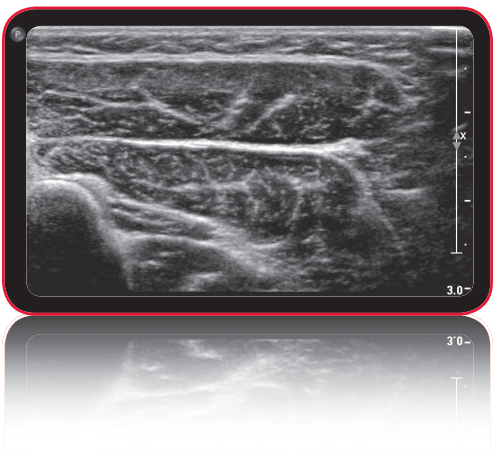
Sono's Anatomy

Focus on Spasticity
Targeting Botulinum Toxin
Children & Adults

Urban M. Fietzek | Steffen Berweck
Jörg Wissel | Florian Heinen



Questions & Answers
52 Targets for Injection
Instruments for
Therapy Evaluation
Comprehensive Literature

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It is each users own personal responsibility to cross-check accuracy of all relevant data.

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Preface

It was in 2002 when two of us, Steffen Berweck and Florian Heinen, first began to use sonographic imaging for improved accuracy of botulinum toxin injections (1,2). During recent years we saw a rapidly increasing acceptance of this technique. It was obvious that more and more users realized the importance of accurate toxin injection for achieving the best possible efficacy of this substance. Today, sonographically guided injection has become a standard procedure in pediatric practice and, generally, for injections into the forearm in upper limb spasticity.

In this book we have tried to summarize the state of the art in the treatment of spasticity with botulinum toxin. Building up on our earlier book on this subject (3,4), we expanded the visual material which we believe allows faster orientation and a clearer approach. Part A of this book provides a text-based introduction using a questions and answers style. Read this section before your first consultation with the patient.

Therapy with botulinum toxin has become increasingly complex and requires a great deal of expertise. For therapy to be successful, it needs a bit more than just injecting a few muscles. Therapists have to understand the intricacies of movement and should have experience in the field of spastic movement disorders and be familiar with the course such disorders can take . Part B gives a detailed description of the muscles that have been identified as useful targets for treatment with botulinum toxin. Read this section when deciding how to treat your patient.

Therapy will be only as good as the results achieved with it and these can greatly vary between individuals. To reliably judge the success of botulinum toxin treatment requires reliable outcome measures. Part C describes a choice of such treatment outcome measures that proved useful for children

as well as for adult patients with spastic motor disorders.

We hope that readers will find this book a source of helpful information for the effective and safe use of botulinum toxin in the treatment of spastic movement disorders.

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Jörg Wissel
Florian Heinen

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A – Basic information on spasticity and Botulinum Toxin

1 Spasticity
Basic questions – Treatment algorithms

HOW IS SPASTICITY DEFINED?

Background
Damage to the motor areas of the central nervous system (brain or spinal cord) may give rise to a specific type of movement disorders subsumed under the term pyramidal tract syndrome or upper motor neuron syndrome (UMNS). [1] In the context of this syndrome, a more easily triggered muscle stretch reflex and a velocity dependent increase of muscle tone upon passive stretching of affected motor segments are considered the most important clinical criteria for the presence of spasticity. [2]

Classic descriptions of UMNS differentiate between clinically negative and clinically positive symptoms. [1] Negative symptoms include paresis, impaired control and coordination of movement, and easy fatigability of the motor system. Positive symptoms are spasticity [2], more easily triggered cutaneous reflexes, mass reflexes, abnormal posture (spastic dystonia) and changes in the mechanical properties of muscles with a tendency to develop contractures. [1, 3-8]
Spasticity may lead to considerable restrictions in joint motility and as a consequence to impaired mobility. About 30 % of those affected suffer from chronic pain. Important areas of life including participation in work-related and social activities are affected. [1, 9, 10]

Authors' comments
The UMNS provides a useful theoretical concept but not a satisfactory definition that would take all clinically relevant details of spasticity from childhood to adult age into account. For clinicians there is a whole range of questions that have not been satisfactorily answered. In

the quest of finding a therapeutic approach most suitable for the individual patient, this theoretical concept can only contribute partial solutions.

Depending on the specific pattern of injuries involved, each patient shows a very individual combination of spastic posture and motor elements. This combination may change in the course of time as additional secondary and tertiary dysfunction of the musculoskeletal system appear. Therefore, every time before the patient undergoes a new treatment cycle it is necessary to update assessment and documentation of neurological symptoms.

In addition to the clinico-neurologic examination and a video documentation of the patient's initial state, the therapist should evaluated function, activity and participation based on appropriate, validated and reliable clinical scales and tests. (see part C of this book)

IS THERE ANY RECOMMENDED TREATMENT ALGORITHM FOR SPASTICITY?

Background

The modern approach to neurological rehabilitation is based on the integrative, bio-psycho-social model of the ICF (International Classification of Functioning, Disability and Health of the WHO). In this approach, singular measures are coordinated with the aim to optimize time course and intensity of treatment for each individual patient. This helps in achieving the best possible therapeutic outcome for UMNS with its greatly variable clinical manifestations. [9, 11-14]

Treatment of spasticity at the level of body functions primarily aims to lower spastic muscle tone in the affected motor segments on passive muscle stretching as well as on active movement. In addition, it is important to attain normal muscle length in order to improve active motor competence through biomechanical relief.

To treat spasticity in adults, local as well as systemic approaches are available [15-18]:

- physical therapy (e.g.

stretching, positioning, thermal stimulation)
- classic kinesitherapy (e.g. Bobath method)
- self-control techniques (e.g. biofeedback)
- neuromodulation therapy (e.g. forced-use / constraint-induced movement therapy)
- repetitive motor exercises (e.g. treadmill therapy)
- systemic pharmacotherapy (e.g. baclofen, tizanidine, dantrolene)
- neurosurgical intervention (e.g. neurotomy and baclofen pumps)
- neuro-orthopedic surgery (e.g. myotomy, tenotomy)
- focal denervation (BoNT, phenol, alcohol)
- robotic therapy methods (e.g. Lokomat®)

Authors' comments
The reasons for the successful focal treatment of spasticity with BoNT are high treatment efficacy, low incidence of unwanted side effects, the adaptive possibilities, and compatibility of BoNT with all the other treatment options listed above.

CAN THE ICF ASSIST IN SPECIFYING THE IMPACT OF SPASTICITY ON THE PATIENT'S LIFE?

Background
The International Classification of Functioning, Disability and Health (ICF) of the WHO presents an operationalized catalog that provides a framework for describing the effect of illnesses on the patient in an internationally standardized way. Based on this framework, the restrictions that a patient experiences due to illness are assigned to various body functions as well as to various areas of life (domains) and considered in relation to contextual factors. This allows to deduce individual therapy goals and treatment measures for the patient.

The ICF is organized around the following major categories

- Body Functions and Structure
- Activities and Participation
- Contextual Factors

To describe the impact of spasticity, the ICF catalog offers in the category Body Functions various

assessment parameters, for example joint motion (passive and active range of motion), muscular strength (muscle function assessed as recommended by the British Medical Research Council) and tonus (modified rating according to Ashworth), but also muscular endurance, involuntary muscle contraction (spasm) and control of voluntary movement.

The Activities and Participation category is addressing operationally defined areas of life, i.e. areas of activity and action. Every restriction within a domain can be described in terms of competence (that is performance under optimized / standardized conditions, "what the affected person is able to do") or in terms of performance (that is performance under the actual conditions the person is exposed to in real life, "what the affected person is actually doing").

Contextual Factors (environmental conditions) have a major influence on performance and should therefore always be included (description of functioning within optimal / actual context – e.g. the need for special aids such as splints or for structural adaptation of buildings).

The ICF provides adequate suggestions for describing restrictions both in body functions and structure and in areas of life domains due to spasticity. Within the ICF Research Branch of the WHO, various work groups are currently compiling condition-specific core-sets that can be used in the clinical operationalization of the effect of illnesses on the patient. [19]
Thus, when defining goals and assessing progress in spastic motor disorders of the lower extremities after stroke, the following parameters in the domain Mobility come into consideration: the ability of the affected person to, e.g., maintain a certain body position (sitting – standing), move around with the use of aids (wheelchair or walking frame), or walk (walking distance, distance-time parameter, aids required).

