Consensus guidelines for botulinum toxin therapy: general algorithms and dosing tables for dystonia and spasticity

Dirk Dressler1 · Maria Concetta Altavista2 · Eckart Altenmüller3 · Roongroj Bhidayasiri4 · Saeed Bohlega5 · Pedro Chana6 · Tae Mo Chung7 · Carlo Colosimo8 · Klemens Fheodoroff9 · Pedro J. García-Ruiz10 · Beomseok Jeon11 · Lingjing Jin12 · Petr Kanovsky13 · Ivan Milanov14 · Federico Micheli15 · Olga Orlova16 · Sanjay Pandey17 · Zvezdan Pirtosek18 · Maja Relja19 · Raymond Rosales20 · José Alberto Sagástegui-Rodríguez21 · Gholam Ali Shahidi22 · Sofia Timerbaeva23 · Xinhua Wan24 · Uwe Walter25 · Fereshte Adib Saberi26

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Abstract
Botulinum toxin (BT) therapy is a complex and highly individualised therapy defined by treatment algorithms and injection schemes describing its target muscles and their dosing. Various consensus guidelines have tried to standardise and to improve BT therapy. We wanted to update and improve consensus guidelines by: (1) Acknowledging recent advances of treatment algorithms. (2) Basing dosing tables on statistical analyses of real-life treatment data originating from a reference centre with a minimum of legal and economic restrictions to perform BT therapy. (3) Providing more detailed dosing data including typical doses, dose variabilities, and dosing limits. (4) Including total doses and target muscle selections for typical clinical entities thus adapting dosing to different aetiologies and pathophysiologies. (5) In addition, providing a brief and concise review of the clinical entity treated together with general principles of its BT therapy. For this, we collaborated with IAB—Interdisciplinary Working Group for Movement Disorders which invited an international panel of experts for the support.

Keywords Botulinum toxin · Therapy · Consensus guidelines · Dystonia · Spasticity · Treatment algorithms · Dosing tables · Target muscles · Total dose · Typical dose · Dose limits · Dose variability

Introduction
Botulinum toxin (BT) therapy is a complex and highly individualised therapy defined by treatment algorithms and injection schemes. The treatment algorithms consist of the set of parameters describing BT therapy and the ways they are combined and modified to adapt them to the individual patient’s treatment situation. The injection scheme describes the individual patient’s target muscles and their dosing.

Consensus guidelines have tried to standardise and to improve BT therapy. There have been several attempts to develop such guidelines and to make them publicly available. The most widespread ones have been produced by We Move Inc, New York City, NY, USA for dystonia, spasticity, cerebral palsy, and BT type B some 15 years ago and were based on original work by Brin (1997). More recent guidelines cover dystonia only (Albanese et al. 2011, 2015), whilst another one also covers spasticity and several other indications (Simpson et al. 2016). However, two of them (Albanese et al. 2011; Simpson et al. 2016) are presenting treatment algorithms only and do not include dosing tables. The dosing table included in the third guideline (Albanese et al. 2015) covers cervical dystonia only and—due to a very heterogenous database—recommends BT doses varying by factors from two to six for individual muscles, thus reducing their practical usefulness considerably.

We wanted to update and improve consensus guidelines by: (1) acknowledging recent advances of treatment algorithms (2) basing dosing tables on statistical analyses of real-life treatment data originating from a reference centre with a minimum of legal and economic restrictions to perform BT therapy; (3) providing more detailed dosing data, including typical doses, dose variabilities, and dosing limits for all relevant target muscles; (4) including total doses and target...
muscle selections for typical dystonia (cervical dystonia, facial dystonia, oromandibular dystonia, arm dystonia, and axial dystonia) and spasticity indications (arm spasticity, leg spasticity, hemispasticity, paraspasticity, and tetraspasticity) thus adapting dosing to different aetiologies (spasticity and dystonia) and pathophysiologies (task-specific dystonia and non-task-specific dystonia); (5) in addition, providing a brief and concise review of the clinical entity treated together with general principles of its BT therapy.

This project was organised by IAB—Interdisciplinary Working Group for Movement Disorders, a German organisation with a worldwide reach to promote interdisciplinary collaboration for improving the understanding and therapy of movement disorders. IAB invited an international panel of experts with an outstanding reputation for BT therapy to provide their input.

**Methods**

**Definitions**

The following definitions are used:

| Term                                      | Definition                                                                                                                                 |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Treatment algorithms                      | The set of parameters used to describe a BT therapy and the ways they are combined and modified to adapt it to the individual patient’s treatment situation |
| Injection scheme                          | Describes the individual patient’s target muscles and their dosing                                                                        |
| Dosing table                              | Describes BT doses for target muscles                                                                                                     |
| Real-life treatment data                  | Treatment data derived from the actual use of BT therapy                                                                                   |
| Target muscle                             | A muscle selected to receive BT applications                                                                                                 |
| Total dose                                | The amount of BT applied to a patient at one injection series                                                                               |
| Interinjection interval                    | The interval between two subsequent injection series                                                                                         |
| Therapeutic window                        | The sensitivity of a target muscle to receive BT without showing functional impairment                                                   |
| Dystonia ratio                            | The amount of dystonic muscle activity in relation to the target muscle’s maximal voluntary activity                                         |
| Drug potency labelling                     | The potency of a BT drug as described by the manufacturer                                                                                    |
| Drug stability                            | The potency changes of the unreconstituted or reconstituted BT drug over time                                                               |
| Guidance techniques                       | Techniques including ultrasound and EMG (with or without electric stimulation) to control the application of BT                               |
| Dosing variability                        | Indicated by the standard deviation of the BT doses applied to a target muscle as documented in the reference centre’s database               |

**Dosing limits**

Indicated by the minimum and maximum of the BT doses applied to a target muscle as documented in the reference centre’s database.

**Typical dose**

Indicated by the mean BT dose applied to a target muscle as documented in the reference centre’s database.

**Design**

These consensus guidelines are based on a panel review of current treatment algorithms and statistical analysis of real-life treatment data deriving from a specialised reference centre.

