduce the threshold for systemic toxicology so that higher total BT doses may be applied.

References

1. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. J Pediatr Ophthalmol Strabismus. 1980;17:21–5.
2. Scott AB, Rosenbaum A, Collins CC. Pharmacologic weakening of extraocular muscles. Invest Ophthalmol. 1973;12:924–7.
3. Frueh BR, Felt DP, Wojno TH, Musch DC. Treatment of blepharospasm with botulinum toxin. A preliminary report. Arch Ophthalmol. 1984;102:1464–8.
4. Tsui JK, Eisen A, Mak E, Carruthers J, Scott A, Calne DB. A pilot study on the use of botulinum toxin in spasmodic torticollis. Can J Neurol Sci. 1985;12:314–6.
5. Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, DeGryse RE, VanDenburgh AM, Nolan ME, Turkel CC. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache. 2011;51:1358–73.
6. Truong D, Dressler D, Hallett M, Zachary C. Manual of botulinum toxin therapy. 2nd ed. Cambridge: Cambridge University Press; 2013.
7. Frevert J, Dressler D. Complexing proteins in botulinum toxin type A drugs – a help or hindrance? Biologics. 2010;4:325–32.
8. Dressler D. Five-year experience with incobotulinumtoxinA (Xeomin®): the first botulinum toxin drug free of complexing proteins. Eur J Neurol. 2012;19:385–9.
9. Dong M, Richards DA, Goodnough MC, Tepp WH, Johnson EA, Chapman ER. Synaptotagmins I and II mediate entry of botulinum neurotoxin B into cells. J Cell Biol. 2003;162:1293–303.
10. Dong M, Yeh F, Tepp WH, Dean C, Johnson EA, Janz R, Chapman ER. SV2 is the protein receptor for botulinum neurotoxin A. Science. 2006;312:592–6.
11. Mahrhold S, Rummel A, Bigalke H, Davletov B, Binz T. The synaptic vesicle protein 2C mediates the uptake of botulinum neurotoxin A into phrenic nerves. FEBS Lett. 2006;580:2011–4.
12. Rummel A, Karnath T, Henke T, Bigalke H, Binz T. Synaptotagmins I and II act as nerve cell receptors for botulinum neurotoxin G. J Biol Chem. 2004;279:30865–70.

13. Pellizzari R, Rossetto O, Schiavo G, Montecucco C. Tetanus and botulinum neurotoxins: mechanism of action and therapeutic uses. Philos Trans R Soc Lond B Biol Sci. 1999;354:259–68.
14. Brin MF, Dressler D, Aoki R. Pharmacology of botulinum toxin therapy. In: Jankovic J, Comella C, Brin MF, editors. Dystonia: etiology, clinical features, and treatment. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 93–112.
15. Dressler D, Eckert J, Kukowski B, Meyer BU. Somatosensorisch Evozierte Potentiale bei Schreibkrampf: Normalisierung pathologischer Befunde unter Botulinum Toxin Therapie. Z EEG EMG. 1993;24:191.
16. Filippi GM, Errico P, Santarelli R, Bagolini B, Manni E. Botulinum A toxin effects on rat jaw muscle spindles. Acta Otolaryngol. 1993;113:400–4.
17. Rosales RL, Arimura K, Takenaga S, Osame M. Extrafusal and intrafusal muscle effects in experimental botulinum toxin-A injection. Muscle Nerve. 1996;19:488–96.
18. Kaji R, Kohara N, Katayama M, Kubori T, Mezaki T, Shibasaki H, Kimura J. Muscle afferent block by intramuscular injection of lidocaine for the treatment of writer's cramp. Muscle Nerve. 1995;18:234–5.
19. Kaji R, Rothwell JC, Katayama M, Ikeda T, Kubori T, Kohara N, Mezaki T, Shibasaki H, Kimura J. Tonic vibration reflex and muscle afferent block in writer's cramp. Ann Neurol. 1995;38:155–62.
20. Caleo M, Schiavo G. Central effects of tetanus and botulinum neurotoxins. Toxicon. 2009;54:593–9.
21. Wiegand H, Erdmann G, Wellhoner HH. 125I-labelled botulinum A neurotoxin: pharmacokinetics in cats after intramuscular injection. Naunyn Schmiedebergs Arch Pharmacol. 1976;292:161–5.
22. Cui M, Li Z, You S, Khanijou S, Aoki R. Mechanisms of the antinociceptive effect of subcutaneous Botox: inhibition of peripheral and central nociceptive processing. Arch Pharmacol. 2002;365:R17.
23. Ishikawa H, Mitsui Y, Yoshitomi T, Mashimo K, Aoki S, Mukuno K, Shimizu K. Presynaptic effects of botulinum toxin type A on the neuronally evoked response of albino and pigmented rabbit iris sphincter and dilator muscles. Jpn J Ophthalmol. 2000;44:106–9.
24. McMahon H, Foran P, Dolly J. Tetanus toxin and botulinum toxins type A and B inhibit glutamate, gamma-aminobutyric acid, aspartate, and met-enkephalin release from synaptosomes: clues to the locus of action. J Biol Chem. 1992;267:21338–43.
25. Morris J, Jobling P, Gibbins I. Differential inhibition by botulinum neurotoxin A of cotransmitters released from autonomic vasodilator neurons. Am J Physiol Heart Circ Physiol. 2001;281:2124–32.
26. Purkiss J, Welch M, Doward S, Foster K. Capsaicin-stimulated release of substance P from cultured dorsal root ganglion neurons: involvement of two distinct mechanisms. Biochem Pharmacol. 2000;59:1403–6.
27. Shone CC, Melling J. Inhibition of calcium-dependent release of noradrenaline from PC12 cells by botulinum type-A neurotoxin. Long-term effects of the neurotoxin on intact cells. Eur J Biochem. 1992;207:1009–16.
28. Welch MJ, Purkiss JR, Foster KA. Sensitivity of embryonic rat dorsal root ganglia neurons to Clostridium botulinum neurotoxins. Toxicon. 2000;38:245–58.
29. Dressler D, Rothwell JC. Electromyographic quantification of the paralysing effect of botulinum toxin. Eur Neurol. 2000;43:13–6.
30. Dressler D, Tacik P, Adib Saberi F. Botulinum toxin therapy of cervical dystonia: duration of therapeutic effects. J Neural Transm. 2013;120:1142.
31. Dressler D, Tacik P, Adib Saberi F. Botulinum toxin therapy of cervical dystonia: comparing Botox® and Xeomin®. J Neural Transm. 2014;121:29–31.
32. Benecke R, Jost WH, Kanovsky P, Ruzicka E, Comes G, Grafe S. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. Neurology. 2005;64:| 1949–51.