Authors' comments
The ICF classification sys-

tem provides very helpful guidance for taking all relevant and interdependent effects of an illness on the patient into account including contextual factors. Bear in mind that
- use of the ICF is very time-consuming, and
- the ICF is a classification system neither developed nor intended for evaluating outcome of treatment; this requires specific tests. (see part C)

WHAT IS THE TOXIN'S MODE OF ACTION?

Evidence
BoNT A is produced by Clostridium botulinum – a sporiferous, gram-positive, anaerobic bacterium that requires special conditions for growth (pH 4.5, protein-rich growth medium, 40oC). There are seven known, immunologically distinct serotypes of botulinum toxins. BoNT is a zinc-dependent endopetidase composed of a light (50 kD) and a heavy (100 kD) chain held together via a disulfide bond. BoNT does not pass through the skin. It is not cytotoxic but inhibits cholinergic neuromuscular and neuroglandular transmission. [20] The molecular mode of action at the cholinergic nerve endings involves three main steps: [21]:

Binding
After injection, the toxin accumulates on glycosidic receptors near the preterminal nerve endings. The C-terminal end of the toxin's heavy chain specifically binds to SV2, a vesicular membrane protein presented on the surface of the terminal axon during acetylcholine release. [22] Binding and uptake of BoNT require the presence of active vesicles and thus currently active neuromuscular transmission. [23, 24]

Internalization
BoNT enters the axon terminal by means of energy-dependent, receptor-mediated endocytosis and ends up in the endosomal compartment. Under the acidic conditions inside the endosome BoNT undergoes conformational changes leading to separation of heavy and light chain and transfer of the latter from the endosomal compartment into the cytosol.

Toxic action
The light chain irreversibly

cleaves the membrane-associated fusion complex (SNARE complex) responsible for exocytosis of acetylcholine. The fusion complex consists of three proteins: VAMP (vesicle associated membrane protein), SNAP-25 (synaptosome-associated protein), and syntaxin. BoNT types A, C and E cleave SNAP-25, types B, D, F and G cleave VAMP, and type C cleaves syntaxin. As a result, the release of acetylcholine into the synaptic cleft is blocked for a certain length of time depending on the type of BoNT involved.

Three to 14 days after BoNT injection, the injected muscle begins to show clinical signs of a dose-dependent flaccid paresis with atrophy and inhibition of the disinhibited stretch reflex. [25] The maximum effect is reached after three to four weeks, remains at this level for a certain time and then slowly decreases. In striated muscles the clinical effect is usually apparent for about three to six months. [26]

Eventually the neurotoxin will be proteolytically degraded in the preterminal axon. This allows the fusion complexes that are necessary for exocytosis to be newly formed so that synaptic function is resumed about three to six months after functional denervation. Muscular paresis subsides with the restitution of neuromuscular junctions.

HOW STRONGLY DOES BoNT INHIBIT CHOLINERGIC TRANSMISSION?

Evidence

After intramuscular injection into the gastrocnemius in children with cerebral palsy the EMG amplitude was reduced by 20% [27], after injection into the forearm muscles or the pericranial musculature in adults (distonic motor disorder!) by up to more than 90%. [28, 29]

Author's comments

The effect is non-toxic, confined to a small area, temporary, reversible and dose dependent. Toxin uptake is dependent on the activity level of motor or autonomic cholinergic synapses, or more specifically, on the presentation of the SV2-receptor on the membrane surface after acetylcholine release.

With increasing synaptic activity the chances that BoNT locks on to this particular synapse and blocks further acetylcholine release also increase.

WHICH CONTRAINDICATIONS HAVE TO BE CONSIDERED FOR THE TREATMENT WITH BoNT?

- Any illness with muscular weakness as a cardinal symptom [30, 31]
- Pregnancy & nursing (lactation) [32]
- Disorders of blood coagulation

Author's comments
If the patient has no medical history of myasthenia or hypersensitivity there is no need for any diagnostic investigation into these exclusion conditions. All BoNT serotypes principally can end up in the infant's organism both by crossing the placenta and via breast milk. Pregnancy and nursing period are therefore contraindicated. Nevertheless, there are known cases in which BoNT was used during pregnancy. This remained without any identifiable consequences for the child. [32] If administering BoNT to a mother during the nursing period, the mother should as a precaution discontinue breast feeding her baby for at least one week.
Contraindication of coagulation disorders depends on severity of the disorder. In patients with INR < 1.5, Quick > 30 %, PTT < 40 seconds, BoNT can be injected in regions with good compressibility of the injection site.

HOW ARE DOSE AND BIOLOGICAL ACTIVITY OF BoNT DEFINED?

Background
BoNT doses are specified as units of biological activity (mouse units, MU). One MU corresponds to an amount of toxin that after intraperitoneal injection of female Swiss Webster mice with a body weight of 18-20 gram causes 50% of these mice to die. This dose is also called lethal dose 50 or LD 50. [32, 33]

Author's comments
Clinical efficacy and the adverse effects profile of different, commercially available BoNT preparations are not directly comparable on the basis of the

respectively stated mouse units. The use of fixed conversion factors proved unsatisfactory.

WHAT ARE THE ADVERSE EFFECTS AND HOW OFTEN DO THEY OCCUR?

Evidence

Adverse effects of BoNT may occur if through local or systemic dispersal of the injected toxin cholinergic synapses outside the targeted muscle or body region are blocked. Adverse effects may result in local impairment but can also reach a generalized extent (even with fatal outcome). Adverse effects are altogether rare, generally only temporary and principally related to the dose and the type of commercial preparation used. [34-39]

In children and young adults with cerebral palsy the most frequently observed adverse effect is excessive paresis of the injected musculature or nearby muscles. When concurrently treating a number of muscles with the involvement of several joints, such excessive paresis may cause (temporary) unstable standing and walking. This should not be confused, however, with generalized muscle paresis resulting from a systemic adverse effect. A common focal adverse event is pain at the injection site.

Unintentional distant focal effects include strabismus and impaired function of the urinary bladder or of the rectum.

Possible systemic adverse effects are: general fatigue and weakness, ptosis, fever, flue-like symptoms, and dysphagia. The latter is associated with an increased risk for the affected patient to develop aspiration pneumonia. [40]
Isolated cases with fatal outcome in connection with BoNT treatment have been reported. The FDA (www.fda.org) and Swissmedic (www.swissmedic.ch) are currently investigating the safety situation (status 2008). A final causality assessment has not yet been filed.

Analysis of adverse events recorded in 9 double-blind, placebo-controlled studies on the treatment

of adults with Botox® (792 patients, 482 upper, 310 lower extremities) showed that there were no significant differences between the adverse events recorded in the treatment group (mean dose of 231 MU; n = 534) and those recorded in the placebo group (n = 258) as supposedly clearly related to BoNT (!). All recorded adverse events were of transient nature. The incidence of reported nausea was significantly higher in the BoNT group, (12/534 vs 0/258; P=.011), while the incidence of reported pain at the injection site, chest pain and allergic reactions was significanly higher in the placebo group. [41]

In conclusion, placebo-controlled studies with adults have shown that BoNT/A can be considered safe with a low risk of adverse effects for doses up to 400 MU Botox® or 1500 MU Dysport® per treatment session. Only in a few isolated cases was an unwanted, temporary local weakness of injected or nearby muscles observed. [42-46]

When using higher doses of BoNT (> 400 MU Botox®, > 1500 MU Dysport®, > 15000 MU NeuroBloc® per treatment session various adverse effects were observed, for example, generalized muscle weakness, dry mouth, dry eyes, impaired gallbladder motility, flue-like symptoms, dysphagia, double vision and impaired micturition. [30, 31, 36, 47-50]

However, there are also reports on high doses, for example, of Botox® (up to 600 MU per treatment session) that could be used without any relevant adverse effects, provided (i) injections are carefully guided into the target muscle, (ii) the dose is distributed over at least five muscles, and (iii) the dose per injection site does not exceed 50 MU (25 MU in small muscles). [51-53]

Author's comments
Depending on registration status, the patient's risk profile, published opinion of national societies, and guidelines and reports of the health authorities it is the responsibility of the treating physician to supply patients or family members with the available, case-relevant information on BoNT.