**Reference centre**

The reference centre is the Movement Disorders Section, Department of Neurology, Hannover Medical School, Hannover, Germany. It was founded 12 years ago by one of the authors (DD) and is specialised in BT therapy. Currently, the centre’s annual BT usage is in excess of 20,000 100 MU vials of onabotulinumtoxinA (ONA, Botox®, Allergan, Dublin, Ireland) and incobotulinumtoxinA (INCO, Xeomin®, Merz Pharmaceuticals, Frankfurt/M, Germany).

**Database**

Data used for this evaluation derived from real-life data routinely collected in the computerised reference centre’s database during the last 11 years. For this study, 420 dystonia patients (59.8 ± 14.0 years, 38% males, 62% females) with cervical dystonia (n = 200), facial dystonia (n = 100), writer’s cramp (n = 50), oromandibular dystonia (n = 50), arm dystonia (n = 10), and axial dystonia (n = 10) and 240 spasticity patients (55.8 ± 15.3 years, 59% males, 41% females) with arm spasticity (n = 80), hemispasticity (n = 85), leg spasticity (n = 25), paraspasticity (n = 20), and tetraspasticity (n = 30) were consecutively collected until pre-set numbers of patients for each indication were reached. All patients had undergone a phase of BT therapy optimisation and had to be on a stable BT therapy regimen for at least 1.5 years. The total number of patients evaluated reflect about 30% of all dystonia patients and about 15% of all spasticity patients receiving BT therapy at this institution. Altogether, 1831 BT injections in 36 different target muscles were analysed for the treatment of dystonia and 1593 BT injections in 31 different target muscles were analysed for the treatment of spasticity.

All data storage and analysis were performed anonymised and according to the regulations applicable.
BT drugs analysed

This evaluation is based on an analysis of BT therapy using ONA and INCO. AbobotulinumtoxinA (ABO, Dysport®, Ipsen, Billancourt, France) was not included in this evaluation as its potency labelling is substantially different from the potency labelling of ONA and INCO. With uncertain conversion factors ranging from 1:2 to 1:5 between the potency labelling of ONA/INCO and ABO, we found it unsafe to include ABO. RimabotulinumtoxinB, a BT-type B drug, was also not included as its therapeutic profile is principally different from BT-type A drugs.

Treatment algorithms used by the reference centre

BT therapy at the reference centre is based on algorithms developed during the last 34 years by one of the authors (DD) and his team. The reference centre is able to perform BT therapy with a minimum of economic and legal restrictions. It is thus able to exploit BT therapy’s maximum benefit. For all patients treated, BT therapy is free of costs. Regulatory recommendations on target muscle selection and dosing, total doses, inter-injection intervals and contraindications are modified wherever necessary. Permission to perform quantitative and qualitative off-label use was generally granted. Total doses of up to INCO 1500 MU according to the concept of the ‘BT high dose therapy’ and inter-injection intervals down to 6 weeks according to the concept of the ‘BT short interval therapy’ may be applied where necessary. They will be discussed in the section ‘General treatment algorithms’. The standard dilution is 2.5 ml 0.9% NaCl/H₂O per ONA/INCO 100 MU. The standard volume per injection site is 0.5 ml (20 MU), for facial injections 0.2 ml (4 MU). The number of injection sites is determined by the BT doses applied to each target muscle.

General treatment algorithms

Principle of BT therapy

The basic principle of BT therapy for motor indications is to select the appropriate target muscles and to apply appropriate BT doses to them, or in short: ‘Hit the right muscle with the right dose’. These two aspects are documented in the injection scheme. The development of the injection scheme is based on knowledge and experience, and will be highly individualised for each patient treated. It may require several subsequent injection series to be optimised.

Target muscle selection (‘the right muscle’)

Target muscles are selected by documentation of the patient’s pathological positioning and movements. Based on the understanding of physiological muscle functioning, pathologically active muscles are identified. Muscle pain may contribute to additional information. Compensatory muscle activity and protective postures have to be identified and need to be distinguished from primary pathological muscle activity.

Target muscle dosing (‘the right dose’)

Once a target muscle is identified, the degree of BT-induced paresis, i.e., the BT dose applied, has to be decided. Only necessary BT doses should be applied. They should be as low as possible to reduce functional impairment, BT spread into adjacent muscles, excessive total doses and unnecessary costs. However, they should be high enough to produce robust and lasting therapeutic effects. Dosing depends on the target muscle’s mass, its therapeutic window and the paresis risk in adjacent muscles. Therapeutic windows (Dressler 2000) are shown in Table 1. The dosing tables provided here describe typical doses with their variability and limits. Individual BT dosing within these limits will be higher when the pathological muscle activity is high and when supportive agonistic muscles are available. BT doses will be lower when the pathological muscle activity is functionally useful, as in spasticity’s paresis or in dystonic tremor (see Table 2). For dystonia, the degree of dystonic involvement may be calculated with the dystonia ratio (dystonic muscle activity in relation to the maximal muscle activity as measured by the surface EMG amplitude) (Dressler 2000). General dose modifiers (see Table 2) (Dressler et al. 2018) are also applicable.

Total BT doses

Registration documents usually recommend maximal total BT doses in the region of 300–400 MU. Recent studies introducing the BT high dose therapy, however, demonstrate the

| Therapeutic window | Target muscle |
|--------------------|---------------|
| Narrow             | Finger extensors |
|                    | Muscles of the angle of the mouth |
|                    | Finger flexors |
| Medium             | Neck muscles |
| Wide               | M. orbicularis oculi |
toxicological and immunological safety of maximal total INCO doses of up to 1250 MU, thus establishing the ‘BT high dose therapy’ (Dressler 2014a; Wissel et al. 2017). Note that these doses originate from an increase in the number of target muscles rather than from excessive BT dosing in individual target muscles. Note also that maximal total doses are influenced by the dilution used and the number of target muscles selected.