33. Dressler D, Adib Saberi F. Safety aspects of high dose Xeomin® therapy. J Neurol. 2006;253(2):II/141.
34. Dressler D, Mander X, Fink K. Measuring the potency labelling of onabotulinumtoxinA (Botox®) and Xeomin® in an LD50 assay. J Neural Transm. 2012;119:13–5.
35. Dressler D, Muenchau A, Bhatia KP, Quinn NP, Bigalke H. Antibody induced botulinum toxin therapy failure: can it be overcome by increased botulinum toxin doses? Eur Neurol. 2002;47:118–21.
36. Dressler D, Dirnberger G. Botulinum toxin therapy: risk factors for therapy failure. Mov Disord. 2000;15(2):51.
37. Dressler D, Benecke R. Xeomin® eine neue therapeutische botulinum toxin typ A-Präparation. Aktuelle Neurol. 2006;33:138–41.
38. Jankovic J, Vuong KD, Ahsan J. Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. Neurology. 2003;60:1186–8.
39. Pickett A, Panjwani N, O'Keeffe RS (2003) Potency of Type A botulinum toxin preparations in clinical use. 40th annual meeting of the Interagency Botulism Research Coordinating Committee (IBRCC), Nov. 2003; Atlanta.
40. Setler P. The biochemistry of botulinum toxin type B. Neurology. 2000;55(5):S22–8.
41. Dressler D. Complete secondary botulinum toxin therapy failure in blepharospasm. J Neurol. 2000;247:809–10.
42. Dressler D. New formulation of BOTOX®: complete antibody-induced therapy failure in hemifacial spasm. J Neurol. 2004;251:360.
43. Dressler D. Dysport produces intrinsically more swallowing problems than Botox: unexpected results from a conversion factor study in cervical dystonia. J Neurol Neurosurg Psychiatry. 2002;73:604.
44. Probst TE, Heise H, Heise P, Benecke R, Dressler D. Rare immunologic side effects of botulinum toxin therapy: brachial plexus neuropathy and dermatomyositis. Mov Disord. 2002;17(5):S49.
45. Dressler D. Subclinical myasthenia gravis causing increased sensitivity to botulinum toxin therapy. J Neural Transm. 2010;117:1293–4.
46. Erbguth F, Claus D, Engelhardt A, Dressler D. Systemic effect of local botulinum toxin injections unmasks subclinical Lambert-Eaton myasthenic syndrome. J Neurol Neurosurg Psychiatry. 1993;56:1235–6.
47. Naumann M, Albanese A, Heinen F, Molenaers G, Relja M. Safety and efficacy of botulinum toxin type A following long-term use. Eur J Neurol. 2006;13 Suppl 4:35–40.
48. Dressler D, Benecke R. Autonomic side effects of botulinum toxin type B treatment of cervical dystonia and hyperhidrosis. Eur Neurol. 2003;49:34–8.
49. Dressler D, Eleopra R. Clinical use of non-A botulinum toxins: botulinum toxin type B. Neurotox Res. 2006;9:121–5.
50. Adib Saberi F, Dressler D. Interdisziplinärer Arbeitskreis Bewegungsstörungen (IAB): a new approach for promoting interdisciplinary therapy of movement disorders. J Neural Transm. 2013;120:705–10.
51. Barth K, Dressler D. Die krankengymnastische Zusammenarbeit mit Schiefhalspatienten nach der Behandlung mit Botulinum Toxin. Krankengymnastik. 1993;45:134–42.
52. Dressler D. Electromyographic evaluation of cervical dystonia for planning of botulinum toxin therapy. Eur J Neurol. 2000;7:713–8.
53. Berweck S, Feldkamp A, Francke A, Nehles J, Schwerin A, Heinen F. Sonography-guided injection of botulinum toxin A in children with cerebral palsy. Neuropediatrics. 2002;33:221–3.
54. Tsui JK, Eisen A, Stoessl AJ, Calne S, Calne DB. Double-blind study of botulinum toxin in spasmodic torticollis. Lancet. 1986;2(8501):245–7.
55. Consky ES, Basinki A, Belle L, Ranawaya R, Lang AE. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS): assessment of validity and inter-rater reliability. Neurology. 1990;40(1):445.

56. Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology. 1985;35:73–7.
57. Dressler D, Kupsch A, Paus S, Seitzinger A, Minnasch P. The Dystonia Discomfort Scale (DDS): a novel instrument to monitor the temporal profile of botulinum toxin therapy in cervical dystonia. Eur J Neurol. 2014;21:459–62.
58. Alonso-Navarro H, Puertas I, Cabrera-Valdivia F, de Toledo-Heras M, García-Albea E, Jiménez-Jiménez FJ. Posterior auricular muscle 'dystonia'. Eur J Neurol. 2007;14:e14–5.
59. Costa J, Espírito-Santo C, Borges A, Ferreira JJ, Coelho M, Moore P, Sampaio C (2005) Botulinum toxin type A therapy for blepharospasm. Cochrane Database Syst Rev. (1):CD004900.
60. Aramideh M, Ongerboer de Visser BW, Koelman JH, Bour LJ, Devriese PP, Speelman JD. Clinical and electromyographic features of levator palpebrae superioris muscle dysfunction in involuntary eyelid closure. Mov Disord. 1994;9:395–402.
61. Jankovic J. Pretarsal injection of botulinum toxin for blepharospasm and apraxia of eyelid opening. J Neurol Neurosurg Psychiatry. 1996;60:704.
62. Roggenkämper P, Nüssgens Z. Frontalis suspension for essential blepharospasm unresponsive to botulinum toxin therapy. First results. Ger J Ophthalmol. 1993;2:426–8.
63. Marsden CD. The problem of adult-onset idiopathic torsion dystonia and other isolated dyskinesias in adult life (including blepharospasm, oromandibular dystonia, dystonic writer's cramp, and torticollis, or axial dystonia). Adv Neurol. 1976;14:259–76.
64. Zwirner P, Dressler D. Dystonie als Ursache pharyngo-laryngealer Motilitätsstörungen. HNO. 1995;43:498–501.
65. Marsden CD, Sheehy MP. Spastic dysphonia, Meige disease, and torsion dystonia. Neurology. 1982;32:1202–3.
66. Whurr R, Nye C, Lorch M. Meta-analysis of botulinum toxin treatment of spasmodic dysphonia: a review of 22 studies. Int J Lang Commun Disord. 1998;33(Suppl):327–9.
67. Zwirner P, Dressler D, Kruse E. Spasmodic laryngeal dyspnea: a rare manifestation of laryngeal dystonia. Eur Arch Otorhinolaryngol. 1997;254:242–5.
68. Sheehy MP, Rothwell JC, Marsden CD. Writer's cramp. Adv Neurol. 1988;50:457–72.
69. Das CP, Dressler D, Hallett M. Botulinum toxin therapy of writer's cramp. Eur J Neurol. 2006;13(1):55–9.
70. Zeuner KE, Bara-Jimenez W, Noguchi PS, Goldstein SR, Dambrosia JM, Hallett M. Sensory training for patients with focal hand dystonia. Ann Neurol. 2002;51:593–8.
71. Jabusch HC, Zschucke D, Schmidt A, Schuele S, Altenmüller E. Focal dystonia in musicians: treatment strategies and long-term outcome in 144 patients. Mov Disord. 2005;20:1623–6.
72. Dressler D. Botulinum toxin therapy. Stuttgart: Thieme Verlag; 2000.
73. Dressler D. Clinical features of secondary failure of botulinum toxin therapy. Eur Neurol. 2002;48:26–9.
74. Dressler D, Benecke R. Pharmacology of therapeutic botulinum toxin preparations. Disabil Rehabil. 2007;29:1761–8.
75. Dressler D, Benecke R, Bigalke H. Botulinum toxin type B (NeuroBloc®) in patients with botulinum toxin type A antibody-induced therapy failure. J Neurol. 2003;250:967–9.
76. Dressler D, Bigalke H. Antibody-induced failure of botulinum toxin type B therapy in de novo patients. Eur Neurol. 2004;52:132–5.
77. Moore AP, Naumann M, editors. Handbook of botulinum toxin treatment. 2nd ed. Malden: Blackwell Science; 2003.