The expected effect of BoNT and all its possible local and systemic adverse effects should be carefully explained in easily understood terms to the patient and parents / family members. As part of this procedure, patients and / or their caregivers / legal representatives should receive this information also in writing, as a standardized document in duplicate, and be given adequate time for reading before returning a signed duplicate to their physician and receiving their first BoNT injections.

Patients complaining about local pain after injection may be given an appropriate analgesic (NSAID). In children the use of analgetics in combination with sedatives if needed is precondition for accurate placement of the injection and a necessity to avoid repeated harmful events. Transient reddening of the injection site is rare and usually does not require treatment, but if desirable may be treated with application of cold or with topical antiphlogistics.

In terms of pharmacovigilance, each adverse event observed in connection with BoNT injections should be reported to the health authorities.

CAN ANY ALLERGIC REACTIONS OCCUR?

Evidence
In the author's experience, some patients may develop a slight reddening of the skin for a few minutes after injection. There have not been any reports on anaphylaxis in connection with BoNT injection although such reactions theoretically would seem possible.

Author's comments
Based on current experience there is no need to expect any allergic reactions.

DO ANY STRUCTURAL CHANGES OCCUR IN THE INJECTED MUSCLE?

Evidence
In adults, there is so far no evidence for any lasting structural changes in the injected muscle. [54]
In children with cerebral palsy this question has not yet been conclusively re-

solved. [55, 56] There is no evidence to date that fibrosis of muscle tissue would progress any faster than to be expected anyway in cerebral palsy.

Author's comments
This is an important question for further research. Injections should only be given after accurate diagnosis was established. Looking at the long-term results, for example the reduction in the total number of necessary operations, there can be little doubt that the overall effect is positive. [57]

ARE THERE ANY OTHER EFFECTS BESIDES PARESIS?

Evidence
BoNT acts on the extrafusal and intrafusal musculature. [58, 59]. Inhibition of intrafusal synapses by BoNT causes a change in the pretension of the neuromuscular spindle which results in reduced spinal motor neuron activity via the 1a afference [58, 60]
Normalization of reciprocal and intracortical inhibition [61, 62] and topographic representation in the motor cortex has been reported to occur in patients with dystonia. [63] Furthermore, there is one report on patients with spasticity showing that central motor latency is prolonged. This was interpreted as central effect of BoNT on the spinal motor neuron response to efferent corticospinal impulses. [64]
Retrograde axonal transport was demonstrated recently in a rat model and the authors discuss possible clinical implications [65].
Intramuscular applications BoNT had no effect at the first motor neuron in two studies in a cat model. [66, 67]

Author's comments
Occasionally the clinically positive effect outlasts BoNT-induced paresis suggesting that BoNT might also have neuromodulatory or neuroplastic effects. This is a matter that has not yet been systematically studied.

2 Establishing the indications for treatment

HOW TO DECIDE ON THE GOALS FOR TREATMENT

E v i d e n c e
In psychiatry and physiotherapy therapeutic success is partly determined by, among others, predefined therapy goals. [68, 69] Such goals, on which therapist and patient, parents or caregiver agree before beginning therapy, form the basis for a successful therapeutic outcome – provided goals are carefully set and realistically achievable. Agreements always should be put in writing and include specifications of time intervals to next check-up and to next treatment session including the planned therapeutic measures. (see Goal Attainment Scaling, part C of this book)

Sensible goals for treatment with BoNT may include:
• improved function (increase control of voluntary movement)
• improved possibilities for other therapeutic options (open a "therapeutic window": a reduced stretch reflex, for example, might improve tolerance for wearing splints or orthotic devices)
• easier nursing care and improved body hygiene (e.g., washing, dressing and undressing)
• reduced pain (e.g., pain during passive stretch of the spastic motor segment)
• increased self-esteem (suppress involuntary movements and reduce spastic posture).

In broader terms, the treatment with BoNT as part of a multidisciplinary treatment approach should take into account the category of participation and aim at enhancing improving the patients life quality.

WHAT IS THE OPTIMUM POINT IN TIME FOR INITIATING TREATMENT?

Evidence
There are no controlled studies that would address this question. The available studies that form part of the registration of BoNT for treating spasticity in adults only included patients with a chronic stage of spasticity (this applies to all commercially available BoNT preparations).
For cerebral palsy, on the other hand, it is clear that early treatment of spasticity can postpone or even prevent the need for surgical intervention. [57] In children with cerebral palsy, motor development of gait takes place before the age of seven. [70, 71] Treatment of pes equinus in patients with cerebral palsy becomes less effective with increasing age of the patient. [72, 73] For other indications such age dependence of therapeutic outcome is less clear. [74] Pain can be successfully treated even in patients with advanced tissue transformation in the affected muscles. [10]

Author's comments
Early treatment during developing spasticity is desirable both for children and adults. There is a need for controlled studies that focus on the question of the most favorable point in time for BoNT application in cerebral palsy and spasticity in adults and hopefully come up with clear recommendations.

Considering cerebral palsy: Optimum benefits for gait motoric functions are achieved with early treatment, ideally before the age of six. Other functional objectives, such as improved gait economy, sustained transfer, and fine motor function, are often still achievable also in older patients. With regard to easier nursing care and reduced pain, successful treatment is possible any time.

DOES THE "DYNAMIC COMPONENT" OF THE MUSCLE DETERMINE EFFICACY?

Evidence
The extent of structural changes in the muscle is a limiting factor in the efficacy of BoNT treatment. [3] There is a positive correlation between dynamic component and therapeutic success. [75]

Authors' comments
The dynamic component plays a crucial role in therapeutic outcome. Therefore, determining the dynamic component has a very important place in every clinical examination of spasticity. It involves assessing the joint range of motion during fast and during slow movement (Tardieu maneuver). The less the range of motion is restricted during slow movement the better are the chances for a successful outcome of therapy.

HOW SHOULD THE PATIENT BE CLINICALLY EXAMINED BEFORE STARTING BoNT TREATMENT?

Evidence
Required are slowly performed „static measurements" (joint range of motion) as well as „dynamic measurements" (spasticity, strength, selective voluntary control, possible activities and participation). Instrumental motion and gait analysis may contribute valuable additional information. [76] If there is any anamnestic and current clinical evidence suggesting the presence of considerable structural restrictions of movement, heterotopic ossification (a frequent complication after craniocerebral trauma or bleeding) should be excluded by radiologic examination. Sonography should be used to exclude other possible causes for the restricted passive joint motility, for example luxation, interposition or subluxation.

Authors' comments
When establishing the diagnosis, the clinical examination should include and assess all primary elements of the upper motor neuron syndrome as well as related secondary signs and symptoms. Instrumental motion and gait analysis is a matter for special problem cases.

WHICH BASIC DATA SHOULD OUTCOME EVALUATION IN CEREBRAL PALSY INCLUDE?

Authors' comments
Examination should include the local effect of BoNT on the injected muscle. A first orientation is obtained using the modified Tardieu-Scale (see part C of this book). However, it is more important to set

appropriate therapy goals and then evaluate how well these were met using . Goal Attainment Scaling or the Canadian Occupational Performance Measure (COPM) as described in part C of this book. In addition it is advisable to involve evaluation instruments that address the Activity and Participation category (see part C) which may not be applied to each treatment session but, for example, at 12-months intervals.

WHICH BASIC DATA SHOULD OUTCOME EVALUATION IN ADULTS WITH SPASTICITY INCLUDE?

Authors' comments
At least one of the following evaluation instruments in the category Body Structure and Function should be used:

- Passive joint range of motion (passive ROM by neutral-0-method)
- Muscle tone (modified Ashworth, modified Tardieu)
- Voluntary motion (active ROM by neutral-0-method) and assessment of muscle strength (Medical Research Council scale)
- Pain: VAS (visual analogue scale) or NRS (numeric rating scale) in resting and in passive motion

DO COGNITIVE ABILITY AND SELECTIVE MOTOR CONTROL INFLUENCE OUTCOME?

Evidence
For therapeutic success it is essential that the child is able to handle the changed muscle tone induced by BoNT and thus is able to realize functional gains (authors' own observations and [73]). The term 'selective motor control' describes the child's ability to plan and execute selective voluntary movements, such as dorsiflexion of wrist or foot without associated finger or toe movement and without concomitant knee or hip flexion [77]

Authors' comments
Therapy goals must be set in accordance with the child's cognitive abilities and the expectations of patients or caregivers. The greater the child's ability of selective motor control before treatment, the better the prospects are of achieving functional gains with BoNT treatment.