Interinjection intervals

Reduced therapeutic effects at the end of the injection cycle may be compensated by increased BT doses. However, this effect is limited. Alternatively, interinjection intervals may be reduced. Originally, interinjection intervals were recommended to be not less than 12 weeks. Recent studies indicate that INCO may be applied without toxicological or immunological complications at intervals of less than 12 weeks (Dressler et al. 2014a), thus establishing the ‘BT short interval therapy’. Interinjection intervals may be as short as 6 weeks (Dressler and Saberi 2017).

BT drugs

BT drugs differ in many aspects. As biologicals, their manufacturing process influences them beyond their physical and chemical properties. With respect to therapeutic and adverse effects, BT drugs based on different BT types show considerable differences, whereas BT drugs based on the same BT type are very similar. The effects of different excipients including the use of human serum albumin, gelatine and polysorbate are controversially discussed. The lack of complexing proteins and the particular manufacturing process used in INCO has reduced antigenicity.

Drug potency labelling

Despite governmental regulations on standardised potency measurements, the potency labelling of BT drugs is not directly comparable. The potency labelling of ONA and INCO may be compared with a conversion factor of 1:1 (Dressler et al. 2012, 2014b, 2018). Conversion factors between ONA/INCO and other BT drugs are still controversial.

BT application

All BT-type A drugs need to be reconstituted with 0.9% NaCl/H2O. This generates and determines a dilution effect. Unless for special indications, e.g., treatment of hyperhidrosis, dilutions should not vary to increase patient safety. A dilution of 100 MU of ONA/INCO in 2.5 ml 0.9% NaCl/H2O produces volumes that are easily injectable and adequate in relation to the target muscle volume. An injection volume of 0.5 ml per injection site seems to be best suited.

Drug stability

Unreconstituted BT drugs have very long shelf lives. Most BT drugs require temperature restrictions. Only INCO may be stored and transported at room temperature. Reconstituted BT drugs should be used within 24 h. Recently published INCO data, however, indicate a stability of at least 1 year (Dressler and Bigalke 2017). Obviously, this has considerable economic implications.

Guidance techniques

Usually, the BT application is performed using basic anatomical techniques including palpation of the target muscle’s belly, its tendons and insertions and references to landmarks. Muscle pain and its localisation provide additional orientation. Target muscle palpation should only be performed when the target muscle is activated. For identification of deeper laying target muscles, application of some gentle pressure will become necessary. Special guidance techniques may be useful to target forearm muscles and to separate individual muscle fascicles when they are involved individually as it is typically the case in writer’s cramp. Guidance techniques may be EMG with and without electric stimulation (O’Brien 1997; Ajax et al. 1998) and ultrasound (Walter and
Dressler 2018). Tomographic imaging techniques are not useful especially when they involve radiation.

**Dosing tables for BT therapy of dystonia**

When the reader wants to treat a specific BT indication, he or she will find a brief review of its clinical presentation together with a general description of the principles of its BT therapy. For each target muscle, the reader will then find typical BT doses, dose variabilities and dose limits. The usage indicates the likelihood of the target muscle’s clinical involvement.

**Cervical dystonia (Table 3)**

Cervical dystonia is the most common form of dystonia. In our group of 200 consecutive cervical dystonia cases, the patient age was 58.4 ± 13.5 years and the patient sex ratio 38% males and 72% females. 23% of patients with predominant cervical dystonia had additional facial dystonia, 17% oromandibular dystonia, 7% axial dystonia, 6% arm dystonia, and 1% leg dystonia. The total BT dose in cervical muscles was 262.6 ± 141.6 MU (minimum 40 MU, maximum 860 MU). The number of cervical target muscles was 5.7 ± 1.8 (minimum 1, maximum 13). Most frequently used target muscles were M. trapezius/Pars descendens (78%), M. splenius capitis (75%), M. sternocleidomastoideus (52%), M. levator scapulae (31%), Mm. scaleni (29%), M. trapezius/Pars horizontalis (20%) and the deep neck muscles (3%). Occasionally, the suprahyoid muscles and the platysma were also target muscles.

The highly visible sternocleidomastoid muscle is not the most frequently involved target muscle. Bilateral BT injections into the M. sternocleidomastoid are possible necessarily producing dysphagia. Throughout the literature, there is confusion about the anatomical attribution of the nuchal muscles. For historical reasons, we use M. trapezius/Pars descendens to describe the nuchal paravertebral muscles including the M. splenius cervicis and M. semispinalis capitis. The actual M. trapezius/Pars descendens is a very thin muscle rotating the head into the opposite direction—similar to the M. sternocleidomastoideus. Its force and functional relevance are negligible. Deep neck muscles describe a muscle group including M. rectus capitis posterior minor, M. rectus capitis posterior major, M. obliquus superior, and M. capitis obliquus inferior. They are strong head rotators and head extensors. Similar functionality makes selective BT injections requiring EMG or ultrasound identification unnecessary.

| Table 3 Dosing table for cervical dystonia |
|------------------------------------------|
| (A) Patient age (M ± SD) (years) | Patient sex ratio (%) | Additional dystonia manifestations (%) | Number of target muscles (M ± SD) (min–max) (n) | Total botulinum toxin dose (M ± SD) (min–max) (MU) |
| 58.5 ± 13.5 | Males: 38 | Facial: 23 | 5.7 ± 1.8 | 262.6 ± 141.6 |
| | Females: 62 | Oromandibular: 17 | 1–13 | 40–860 |

| (B) Target muscle | Botulinum toxin dose (M ± SD) (MU) | Dose variability (standard deviation) (MU) | Dose limits (min–max) (MU) | Target muscle usage (% per indication) |
|------------------|----------------------------------|------------------------------------------|---------------------------|---------------------------------------|
| M. trapezius/Pars descendens | 44.7 | 27.5 | 10–200 | 78 |
| M. splenius capitis | 55.2 | 33.2 | 10–300 | 75 |
| M. sternocleidomastoideus | 46.4 | 21.1 | 10–120 | 52 |
| M. levator scapulae | 34.2 | 15.3 | 10–80 | 31 |
| Mm. scaleni | 36.5 | 14.9 | 20–80 | 29 |
| M. trapezius/Pars horizontalis | 46.0 | 27.4 | 20–180 | 20 |
| Deep neck muscles | 32.2 | 15.4 | 20–60 | 3 |
| Additional muscles | Suprahyoid muscles platysma |