HOW MANY MUSCLES CAN BE TREATED IN ONE SESSION?

Evidence
BoNT is registered for focal treatment of specific indications. Following clinical necessity, the areas in which BoNT is used for the relief of focal problems have been continually extended. Thus, in cerebral palsy and in adults spasticity BoNT is used to treat spasticity of, for example, shoulder muscles, adductors, and knee and hip flexion. [78, 79] Analogous to orthopedic surgery, optimal therapy is only achieved when injecting several muscles during one and the same treatment session. [53, 80, 81]

Authors' comments
We have now several years of preparation-specific experience with the efficacy and safety of BoNT in the simultaneous treatment of several muscles. The decision on how many muscles to inject should be made with careful consideration of the patient-specific clinical needs and safety risks.

ARE THERE ANY PRINCIPAL RULES ON INJECTION PROCEDURES AND ON THE RECOMMEND DOSE PER INJECTION SITE?

Evidence
For the local treatment of spasticity and movement disorders in cerebral palsy, BoNT should be accurately injected into the target muscle and as close as possible to the motor endplate region. [12, 52] [82] This helps to optimize the intended effect and reduce the probability of systemic adverse effects. Instrument-assisted control techniques (e.g. EMG or sonography) should be used whenever clinically correct delivery of the injection cannot be assured by any other, less involved means. [83]
If feasible, BoNT should be distributed between two to four injection sites per muscle, depending on the intended total dose per muscle. [84]

Authors' comments
The higher the chosen total dose, the greater the need to distribute the dose over several injection sites. The location of motor endplate regions are known for only a few

muscles. Cases where the endplate regions cannot be located should be approached pragmatically and the dose distributed over several injection sites in the muscle belly. Often, and this goes especially for small or poorly accessible muscles, correct injection will be possible only with the help of instrument-assisted control techniques.

3 Common indications for BoNT therapy

PES EQUINUS / PES EQUINOVARUS (CLUBFOOT)

Evidence
So far this is the best studied and the only registered indication for treatment in children with cerebral palsy. High quality, well controlled studies are also available for the treatment of pes equinus and pes equinovarus in adults. However, in most European countries and in North America BoNT is not registered for treatment of spastic equinus in adults. The pediatric registration specifies upper dose limits. This means that in those countries without registration, spastic equinus in adults represents an off-label indication. The same is true for children with cerebral palsy whenever registered dose limits are exceeded.
As would be expected, fixed equinus is neither in children nor in adults an indication for use of BoNT. [85]

Authors' comments
Possible treatment goals would be: improved gait pattern, walking speed, safety and endurance of walking, walking without pain, and tolerance of orthotic devices, and arrested progress of foot deformity. Conditions for a successful outcome of therapy are optimal in patients presenting with a so called "dynamic spastic equinus", which implies that hyperactivity of the calf muscles is still exceeding the structural changes that develop in the muscle. The Achilles tendon clonus usually responds very well to treatment with BoNT.

ADDUCTOR SPASTICITY AND PREVENTION OF HIP JOINT LUXATION

Evidence
Several open and controlled studies document local and functional efficacy of BoNT in this indi-

cation. Successful pain relief and improved nursing care are also documented in several high-quality studies (see section 12 of part A). [45, 74, 86-89]
Hip joint luxation is common in children with cerebral palsy. [90, 91] Early treatment of the spasticity reduces the frequency of necessary surgical corrections and postpones the patient's need for surgical intervention to an older age. [92] Open data [93] and a methodologically critical, controlled study [94] suggest that treatment with BoNT has more of a preventive effect. Another controlled study, however, found no positive effect on preventing hip joint luxation by treatment of adductor muscles in children with cerebral palsy [95].

Authors' comments
Focal restriction of movement by adductor spasticity or painful adductor spasms may be treated at any time of a patient's life. Because BoNT is not registered for this indication, every use for this indication will always be off-label. Possible treatment goals would be: easier nursing care, pain relief, improved transfer, standing and walking (reduced adductor interference).

In cerebral palsy with >50% hip displacement according to the migration index of Reimers, the prospects for successful treatment are poor. A possible goal for BoNT treatment would be to prevent progression of hip joint subluxation. Clinical studies to date did not provide conclusive evidence but may have failed to consider all relevant muscles. In addition to adductor longus and gracilis muscles, treatment of spasticity-related hip joint subluxation should include also hip and knee flexors. Postural management and weight-bearing therapy e.g. through standing frames should be included in the treatment of hip subluxation.

HIP FLEXION SPASTICITY

Evidence
There are no controlled studies. Open studies have shown positive results.
Injections may be administered using a ventral-proximal, ventral-distal, or a dorsal access route. [96, 97] Our own retrospecti-

ve study in children with cerebral palsy shows that based on goal attainment measurements the ventral-proximal and ventral-distal routes of injection are similarly effective. Rectus femoris and iliopsoas often contribute to the pathological gait pattern.

Authors' comments
Hip flexion spasticity is a common and important indication in children with cerebral palsy and also often considered in adults with severe bilateral spasticity in connection with a transverse spinal cord syndrome, multiple sclerosis. Hip flexion spasticity is less common in hemispastic adults. Injection of the iliacus muscle via the distal access route is easy with sonographic guidance and usually sufficiently effective. Injection of the psoas from dorsal (through the erector trunci) was described also for adults but should not be attempted without a suitable control technique. [98] Results from controlled studies on the efficacy of the different approaches in adults are lacking. None of the commercial BoNT products is registered for this indication. Therefore, treatment always would be off-label.

SPASTICITY OF UPPER EXTREMITIES

Evidence
High-quality, controlled studies document the local efficacy in children with cerebral palsy [99-102] and in adults, e.g. [103]. In order to achieve functional gains of the upper extremities, adequate accompanying occupational therapy, accuracy of the injection technique and the use of a moderate BoNT dosage administered as a fairly concentrated injection solution all seem to play an important role. [28, 104, 105]

In adults, so far only one controlled study shows that effective local treatment (decreased score in the Ashworth scale) can lead to reduced disability (as assessed with the Disability Assessment Scale). [103] So far, there are no controlled studies that would have shown any measurable gains of motor control in response to BoNT treatment.
BoNT injections can improve some troubling malpo-

sitions and make it easier to provide nursing care to the patient. [99, 106, 107]

Authors' comments
BoNT treatment is indicated for patients with spastic tone increase that leads to painful, anomalous movements and malposition with restricted use of the hand. BoNT treatment aims to improve arm/hand function (improved assisting hand or functional ambidexterity), make nursing care easier (dressing and undressing, improved palmar care), correct the appearance, reduce pain and spasms during movement and improve tolerance for orthotic devices. Functional improvements are only achievable in patients still able to initiate sufficient voluntary activity in those muscles that act as antagonists to the hypertonic muscles. Functional gains after BoNT injections alone seem possible in only a few cases (see Evidence and our own data) and usually are only obtained when BoNT treatment is combined with functional therapy. Elaborate control of injections (sonography or muscle stimulation) is not that important when treatment is aimed to improve "passive function" (easier nursing care, improved hygiene and reduced pain) but demanding when the aim is to improve "active function".

PAIN IN SPASTICITY?

Evidence
Treatment with BoNT is indicated and effective in patients with pain due to muscular hyperactivity (passive stretch or muscle spasms). [10, 108] Controlled studies have shown positive results in the treatment of spastic shoulder pain after stroke. [109-112] Painful adductor and extremity spasms are further indications for treatment with good chances for a positive outcome. In children with cerebral palsy, BoNT can reduce postoperative pain and the need for analgesics after adductor tenotomy. [88]

Authors' comments
Stretch- or spasm-dependent pain is a reasonable indication for BoNT treatment in any affected body segment.

4 Dosage

ARE THE DOSE SPECIFICATIONS FOR THE VARIOUS BoNT PREPARATIONS INTERCHANGEABLE?