Analysis of 200 consecutive patients. (A) Patient characteristics, additional dystonia manifestations, and general botulinum toxin therapy characteristics. (B) Target muscles, botulinum toxin doses and target muscle usage. $M ± SD$ mean ± standard deviation.
Facial dystonia (Table 4)

Facial dystonia is the second most common form of dystonia. In our group of 100 consecutive facial dystonia patients, their age was $65.2 \pm 13.3$ years and the sex ratio was 31% males and 69% females. 45% of these patients had additional cervical dystonia and 25% oromandibular dystonia. The total facial BT dose was $78.8 \pm 31.6$ MU (minimum 4 MU, maximum 220 MU). The number of target muscles was $3.7 \pm 1.8$ (minimum 1, maximum 10). Most frequently used target muscles were M. orbicularis oculi/Pars orbitalis (91%), M. procerus (32%), M. orbicularis oculi/Pars palpebral (26%), M. mentalis (12%), M. frontalis (9%), M. risorius (9%), Platysma (8%), M. nasolabialis (4%), M. depressor anguli oris (2%) and M. nasalis (2%). Occasionally, the M. orbicularis oris may be target muscle.

BT injections into perioral muscles are prone to produce paretic adverse effects. The M. frontalis should be used carefully as it is an auxiliary eyelid opening muscle. The M. orbicularis oculi/Pars palpebral is used when there is a component of eyelid opening apraxia.

| (A) Patient age ($M \pm SD$) (years) | Patient sex ratio (%) | Additional dystonia manifestations (%) | Number of target muscles ($M \pm SD$) (min–max) ($n$) | Total botulinum toxin dose ($M \pm SD$) (min–max) (MU) |
|---|---|---|---|---|
| $65.2 \pm 13.3$ | Males: 31<br>Females: 69 | Cervical: 45<br>Oromandibular: 25 | $3.7 \pm 1.8$<br>1–10 | $78.8 \pm 31.6$<br>4–220 |

(B) Target muscle Botulinum toxin dose

| Typical dose (mean) (MU) | Dose variability (standard deviation) (MU) | Dose limits (min–max) (MU) | Target muscle usage (% per indication) |
|---|---|---|---|
| M. orbicularis oculi/Pars orbitalis | 32.9 | 9.9 | 8–80 | 91 |
| M. procerus | 6.0 | 3.5 | 2–20 | 32 |
| M. orbicularis oculi/Pars palpebral | 12.9 | 4.8 | 4–24 | 26 |
| M. mentalis | 6.2 | 2.6 | 2–10 | 12 |
| M. frontalis | 6.2 | 2.3 | 4–10 | 9 |
| M. risorius | 5.3 | 2.9 | 2–12 | 9 |
| Platysma | 33.0 | 21.0 | 4–80 | 8 |
| M. nasolabialis | 7.0 | 3.5 | 4–12 | 4 |
| M. depressor anguli oris | 4.8 | 3.3 | 4–8 | 2 |
| M. nasalis | 5.0 | 1.2 | 4–6 | 2 |

Analysis of 100 consecutive patients. (A) Patient characteristics, additional dystonia manifestations, and general botulinum toxin therapy characteristics. (B) Target muscles, botulinum toxin doses and target muscle usage.

$M \pm SD$ mean ± standard deviation

Writer’s cramp (Table 5)

Writer’s cramp is another common manifestation of dystonia. Unlike most other dystonias, it is task-specific, i.e., it only occurs when the specific motor program of writing is executed. In our group of 50 consecutive writer’s cramp patients their age was $61.6 \pm 20.8$ years and the sex ratio was 60% males and 40% females. 2% of these patients had additional cervical dystonia. The total arm BT dose was $70.3 \pm 55.3$ MU (minimum 8 MU, maximum 230 MU). The number of target muscles in the arm was $2.5 \pm 1.5$ (minimum 1, maximum 6). Most frequently used target muscles were M. flexor digitorum superficialis (48%), M. flexor carpi ulnaris (42%), M. extensor carpi ulnaris (34%), M. extensor carpi radialis (30%), M. flexor digitorum profundus (30%), M. flexor pollicis longus (28%), M. flexor carpi radialis (12%), M. pronator teres (8%), M. extensor indicis (8%), and M. extensor pollicis (6%). Occasionally, the M. extensor digitorum, M. flexor indicis, M. supinator, M. deltoideus, M. trapezius/Pars horizontalis and the M. triceps brachii may be target muscles.

BT application in writer’s cramps frequently requires guidance either by ultrasound or by electromyography with or without electrostimulation. BT dosing in writer’s cramp is highly individual including a large number of potential
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Table 5  Dosing table for writer’s cramp

| (A) Patient age (M ± SD) (years) | Patient sex ratio (%) | Additional dystonia manifestations (%) | Number of target muscles (M ± SD) (min–max) | Total botulinum toxin dose (M ± SD) (min–max) (MU) |
|----------------------------------|-----------------------|----------------------------------------|---------------------------------------------|-----------------------------------------------|
| 61.6 ± 20.8                      | Males: 60             | Cervical: 2                             | 2.5 ± 1.5                                   | 70.3 ± 55.3                                  |
|                                  | Females: 40           |                                        | 1–6                                         | 8–230                                        |

(B) Target muscle  

| Botulinum toxin dose | Target muscle usage (% per indication) |
|----------------------|----------------------------------------|
| Typical dose (mean) (MU) | Dose variability (standard deviation) (MU) | Dose limits (min–max) (MU) |
|-----------------------|----------------------------------------|
| M. flexor digitorum superficialis | 21.8 | 13.9 | 8–70 | 48 |
| M. flexor carpi ulnaris | 32.7 | 18.2 | 10–80 | 42 |
| M. extensor carpi ulnaris | 35.4 | 13.1 | 10–60 | 34 |
| M. extensor carpi radialis longus | 28.0 | 13.2 | 10–50 | 30 |
| M. flexor digitorum profundus | 19.9 | 10.3 | 8–40 | 30 |
| M. flexor pollicis longus | 22.7 | 13.5 | 6–60 | 28 |
| M. flexor carpi radialis longus | 13.0 | 5.5 | 8–20 | 12 |
| M. pronator teres | 47.0 | 39.3 | 8–100 | 8 |
| M. extensor indicis | 34.3 | 43.8 | 10–100 | 8 |
| M. extensor pollicis | 9.3 | 1.2 | 8–10 | 6 |
| Additional muscles | M. extensor digitorum superficialis |
|                     | M. flexor indicis |
|                     | M. supinator |
|                     | M. deltoideus |
|                     | M. trapezius/Pars descendens |
|                     | M. triceps brachii |

Analysis of 50 consecutive patients. (A) Patient characteristics, additional dystonia manifestations, and general botulinum toxin therapy characteristics. (B) Target muscles, botulinum toxin doses and target muscle usage

M ± SD mean ± standard deviation

target muscles in a wide range of BT doses. BT should be dosed carefully to avoid paretic adverse effect easily occurring because of the narrow therapeutic window of the target muscles.

Oromandibular dystonia (Table 6)

In our group of 40 consecutive oromandibular dystonia patients, their age was 57.9 ± 14.6 years and the sex ratio was 40% males and 60% females. 38% of these patients had additional cervical dystonia, 30% facial dystonia, 10% arm dystonia and 3% axial dystonia. The total oromandibular BT dose was 127.5 ± 69.9 MU (minimum 40 MU and maximum 280 MU). The number of target muscles was 3.7 ± 1.7 (minimum 2, maximum 8). Most frequently used target muscles were M. masseter (97%), Mm. pterygoidei (44%), M. temporalis (24%), M. submandibularis (13%) and Platysma (8%). Occasionally, the M. risorius and the M. mentalis may be target muscles.

The Mm. pterygoidei can easily be injected through the incisura mandibulae. Electromyography requiring thick combination needles seems unnecessary as dystonic involvement is usually affecting both, the lateral and the medial pterygoid muscles.
Arm dystonia (Table 7)

Non-task-specific arm dystonia is a less common manifestation of dystonia. In our group of 10 consecutive arm dystonia patients, their age was 37.2 ± 19.7 years and thus considerably lower than the age of other focal dystonias. The sex ratio was 40% males and 60% females. Its isolated occurrence is very rare. 80% of these patients had additional cervical dystonia and 10% oromandibular dystonia. Total arm BT dose was 156.0 ± 143.3 MU (minimum 40 MU, maximum 540 MU). The number of target muscles was 3.8 ± 2.3 (minimum 1, maximum 10). Most frequently used target muscles were M. deltoideus...
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Axial dystonia (Table 8)

Axial dystonia is another less frequent manifestation of dystonia. In our group of 10 consecutive axial dystonia patients, their age was 61.7 ± 11.6 years and the sex ratio was 30% males and 70% females. Axial dystonia usually occurs together with other dystonia manifestations. In 50% of our patients, it is cervical dystonia, in 30% facial dystonia. The total axial BT dose was 218.0 ± 97.3 MU (minimum 80 MU, maximum 800 MU). The number of segmental levels injected was 3.3 ± 1.8. The dose per segmental level on one side was 40–60 MU.

Leg dystonia

Isolated leg dystonia is very rare. It almost only occurs in widespread dystonia. BT doses are similar to those used in spasticity.

Wide-spread dystonia

Wide-spread dystonia includes all patients with dystonia exceeding two adjacent focal dystonias, i.e., segmental dystonia with more than two localisations, with hemidystonia and with generalised dystonia. BT therapy consists of treatment of the focal dystonic elements. New treatment algorithms allowing high-dose application offer improved treatment options.

Dosing tables for BT therapy of spasticity

General comments

Treatment algorithms for spasticity are similar to those of dystonia. BT dosing, however, differs: the principle difference between spasticity and dystonia is the obligatory presence of paresis in spasticity. This means that functional improvement in spasticity is less pronounced than in dystonia, thus changing the treatment goals in spasticity more towards pain reduction, prevention of contractures and facilitation of physiotherapeutic training programs. BT doses for spasticity tend to be higher than those for dystonia, as paretic adverse effects are a lesser concern and robust antispastic effects are more often required. In principle, BT therapy of dystonia rarely involves leg muscles. Except for writer’s cramp, arm muscles are also rarely involved. If they are involved in dystonia, their involvement is usually proximal, whereas it is usually distal in writer’s cramp. In spasticity, the typical pattern of arm muscle involvement includes shoulder abduction or adduction, elbow flexion, pronation, wrist flexion, finger flexion and thumb flexion. The typical pattern in leg muscles includes hip adduction, knee extension, and equinovarus position of the foot. Facial, cervical, and axial muscles are only rarely involved. Mandibular muscles may be involved and their involvement should be examined on a routine basis.