Evidence
Only a few controlled studies are concerned with dose finding. [105, 114-116] Most dose recommendations, therefore, are based on the experience gathered over the years by various users rather than on the results of the few available clinical studies. BoNT doses reflect the biological activity of the preparation and are quoted in mouse units (MU). [32, 33] However, BoNT preparations from the various manufacturers, even those of the same serotype, show important differences in their biological activity. It is therefore imperative to use each BoNT preparation only in conjunction with its own specified dose recommendations. The use of conversion factors for preparations from different manufacturers as investigated in the treatment of patients with cervical dystonia has been discussed and has been recommended by some authors. We strongly advise against the use of such factors because there is a considerable risk for calculation errors, especially regarding the higher dose ranges. [53]

Authors' comments
Dosages must be calculated separately for each of the various preparations. Children have their own specific dose requirements that cannot be simply extrapolated from the dose requirements in adults.

WHICH PARAMETERS COME INTO CONSIDERATION FOR PLANNING AND CALCULATING THE TREATMENT DOSE?

Evidence
Calculations are based on the published experience with various dose levels

and take into consideration the:

- dose per injection site
- total dose per muscle
- total dose per individual patient / treatment session

Furthermore, when planning dose levels for treatment it is also important to consider:
- the overall severity of the motor disorder (CP: by Gross Motor Function Classification System) and the severity of accompanying disturbances
- the size of the targeted muscle
- muscle thickness
- degree of spasticity
- anticipated active versus fibrotic muscle elements
- effect of previous BoNT injections
- concomitant disorders (e.g. dysphagia)
- body regions involved
- BoNT concentration
- how well the target muscle can be pinpointed
- the preparation-specific behavior of BoNT in the tissue

There are generally accepted upper dose limits

- per muscle
- per injection site
- for the total dose per treatment session

Authors' comments
Planning individualized treatment requires a quite involved decision process that cannot be reduced to any kind of simple formula. As much as suboptimal treatment is not in the best interest of the patient, as much it is imperative not to neglect current safety issues.
Check & balance!

WHICH TREATMENT INTERVALS?

Evidence
The therapeutic effect lasts about 2-6 months. Some therapists treat children with cerebral palsy only once a year with BoNT. [117] Results from retrospective analyses in patients with cervical dystonia suggest that shorter injection intervals (less than 3 month) may increase the incidence of antibody formation against BoNT. [118, 119]

Authors' comments
Based on the currently available data on registered BoNT products, intervals between BoNT

injections should exceed three months. In children with cerebral palsy, therapists should aim to extend injection intervals as far as clinically justifiable while treating the patient with physiotherapy and orthotic devices. By contrast, when treating spasticity in adults, it sometimes would seem advantageous if shorter intervals could be used, for example, to inject additional muscles.

5 Factors with influence on local efficacy

HOW IMPORTANT IS THE INJECTION TECHNIQUE FOR CLINICAL EFFICACY?

Evidence
For a long time the various studies investigating the effect of BoNT treatment on the upper extremities in children with cerebral palsy produced conflicting results. [102] A reduced muscle tone was one of the results common to all studies. Functional gains were seen especially in those studies where the investigators realized how important it is to use a good injection technique and optimize dose and injection volumes and thus designed the study accordingly. Children with cerebral palsy present with a range of challenging characteristics not usually encountered in adults, such as poor cooperation during painful procedures, reduced ability for selective movements, small size of target muscles. This is the reason why the experience and the standards used in the treatment of adults is not that simply applicable to children. [120] Concerning the treatment of spasticity in adults, there is no evidence yet that the functional gains would be any better with instrument-supported injection control than without.

Authors' comments
This is an important topic with regard to clinical outcome, especially the functional gains that treatment is supposed to achieve.

HOW DO DIFFERENT BoNT CONCENTRATIONS AND VOLUMES INFLUENCE THERAPEUTIC OUTCOME IF KEEPING EITHER DOSE, CONCENTRATION OR VOLUME CONSTANT?

Evidence
Experimental animal model: To double the area of denervation requires a

10 to 25 fold higher dose if the volume of the injected solution is held constant. Conversely, if the dose is held constant, a 100-fold larger volume would have to be injected to double the area of denervation. [121] In adults with torticollis, distribution of injections over several sites helped distribute BoNT more evenly. [122] In adults with spastic hemiparesis, spasticity of the affected arm was reduced to the same extent in patients receiving 60 MU Botox® in a small volume compared with patients receiving the same dose in a large volume. [123] Similarly, in children with cerebral palsy, there was no measurable difference between the results after bilateral injection of the gastrocnemius with 100 MU Botox® in 1 ml vs. 100 MU in 4 ml. [124]

Authors' comments
For treatment of cerebral palsy in childhood, BoNT reconstituted in 2 ml of 0,9% NaCl per vial yields a suitable volume for injecting the generally still relatively small muscles in children. For adults, we suggest to use larger volumes: reconstitute BoNT in 2-4 ml per vial for injecting small to medium-sized muscles, and in 4-5 ml per vial for injecting large muscles. Further controlled studies that would provide some further guidance on this issue are desirable.

HOW FAR DOES BOTULINUM TOXIN A DIFFUSE IN THE INJECTED MUSCLE?

Evidence
In the muscle of experimental animal models (rabbit) BoNT diffuses for up to 4.5 cm from the point of injection (10 U/0.1 ml = 100 U/ml). [59, 121]

Authors' comments
It can be expected that injected BoNT is dispersing in a patient's muscle over similar distances as those observed in the experiments with rabbits. Dispersion occurs by both three-dimensional diffusion as well as lateral diffusion guided along intramuscular septa. For big muscles, larger volumes distributed over several injection sites may have advantages. However, convincing clinical studies or experimental in-vivo studies in human muscle do not exist on this topic.

CAN BoNT DIFFUSE ACROSS THE MUSCLE FASCIA?

Evidence

There are some reports on adults with cervical dystonia who had difficulties swallowing due to BoNT diffusion into neighboring muscles after injections in the sternocleidomastoideus muscle. [47] The muscle fascia slows the diffusion rate of BoNT by about 20%. [121] A low-dose/high-concentration approach yielded good results in the upper extremities of children with cerebral palsy. [104, 105]

Authors' comments

The muscle does not retain BoNT like in a sealed container. Diffusion is possible. Therefore, when injecting small muscles, for example, aimed to improve function of the spastic hand, it is advisable to use only a small volume and inject into the center of the targeted muscle.

HOW IMPORTANT IS INJECTION NEAR THE MOTOR ENDPLATE?

Evidence

Motor endplate regions are only known for a few muscles that are of central importance for treating spasticity of the upper extremities. [125] Results from experiments with rats and rabbits indicate that efficacy increased the closer BoNT injections were placed to the motor endplate (BoNT was used at a concentration of 0.2 U/µl = 200 U/ml [59, 121]

Similar observations were made in experiments with dogs. In those experiments, the authors confirmed needle placement by electromyography. [126] In adults with hemiplegic spasticity of the arm, no difference in outcome was observed after injecting the biceps brachii either near the motor endplate with a small volume of BoNT (100 MU Botox® reconstituted in 1 ml) or at a distance away from the motor endplate with a larger volume of BoNT (100 MU Botox® reconstituted in 5 ml) [82]. Another study in adults with spastic hemiparesis shows no difference in outcome between a single injection site and three injection sites in the gastrocnemius. [127]

Authors' comments
If location of the motor endplate region is known, optimum conditions for chemical denervation of the targeted muscles should be achievable if using sonographic guidance for injection. Where the region with the highest density of motor endplates is not known, or if it is not possible to use adequate injection control, best conditions for efficient denervation are achieved by distributing a suitably selected volume of the BoNT solution over several injection sites.

IS IT POSSIBLE TO INCREASE THE PROBABILITY FOR BINDING OF BoNT TO THE PRESYNAPTIC MEMBRANE?

Evidence
Pharmacological studies suggest that direct or neurogenic electrostimulation of the muscle promotes binding to and / or uptake at the neuromuscular junction. [128, 129]

Authors' comments
The clinical importance with regard to therapeutic outcome remains questionable.

DOES MUSCULAR ACTIVITY IMMEDIATELY AFTER INJECTION INCREASE EFFICACY OF BoNT?

Evidence
In patients with writer's cramp, increased activity after BoNT injection was associated with a higher level of induced paresis as compared to relaxation after BoNT injection. [130]

Authors' comments
A possible explanation for this effect could be that nerve stimulation leads to increased exposure of SV2 receptors at the motor endplate where they become accessible to BoNT blockage.
In children with cerebral study results are inconclusive and demand future research on usefulness, optimal timing and technique of muscle stimulation. In adults with spasticity, above findings suggest that efficacy may improve if spastic activity is provoked in the injected muscles during the first hour after injection.

INJECTION — GUIDED BY PALPATION?

Evidence
Palpation is unsatisfactory for accurate muscle identification, even if performed according to the Buchthal technique. [131]

Authors' comments
Accuracy of palpation is greatly overestimated. Palpation is unsuitable for adequate injection control even in superficial and large muscles and not applicable at all to smaller and deep-seated muscles.

INJECTION — GUIDED BY EMG?

Evidence
In adults with cervical dystonia, injections with EMG control are more effective than those without. [132] In pediatrics, EMG is sometimes used to control injections in the upper extremities. [99] Its application is limited because children with cerebral palsy have a limited ability to cooperate and perform selective movements, the acoustic signal is reduced in sedated children and the procedure is painful. All these factors reduce accuracy and practicability of the procedure. For a detailed discussion of the pros and cons see: [133, 134]

Authors' comments
Only very well experienced and competent operators will be able to perform this procedure satisfactorily. In needle EMG, sharp wave signals indicate that the examined muscle is "electrically" active and thus receptive to inhibition with BoNT. In the hands of the experienced operator and if uncertain about which muscles exactly might contribute to the patient's movement disorder, the use of multichannel surface recording of evoked potentials, and in special cases wire and needle EMG, could help.
The use of EMG with special Teflon-coated needles is not the first choice in spasticity. The procedure is time-consuming as it may take many attempts before the needle is correctly placed, with limited potential for muscle differentiation. Teflon-coated EMG needles are expensive and not available in every length required.

INJECTION — GUIDED BY ELECTRICAL STIMULATION OF THE MUSCLE?

Evidence
This method is independent of selective voluntary motor function and the patient's ability to cooperate, is unaffected by sedation and offers, therefore, better accuracy and practicability in cerebral palsy and spasticity than EMG. A disadvantage are the high costs for the Teflon-coated needles and surface electrodes. [98]

Authors' comments
Requires considerable practice and experience with the method. Just as with EMG, to find the correct position for initial needle placement requires a high level of operator competence including an excellent knowledge of applied anatomy for initial orientation. With regard to specific features in the muscle anatomy of the individual patient, muscle stimulation cannot provide the same level of information as that obtained with visual guidance by sonography. A frequent and not to be underestimated source of error with stimulation-guided injection is the possibility to provoke a motor response in the target muscle by inadvertently stimulating one of its motor nerves if the tip of the Teflon-coated needle was not correctly placed inside the muscle. A further drawback is that the Teflon-coated needles are not available in every length required.

INJECTION — GUIDED BY CT OR MRI?

Evidence
Both procedures have the advantage that they enable anatomically correct placement of the radiopaque or MR-competent needle. No need for Teflon-coated needles. Disadvantages are the rather involved procedure, exposure to radiation, high costs and restricted availability (indication and utilization requires an appropriately certified radiologist).

Authors' comments
Should be reserved for those special problem areas where injection with CT or MRI control is essential for accurate injection of the target muscle (e.g. when injecting the piriformis, in difficult cases also

the psoas and the deep-seated nape muscles, as well as the longus colli).

INJECTION — GUIDED BY SONOGRAPHY?

Evidence
Allows quick visual identification of the target muscle, differentiation from adjoining structures, exact localization of the needle tip in the desired position of the muscle belly (near the endplate, central in the muscle volume), and depiction and documentation of the injected volume, its dispersion or depot formation and thus ultimate proof of correct needle placement. [120, 135, 136]

Authors' comments
For achieving the desirable injection accuracy, sonographic control seems on the way to become the future "gold standard", alongside injection control by electrostimulation.

6 Sonography-guided injection of BoNT

WHAT ARE THE TECHNICAL REQUIREMENTS?

Authors' comments
Availability of a linear transducer is essential. For guiding injections in adults, the transducer head should be as wide as possible (4-12 cm). A transducer operating in the 10-15 MHz range is optimal for the upper extremities because it provides good, near-surface resolution. Use a 5 7,5 MHz transducer for deep-seated muscles of the lower extremities.
Normally, small-gauge, long needles (e.g. 27G-30G) are ideal for injection. Treat the skin with a suitable disinfectant before starting the sonographic procedure. When injecting, insert the needle directly through the standard bacteriostatic sonography gel.

HOW SHOULD THE TRANSDUCER BE ALIGNED?

Authors' comments
Only the transverse view allows to differentiate neighboring structures and identify muscles based on their characteristic cross-sectional images.
As suggested eg. by the German Society for Ultrasound in Medicine (DEGUM, section locomotor system) orientation should be: medial / ulnar / tibial to the left, and lateral / radial / fibular to the right side of the sonographic monitor.

HOW ARE MUSCLES AND OTHER STRUCTURES DEPICTED IN THE SONOGRAPHIC IMAGE?

Authors' comments
Musculature: poorly echogenic — with fibrotic metaplasia: echogenic (difficult to quantify)

- Perimysia and fascicular

tissue between individual muscle bellies: echogenic

• Bones / Periosteum: highly echogenic with echo obliteration
• Blood vessels: poorly echogenic, use Doppler mode if available
• Nerves: echogenic myelin sheath, poorly echogenic in the center
• Injection needle: echogenic (for easier detection, move the needle slightly up and down along its longitudinal axis)

HOW TO MONITOR INJECTION?

Authors' comments
Find target muscle and align image in the center of the monitor. Insert needle into the skin while aligning the needle along the center of the broad side of the transducer head but in a safe distance from the head so as not to damage the transducer membrane. Immediately begin to monitor how the needle is pushed forward into the muscle. If the needle point is not immediately visible, move needle slightly up and down its longitudinal axis for easier detection. Alternatively, the needle may be inserted along the narrow side of the transducer head. This would provide a longitudinal view of the needle which often allows easier identification.

HOW IS THE INJECTED SOLUTION DEPICTED IN THE SONOGRAPHIC IMAGE?

Authors' comments
Upon injection, the solution usually spreads in the muscle as echogenic cloud, sometimes with echo obliteration. Sometimes the solution may appear as a poorly echogenic space and rarely does it spread out rapidly along the guiding structures of intramuscular septa while remaining isointense. In most instances, the solution remains visible as echogenic cloud after injection was completed.

7 Multimodal therapy

BoNT PLUS CONSERVATIVE FORMS OF COMBINATION THERAPY?

Evidence
Several authors recommend some form of combination when treating cerebral palsy and spasticity in adults. [12, 52, 137-139] Combination therapy is standard though poorly standardized practice. Only very limited evidence is available from systematic studies. [140]
In a recent case-control study, a six-day therapy with electrostimulation plus splinting was less effective in reducing spasticity than a six-day stretch-taping of the spastic hand after BoNT injection. [141]

Authors' comments
There is wide consensus among users that combination therapy is indispensable for turning the reduced muscle tone into a therapeutic benefit relevant for the patient's everyday life. Treatment with BoNT just opens a therapeutic window that allows effective therapy with physical methods – such as physio- and occupational therapy, treadmill or other device-supported training as well as with splints and orthotic devices (through improved tolerance) – aimed to improve motor control and self-help competence. For successful conservative therapy, also in combination with BoNT, the following factors are of principle importance:

- specific, measurable goals and a suitably designed training program [142-145]
- learning by doing (in order to learn how to walk you have to practice walking) [146, 147]
- intensity [142]
- repetition [148, 149]
- early treatment [150-152]
- strengthen weak muscles [153, 154]

BoNT PLUS SURGICAL INTERVENTION?

Evidence
Refer to part A, Establishing diagnosis: "Pain in spasticity" and "Planning hand surgery". Treatment of upper extremities with BoNT may be carried out concurrently with surgery on the lower extremities. Further correction of muscular hyperactivity may be necessary and also reasonable after surgery.

Authors' comments
BoNT treatment may be reasonably applied in preparation for surgery, perioperatively as well as postoperatively.

BoNT PLUS PHYSIOTHERAPY?