Arm spasticity (Table 9)

Arm spasticity is the largest group of patients treated for spasticity. In our group of 80 consecutive arm spasticity cases, the patient age was 59.1 ± 14.5 years and the patient sex ratio 65% males and 35% females. 8% of patients with arm spasticity also received BT therapy of the M. trapezius/Pars descendens, 4% of the M. levator scapulae, and 3% of the M. splenius capitis. The total BT dose in arm muscles was 386.8 ± 167.2 MU (minimum 60 MU, maximum 900 MU). The number of arm target muscles treated was 6.5 ± 2.7 (minimum 1, maximum 12). Most frequently used target muscles were arm flexors including M. flexor digitorum superficialis (88%), M. biceps brachii (79%), M. flexor digitorum profundus (76%), and M. flexor carpi ulnaris (74%). The total BT dose in arm spasticity was more than double the total BT dose in arm dystonia.

| Table 8  | Dosing table for axial dystonia |
|----------|----------------------------------|
| Patient age (mean ± SD) (years) | Patient sex ratio (%) | Additional dystonia manifestations (%) | Number of segmental levels (mean ± SD) (n) | Botulinum toxin dose per level and side (min–max) (MU) | Total botulinum toxin dose (mean ± SD) (min–max) (MU) |
| 61.7 ± 11.6 | Males: 30 | Cervical: 50 | 3.3 ± 1.8 | 40–60 | 218.0 ± 97.3 |
| Females: 70 | | Oromandibular: 10 | | | 80–400 |

Analysis of 10 consecutive patients. Patient characteristics, additional dystonia manifestations, and general botulinum toxin therapy characteristics and botulinum toxin doses

M ± SD mean ± standard deviation

(70%), M. flexor carpi ulnaris (70%), M. pectoralis (50%), M. brachioradialis (50%), M. flexor carpi radialis (40%), M. biceps brachii (40%), M. pronator (30%) and M. latissimus dorsi/M. teres maior (30%).
and more than 5 times the total BT dose in writer’s cramp. Finger extensors are particularly sensitive to the BT application. Treatment of shoulder muscles may reduce pain considerably, especially on a long-term perspective.

Hemispasticity (Table 10)

Hemispasticity is the second largest group of patients treated for spasticity. In our group of 85 consecutive hemispasticity cases, the patient age was 58.3 ± 14.8 years and the patient sex ratio 60% males and 40% females. The total BT dose in arm and leg muscles was 495.2 ± 189.4 MU (minimum 80 MU, maximum 900 MU). The number of arm and leg target muscles treated was 7.8 ± 3.3 (minimum 2, maximum 16). Most frequently used target muscles were M. biceps brachii (80%), M. pectoralis (77%), M. flexor carpi ulnaris (53%) and M. flexor digitorum profundus (53%).

Leg spasticity (Table 11)

Leg spasticity is the third largest group of patients treated for spasticity. In our group of 25 consecutive leg spasticity cases, the patient age was 53.7 ± 14.2 years and the patient sex ratio 32% males and 68% females. The total BT dose in leg muscles was 270.4 ± 95.7 MU (minimum 40 MU and maximum 400 MU). The number of leg target muscles treated was 4.3 ± 1.4 (minimum 1, maximum 7). Most
frequently used target muscles were M. gastrocnemius/Caput mediale (68%), M. tibialis posterior (68%), M. soleus (48%) and M. gastrocnemius/Caput laterale (44%). Involvement of M. quadriceps femoris should be treated carefully as its muscle tone secures stance. Treatment of the equinovarus posture provides improvement of stance and bears little risk of adverse effects.

## Table 10  Dosing tables for hemispasticity

| (A) Patient age (M ± SD) (years) | Patient sex ratio (%) | Additional target muscles (%) | Number of target muscles (M ± SD) (n) | Total botulinum toxin dose (M ± SD) (MU) |
|----------------------------------|-----------------------|------------------------------|--------------------------------------|----------------------------------------|
| 58.6 ± 14.7                     | Males: 60             | M. masseter: 2               | Average: 7.8 ± 3.3                   | Average: 495.2 ± 189.4                 |
|                                  | Females: 40           | M. trapezius/Pars horizontalis: 5 | Minimum: 2                          | Minimum: 80                            |
|                                  |                       |                              | Maximum: 16                          | Maximum: 900                           |

| (B) Target muscle | Botulinum toxin dose | Target muscle usage |
|-------------------|----------------------|---------------------|
|                   | Typical dose (mean) (MU) | Dose variability (standard deviation) (MU) | Dose limits (min–max) (MU) | Target muscle usage (% per subtype) |
| M. pectoralis      | 59.4                 | 20.6                | 40–100                           | 42                                      |
| Mn. latissimus dorsi/teres maior | 60.0 | 23.1                | 20–100                           | 33                                      |
| M. deltoideus      | 56.9                 | 25.6                | 20–100                           | 15                                      |
| M. biceps brachii  | 62.6                 | 21.1                | 20–100                           | 68                                      |
| M. brachioradialis | 44.8                | 15.4                | 20–80                            | 25                                      |
| M. triceps brachii | 54.3                 | 14.5                | 20–80                            | 16                                      |
| M. brachialis      | 50.0                 | 15.4                | 40–80                            | 7                                       |
| M. flexor carpi ulnaris | 60.8  | 21.7                | 20–100                           | 59                                      |
| M. flexor carpi radialis | 52.7 | 24.3                | 20–100                           | 26                                      |
| M. extensor carpi ulnaris | 20.0 | 0                   | 20                               | 2                                       |
| M. extensor carpi radialis | 40.0 | 28.3                | 20–60                            | 2                                       |
| M. flexor digitorum superficialis | 78.4 | 24.8             | 40–140                           | 75                                      |
| M. flexor digitorum profundus | 78.8 | 25.8             | 40–150                           | 67                                      |
| M. flexor pollicis longus | 43.2 | 10.0              | 20–60                           | 22                                      |
| M. pronator teres   | 35.6                 | 11.0                | 40–60                            | 18                                      |
| Thumb clench       | 40.0                 | 7.8                 | 20–60                            | 16                                      |
| Mn. lumbricales    | 50.0                 | 19.4                | 60–80                            | 12                                      |
| Mn. adductors      | 80.0                 | 26.2                | 40–120                           | 9                                       |
| M. quadriceps femoris | 80.0              | 40.6                | 40–200                           | 20                                      |
| Hamstrings         | 112.9                | 56.9                | 40–260                           | 18                                      |
| M. gastrocnemius/Caput mediale | 72.4 | 51.5          | 20–220                           | 54                                      |
| M. gastrocnemius/Caput laterale | 43.5 | 14.3         | 20–80                            | 27                                      |
| M. soleus          | 49.1                 | 21.0                | 20–100                           | 25                                      |
| M. tibialis posterior | 70.0 | 25.7            | 20–140                           | 52                                      |
| M. tibialis anterior | 70.0            | 38.3               | 40                               | 10                                      |
| M. flexor digitorum brevis | 76.8 | 33.4            | 30–200                           | 26                                      |
| M. flexor digitorum longus | 64.7 | 11.5           | 60–80                            | 4                                       |
| M. extensor hallucis longus | 52.7 | 20.5           | 40–100                           | 13                                      |
| M. flexor hallucis longus | 64.4 | 16.7           | 40–100                           | 11                                      |

Analysis of 85 consecutive patients. (A) Patient characteristics, additional target muscles, and general botulinum toxin therapy characteristics. (B) Target muscles, botulinum toxin doses and target muscle usage

$M \pm SD$ mean ± standard deviation
Table 11 Dosing table for leg spasticity

(A) Patient age ($M \pm SD$) (years) | Patient sex ratio (%) | Additional target muscles (%) | Number of target muscles ($M \pm SD$) ($n$) | Total botulinum toxin dose ($M \pm SD$) (MU)
---|---|---|---|---
53.7 ± 14.2 | Males: 32 Females: 68 | None | Average: 4.3 ± 1.4 Minimum: 1 Maximum: 7 | Average: 270.4 ± 95.7 Minimum: 40 Maximum: 400

(B) Target muscle | Botulinum toxin dose | Dose variability (standard deviation) (MU) | Dose limits (min–max) (MU) | Target muscle usage (% per subtype)
---|---|---|---|---
M. iliopsoas | 50.0 | 14.1 | 40–60 | 8
M. adductors | 83.3 | 36.7 | 20–120 | 24
M. quadriceps femoris | 63.3 | 29.4 | 40–120 | 24
Hamstrings | 65.0 | 25.2 | 40–100 | 16
M. gastrocnemius/Caput medialis | 56.5 | 20.3 | 40–120 | 68
M. gastrocnemius/Caput laterale | 52.7 | 10.1 | 40–60 | 44
M. soleus | 53.3 | 19.7 | 40–100 | 48
M. tibialis posterior | 71.8 | 25.6 | 40–120 | 68
M. tibialis anterior | 50.0 | 14.1 | 40–60 | 8
M. flexor digitorum brevis | 88.0 | 47.3 | 40–200 | 40
M. flexor digitorum longus | 60.0 | 16.3 | 40–80 | 16
M. extensor hallucis longus | 52.5 | 21.2 | 20–80 | 32
M. flexor hallucis longus | 68.6 | 25.4 | 40–100 | 28

Analysis of 25 consecutive patients. (A) Patient characteristics, additional target muscles, and general botulinum toxin therapy characteristics. (B) Target muscles, botulinum toxin doses and target muscle usage

$M \pm SD$ mean ± standard deviation

Table 12 Dosing tables for paraspasticity

(A) Patient age ($M \pm SD$) (years) | Patient sex ratio (%) | Additional target muscles (%) | Number of target muscles ($M \pm SD$) ($n$) | Total botulinum toxin dose ($M \pm SD$) (MU)
---|---|---|---|---
48.3 ± 12.0 | Males: 50 Females: 50 | | Average: 6.8 ± 4.2 Minimum: 2 Maximum: 15 | Average: 584.5 ± 245.8 Minimum: 200 Maximum: 1100

(B) Target muscle | Botulinum toxin dose | Dose variability (standard deviation) (MU) | Dose limits (min–max) (MU) | Target muscle usage (% per subtype)
---|---|---|---|---
M. iliopsoas | 50.0 | 11.5 | 40–60 | 5
M. adductors | 115.8 | 66.7 | 40–200 | 33
M. quadriceps femoris | 60.0 | 28.3 | 40–120 | 15
Hamstrings | 156.3 | 100.4 | 40–400 | 25
M. gastrocnemius/Caput medialis | 57.3 | 38.7 | 20–200 | 28
M. gastrocnemius/Caput laterale | 32.9 | 12.7 | 20–60 | 18
M. soleus | 70.0 | 81.6 | 20–400 | 28
M. tibialis posterior | 66.7 | 24.4 | 40–120 | 18
M. tibialis anterior | 70.0 | 42.4 | 40–120 | 5
M. flexor digitorum brevis | 66.7 | 52.9 | 40–160 | 13
M. flexor hallucis longus | 50.0 | 11.5 | 40–60 | 5

Analysis of 20 consecutive patients. (A) Patient characteristics, additional target muscles, and general botulinum toxin therapy characteristics. (B) Target muscles, botulinum toxin doses and target muscle usage

$M \pm SD$ mean ± standard deviation
Paraspasticity (Table 12)

Paraspasticity is the fourth largest group of patient treated for spasticity. In our group of 20 consecutive paraspasticity cases, the patient age was 48.3 ± 12.0 years and the patient sex ratio 50% males and 50% females. The total BT dose in leg muscles was 584.5 ± 245.8 MU (minimum 200 MU, maximum 1100 MU). The number of leg target muscles treated was 6.8 ± 4.2 (minimum 2, maximum 15). Most frequently used target muscles were Mm. adductores (33%), M. gastrocnemius/Caput mediale (28%), M.