Evidence
If closely timed with BoNT injection, muscle activation (e.g., with help from the physiotherapist) can increase the effect of BoNT on the muscle.
A 30-min activation of voluntary motor function [130] directly after BoNT injection resulted in greater local muscular paresis than that observed in the control group without muscle activation.
In a controlled study (crossover design), patients with multiple sclerosis who received BoNT treatment for spasticity showed a better therapeutic outcome if additionally treated with physiotherapy. [155]

Authors' comments
To make use of the SV2-receptor-mediated uptake of BoNT in activated synapses, we recommend to provoke spastic reactions in the injected muscles directly after injection (e.g. by triggering the tonic stretch reflex and spastic contractions or by applying redressments or air splints).
To make best use of the therapeutic window that the reduced spasticity provides, we suggest that for at least 6-12 weeks after BoNT injection, patients should receive several times a week active training therapy (physiotherapy and/or occupational therapy, optionally in conjunction with other supportive measures). All concerned should agree on specific therapy goals realistically achievable over a period of three months.

Physiotherapy should include the following elements (for overview see [156]).

- stretching exercises
- activation of antagonists (to the injected muscle)
- adaptation of function with the aim to establish safe use of the newly gained mobility
- adaptation of function with the aim to reach the next level of functional gains
- muscle strengthening
- adaption to activities of daily living

BoNT PLUS THERAPEUTIC CASTING / SERIAL REDRESSION?

Evidence
Correction of pes equinus was more effective if therapeutic casting or adjustable taping was applied after BoNT treatment as compared to application without BoNT treatment. [76] Results from some other studies are partly contradictory. [157, 158]. The results of a controlled study [159] and the clinical experience gained by many therapists do speak for a an additive effect.

Individually adjustable taping (synthetic bandage, lightweight and gentle to the skin) is used for stretching the contracted muscle and fibrous structures in chronic spasticity. Taping can be used for elbow, hand, knee and foot and should be gradually adjusted as mobility of the treated joint improves. [160]
Redression therapy applied before or right after BoNT injection helps increase muscle activity and thus promote BoNT uptake.

Authors' comments
Redression therapy has the aim to achieve functional zero position of the treated joint and restore conditions for optimum care of the patient. For elbow, hand, knee and foot, synthetic bandages are ideal. Nowadays, the use of white plaster is indicated only for casting of individually fitted plaster soles as a standing support for the patient.
Three types of redression therapy can be distinguished: encircling, completely immobilizing and partly immobilizing. Encircling strapping is usually used in initial therapy. This should

be changed after about 1-5 days (with adjustments in accordance with the changing joint angle of motion). Redression may have adverse effects such as edema, compressed nerves and skin lesions. In a skilled team, the incidence of adverse effects is less than 10%. Forced redression may cause injury:

- injury to knee joint if dorsal thigh muscles resist stretch, "positive posterior drawer test"
- subluxation of caput radii if the biceps brachii is resistant to stretch
- subluxation of finger and carpal joints if muscles for finger and wrist movement are resistant to stretch

BoNT PLUS ORTHOSES?

Evidence
There are no controlled studies on this combination for the treatment of pes equinus.

Authors' comments
(1) Patients with dynamic pes equinus without contractures:
BoNT, night splints and, where appropriate, therapeutic casting and arch support

(2) Patients insufficiently corrected with measures listed in (1):
Plus ankle foot orthosis according to the gait pattern and treatment goal

Orthoses across the knee joint are rarely tolerated.
About 2/3 of the children tolerate an abduction wedge.

BoNT PLUS MUSCLE STIMULATION VIA SURFACE ELECTRODES?

Evidence
Electrostimulation of muscles with repetitive muscle contraction, applied for about 30 min each day for several days before and after BoNT injection, increased the paretic effect of BoNT. [161, 162]. Results obtained in patients with cerebral palsy are contradictory or negative. [163]

Authors' comments
Very involved procedure regarding time and equipment required, needs a lot of convincing in the face of poorly convincing evidence, is therefore rarely used in adults or cerebral palsy and definitely not recommended for cerebral palsy.

BoNT PLUS NEUROMODULATORY THERAPY?

Evidence
No controlled studies are presently available. We had positive experience with Constrained-Induced Movement Therapy (CIMT) in combination with BoNT treatment. Our experience with robotic-assisted treadmill therapy (Lokomat®): BoNT treatment improves the conditions for optimal treadmill therapy. Evidence for an added therapeutic effect is available from only a few patients. [164, 165]

Authors' comments
Recommendable combinations; controlled studies are in progress to provide data for further discussion and development of this concept.

BoNT PLUS SYSTEMIC / INTRATHECAL PHARMACOTHERAPY OF SPASTICITY?

Evidence
Controlled studies are not available. Case reports show good tolerability and efficacy for a combination of intrathecal baclofen (treatment of bilateral spasticity) with local application of BoNT in severe, generalized spasticity with locally focused disability (BoNT injections in upper extremities or jaw region). [166]

Authors' comments
Adverse effects of antispastics in the systemic pharmacotherapy of patients with cerebral palsy limit widespread use. Nevertheless, in adults with spasticity, therapists often still use antispastics even if focal disability predominates and although treatment is rarely successful. Baclofen administered in the evenings proved effective in treating nightly bursts of painful muscle spasm. Any additional focal disabilities due to the spasticity should be treated with BoNT.

BoNT PLUS NEUROSURGICAL INTERVENTION?

Evidence
No controlled studies.

Authors' comments

Any focal symptoms remaining after surgical interventions are an indication for treatment with BoNT.

8 Procedural analgesia & sedation

WHAT CAUSES PAIN DURING BoNT INJECTION?

Authors' comments
Pain develops during skin puncture and as the needle pierces through the muscle fascia, but mainly when the injected volume is distending the surrounding tissue. Most adults tolerate this pain. Suitable sedatives and analgesics should be given if a patient is uncooperative or if especially delicate injection sites are concerned, or when using injection control techniques to ensure high injection accuracy. However, it should not be expected from a child with cerebral palsy to tolerate repeated exposure to a painful procedure without adequate analgesia and sedation. [167-169] In a struggling child it is almost impossible to place the injection accurately and this, of course, could have a negative influence on therapeutic outcome. Special aspects of pain management and analgesia in children with cerebral palsy are described elsewhere. [170]

IS THERE ANY NEED FOR GENERAL ANESTHESIA?

Evidence
Analgosedation is adequate in children with cerebral palsy and in uncooperative patients, and even in cases with repeated treatment sessions involving numerous injections into many muscles. [171, 172]

Authors' comments
The choice of procedural approach will also depend on the prevailing circumstances in the respective clinic. The sole use of sedation without concomitant analgesia would be inappropriate.

WHICH DRUGS ARE SUITABLE?

For children with cerebral palsy we suggest to use:

Pethidine / meperidine solution: opioid. Administration: may be administered to younger children as rectal application via a small tube. Advantage: acts faster than with oral application. Dose: 1 mg / kg body weight. Good analgetic effect; in younger children often given in combination with midazolam.

Midazolam solution for injection: benzodiazepine. Administration: may be administered to younger children as rectal application via a small tube or as oral application with a pump spray. Advantage: rectal administration acts faster than oral application. Dose: 0.3 0.5(0.7) mg / kg body weight. As a matter of principle, children should be monitored continuously for the next 30-60 min for early signs of respiratory depression. This is a must when using doses >0.5mg / kg body weight.

(S-)Ketamine solution for injection: anesthetic and potent analgesic. This is a good alternative for patients with inadequate response or paradoxical reaction to midazolam. Administration: rectal application via a small tube is possible; always given in combination with a low dose of benzodiazepine. Dose: about 1 3 mg / kg body weight. May be used in combination with, e.g., midazolam 0.2 0.3 mg / kg body weight. Children should be monitored continuously for the next 30-60 min for early signs of respiratory depression.

9 Non-response

ARE THERE ANY PATIENTS WITH PRIMARY NON-RESPONSE?

Evidence
If a patient does not respond to the first BoNT injection, this is usually due to the presence of contractures, poor injection quality (inadequate BoNT quantity, inaccurate placement of injection) or deteriorated toxic activity of the used BoNT preparation (e.g., due to interrupted cooling chain during transport or storage).
Theoretically, there is also the possibility that a patient might have been exposed to the toxin during infancy, with ensuing subclinical botulism and antibody formation to BoNT. Patients who were deliberately immunized against the toxin, such as the US-American troops were before being sent into the war in Iraq, are non-responders. [173]

Authors' comments
Pharmacologic primary non-response is extremely rare. Clinical non-response is usually due to the presence of contractures or caused by incorrect injection, underdosing or other dosing errors.