Table 13 Dosing table for tetraspasticity

| (A) Patient age (M±SD) (years) | Patient sex ratio (%) | Additional target muscles (%) | Number of target muscles (M±SD) (n) | Total botulinum toxin dose (M±SD) (MU) |
|---------------------------------|-----------------------|-------------------------------|------------------------------------|--------------------------------------|
| 43.2±16.5                       | Males: 57 Females: 43 | M. masseter: 10               | Average: 13.1 ± 5.5 Minimum: 2 Maximum: 24 | Average: 806.8±342.3 Minimum: 80 Maximum: 1340 |

| (B) Target muscle | Botulinum toxin dose | Dose variability (standard deviation) (MU) | Dose limits (min–max) (MU) | Target muscle usage (% per subtype) |
|-------------------|----------------------|--------------------------------------------|---------------------------|-------------------------------------|
| Typical dose (mean) (MU) | 40–120 | 77 |
| M. pectoralis | 60.5 | 23.0 |
| Mm. latissimus dorsi/teres mai | 60.0 | 20.5 |
| M. biceps brachii | 47.5 | 22.9 |
| M. brachioradialis | 40.0 | 16.3 |
| M. triceps brachii | 32.5 | 10.4 |
| M. biceps brachii | 30.0 | 4.5 |
| M. flexor carpi ulnaris | 61.7 | 24.8 |
| M. extensor carpi ulnaris | 40.0 | 0 |
| M. flexor digitorum superficialis | 75.2 | 29.0 |
| M. flexor digitorum profundus | 82.5 | 46.5 |
| M. flexor pollicis longus | 30.0 | 11.5 |
| M. pronator teres | 40.0 | 0 |
| Thumb clench | 40.0 | 0 |
| Mm. lumbricales | 75.0 | 30.0 |
| M. ilioptoshas | 80.0 | 18.9 |
| Mm. adductors | 95.6 | 46.8 |
| M. quadriceps femoris | 78.3 | 32.7 |
| Hamstrings | 80.0 | 44.0 |
| M. gastrocnemius/Caput mediale | 44.0 | 16.7 |
| M. gastrocnemius/Caput laterale | 42.2 | 18.6 |
| M. soleus | 43.1 | 7.5 |
| M. tibialis posterior | 66.0 | 18.9 |
| M. tibialis anterior | 40.0 | 0 |
| M. flexor digitorum brevis | 53.3 | 10.0 |
| M. flexor digitorum longus | 50.0 | 11.5 |
| M. extensor hallucis longus | 46.7 | 10.3 |

Analysis of 30 consecutive patients. (A) Patient characteristics, additional target muscles, and general botulinum toxin therapy characteristics. (B) Target muscles, botulinum toxin doses and target muscle usage

M ± SD mean ± standard deviation

Tetraspasticity (Table 13)

Tetraspasticity is the smallest group of patient treated for spasticity. In our group of 30 consecutive tetraspasticity cases, the patient age was 43.2 ± 16.5 years and the patient sex ratio 50% males and 50% females. The total BT dose in leg muscles was 806.8 ± 342.3 MU (minimum 80 MU, maximum 1340 MU). The number of leg target muscles treated was 3.8 ± 0.7 (minimum 2, maximum 6). Most frequently used target muscles were Mm. adductores (33%), M. gastrocnemius/Caput mediale (28%), M.
sex ratio 57% males and 43% females. The total BT dose in arm and leg muscles was 896.8 ± 342.3 MU (minimum 80 MU and maximum 1340 MU). The number of arm and leg target muscles treated was 13.1 ± 5.5 (minimum 2, maximum 24). Most frequently used target muscles were M. biceps brachii (80%), M. pectoralis (77%), M. flexor carpi ulnaris (53%), M. flexor digitorum profundus (53%) and M. flexor digitorum superficialis (47). Additional continuous intrathedral baclofen therapy may become an option, especially to boost efficacy in the legs (Dressler et al. 2015).

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Authors and Affiliations

Dirk Dressler1 · Maria Concetta Altavista2 · Eckart Altenmueller3 · Roongroj Bhidayasiri4 · Saeed Bohlega5 · Pedro Chana6 · Tae Mo Chung7 · Carlo Colosimo8 · Klemens Fheodoroff9 · Pedro J. Garcia-Ruiz10 · Beomseok Jeon11 · Lingjing Jin12 · Petr Kanovsky13 · Ivan Milanov14 · Federico Micheli15 · Olga Orlova16 · Sanjay Pandey17 · Zvezdan Pirtosek18 · Maja Relja19 · Raymond Rosales20 · José Alberto Sagástegui-Rodríguez21 · Gholam Ali Shahidi22 · Sofia Timerbaeva23 · Xinhua Wan24 · Uwe Walter25 · Fereshte Adib Saberi26

1 Movement Disorders Section, Department of Neurology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany
2 Department of Neurology, A.C.O. San Filippo Neri, Rome, Italy
3 Institute of Music Physiology and Musicians’ Medicine, Hanover University of Music, Drama and Media, Hannover, Germany
4 Chulalongkorn Centre for Excellence on Parkinson’s Disease and Related Disorders, King Chulalongkorn Memorial Hospital, Bangkok, Thailand
5 Department of Neurology, King Faisal Specialist Hospital, Riyadh, Kingdom of Saudi Arabia
6 Department of Neurology, University de Santiago de Chile, Santiago de Chile, Chile
7 University of Sao Paulo, Sao Paulo, Brazil
8 Department of Neurology, Santa Maria University Hospital, Terni, Italy
9 Gaital-Klinik, Hermagor, Austria
10 Department of Neurology, Fundacion Jimenez Diaz, Madrid, Spain
11 Department of Neurology, Seoul National University, Seoul, Republic of Korea
12 Department of Neurology, Tongji University School of Medicine, Shanghai, China
13 Department of Neurology, Palacký University, Olomouc, Czech Republic
14 Department of Neurology, Medical University of Sofia, Sofia, Bulgaria
15 Department of Neurology, Hospital de Clínicas José de San Martín, University of Buenos Aires, Buenos Aires, Argentina
16 Clinic ‘Cecil Plus’, Moscow, Russia
17 Department of Neurology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, New Delhi, India
18 Department of Neurology, Ljubljana University, Ljubljana, Slovenia
19 Department of Neurology, University of Zagreb, Zagreb, Croatia
20 Department of Neurology, University of Santo Tomas, Manila, Philippines
21 Department of Neurology, University of Monterrey, Monterrey, Nueva Leon, Mexico
22 Department of Neurology, Iran University of Medical Sciences, Tehran, Iran
23 Scientific Research Institute of Neurology, Moscow, Russia
24 Department of Neurology, Peking Union Medical College, Beijing, China
25 Department of Neurology, Rostock University, Rostock, Germany
26 IAB—Interdisciplinary Working Group for Movement Disorders, Hamburg, Germany