IS THERE ANY SECONDARY NON-RESPONSE DUE TO FORMATION OF ANTIBODIES TO BoNT?

Evidence
Definition: Initial injection is therapeutically effective. Two following injections have no effect.

Review on methods for BoNT antibody detection: [32, 174]

New, not yet established method: : [175]

1) Immunosorbent assays: Problem: poor correlation between detection of antibodies and presence of clinical non-response.

2) In vivo-assay:
a) Mouse assay: possibly underestimates the number of immunoresistant patients compared with the number of clinical non-responders.
b) Nerve-muscle preparation: gold-standard. [176]

3) Clinical tests:
a) FTAT (Frontalis test), EDB test (measures the CAMP amplitude after nerve stimulation) [177]
b) Sudomotor test [178]

In a cohort of children with cerebral palsy treated with BoNT in the 1990s, secondary non-response was observed in 20-30% of patients, with a high correlation to antibody findings. [179] Also in the 1990s, 3-5% of patients in a cohort of adults with cervical dystonia showed secondary non-response. [180] After 2000, a new Botox® preparation with reduced protein content became available which reduced the incidence of non-response in adults with cervical dystonia by a factor of 6. [181].

Authors' comments
As a rule, selection of inappropriate target muscles, inappropriate dose or inaccurate injection are the most likely explanations for secondary non-response. However, secondary non-response due to neutralizing antibodies is principally possible.

10 Long-term outcome

HOW LONG MAY PATIENTS BE TREATED WITH BoNT?

Evidence
A prospective study on safety and efficacy of BoNT in the long-term treatment of flexor spasticity in the upper extremities after stroke shows that 5 treatment cycles with 200-400 MU Botox® each were well tolerated and successively reduced spasticity and disability (as measured with the DAS and the Stroke adapted Sickness Impact Profile). [107] Similarly, data on the long-term treatment of adults with cervical dystonia show that BoNT was used for up to 15 years without any detectable loss of efficacy. [182, 183]

Authors' comments
BoNT can be used as a long-term medication for children with cerebral palsy as well as for adults with spasticity-related focal disabilities.

WHO CONTINUES, WHO DROPS OUT?

Evidence
Several open studies found that BoNT therapy had a sustained effect over several treatment cycles. [27, 107, 184]
The most important reasons for discontinuation of therapy were (1) that the predifined therapy goals had been accomplished, (2) formation of antibodies to BoNT, and (3) unsatisfactory clinical effect due to advanced transformation of muscle tissue requiring orthopedic surgery. [185]

Authors' comments
For children with cerebral palsy, BoNT is a temporary therapy option that can be applied over several years. The situation is similar for the treatment of spasticity in adults. While about 2/3 of all patients respond well to therapy, 1/3 of patients can be expected to discontinue with treatment

after the first few injection cycles. In adults with spasticity, some patients may discontinue treatment because they consider the achieved benefits hardly worth the effort (long travel time, painful injection, patient has unrealistic expectations).

CAN TREATMENT WITH BoNT DELAY OR EVEN AVOID SURGICAL INTERVENTION?

Evidence
Age-conform linear muscle growth can be maintained in the hereditary spastic mouse model by injecting spasticity-affected muscles with BoNT. [186, 187] In children with cerebral palsy, early surgical correction of spastic equinus achieves inferior results when compared with late correction [188]. However, when considering to treat a child with BoNT in order to delay surgery, it should be kept in mind that BoNT in children can only delay the process of muscle shortening rather than restore normal muscle growth as in the spastic mouse model. In a few cases, however, muscle elongation was achieved after a year of BoNT treatment. [75, 189]
A therapeutic program that includes conservative tonus-lowering therapy and soft-tissue surgery can greatly reduce the need for surgical hip reconstruction and multilevel surgery. [92] BoNT in combination with other, conservative modalities did achieve a highly significant reduction not only in the number of surgical interventions required at young age but also in the total number of surgical interventions. [57]

Authors' comments
Restoration of normal longitudinal muscle growth achieved with BoNT in the spastic mouse model could not be confirmed to this extent in humans. Nevertheless, the data from historical control group suggest that BoNT treatment is of long-term benefit for the patient. In conclusion: BoNT delays surgical intervention in children with cerebral palsy and significantly reduces the number of patients and the number of relapses requiring surgery. However, there is no conclusive evidence yet that BoNT would also prevent the need for corrective or-

thopedic surgery of severe spasticity in adulthood.

11 Associated indications

SIALORRHEA

Evidence
Sialorrhea (hypersalivation from the mouth, drooling) can be a functionally relevant and, moreover, also a socially stigmatizing problem. The severity of this disorder can be assessed with the help of simple clinical scales. Since 1997, several placebo-controlled studies involving various etiologies of sialorrhea have shown that this disorder can be successfully treated with BoNT. [190-194] Drooling is often seen in children with cerebral palsy and can be highly stigmatizing. [195, 196] The most common cause of sialorrhea in cerebral palsy is impaired swallowing, but occasionally it may also be due to autonomous dysregulation with hypersecretion. Oral anticholinergics, however, show a high incidence of adverse effects [197] Several open and one controlled study have therefore compared BoNT with scopolamine in children with cerebral palsy. [198, 199] Controlled studies on the optimal dose and concentration of BoNT for this application and on the appropriate selection of glands for injection are still lacking. One report describes a case of secondary non-response due to the appearance of neutralizing antibodies after BoNT/B injection into salivary glands. [200]

Authors' comments
This is an important indication for treatment with BoNT, and patients are usually very happy with the results. We recommend to inject the parotid and/or submandibular glands (bilaterally) and to use sonographic guidance for adequate injection accuracy. It takes about 2-3 days after injection before symptoms begin to subside, and about 10 days to reach the maximum effect. The reported duration of the effect varies

between 2 and 6 months. Unintentional injection of the masseter muscles can cause undesirable paresis and thus adversely affect mastication, especially in patients with ALS. At this point in time, treatment is not yet standardized nor are there any reports on long-term approaches.

FAILURE OF UPPER ESOPHAGEAL SPHINCTER RELAXATION

Evidence

When the upper esophageal sphincter (UES = cricopharyngeus muscle) fails to relax during swallowing, the bolus cannot shift from the pharynx to the upper esophagus. Failed relaxation during swallowing can be attributed to either persisting active sphincter tonus or wrongly timed sphincter relaxation, and patients with this neurogenic dysphagia often develop relapsing aspiration pneumonia. In most cases, such impaired pharyngeal clearance can be traced to the presence of brain stem lesions (pontine or pontomedullary lesions) as the underlying cause. Endoscopic examination of deglutition shows extended periglottic saliva pooling. Diagnosis is confirmed by videofluorographic examination showing failed opening of the UES associated with a nearly normal supraglottic deglutition phase and sufficient pharyngeal pressure buildup. Adequate pressure buildup in the cricopharyngeal region is confirmed by manometric measurements. [201] Before considering invasive therapy, patients should receive functional deglutitive therapy. For patients not responding, alternative specific local therapy options are BoNT injection into the cricopharyngeus [202, 203], balloon dilatation [204], and open or endoscopic myotomy [201].

Open studies show positive results after injection with 30 MU Botox® into the dorsal and ventrolateral parts of the cricopharyngeal muscle using visual injection-control with a diverticuloscope (esophagoscopy) while patients were under general anesthesia. Bolus entry to the upper esophagus became possible about one week after injection and remained so for 3-9 months. Besides a rarely observed dyspho-

nia no other clinically relevant adverse effects were reported. [205-207]

Authors' comments
This is a rare indication for treatment that should be left to centers with the appropriate clientele and expertise in the diagnosis of deglutitive dysfunction.

DETRUSOR-SPHINCTER DYSSYNERGY

Evidence
Simultaneous contraction of the striated external sphincter muscle (sphincter externus urethrae) and the detrusor muscle (detrusor vesicae) after spinal cord or brain injury determines the clinical picture of detrusor-sphincter dyssynergy (DSD) and results in neurogenic dysfunction of bladder voiding and increased volume of residual urine. For symptomatic therapy of patients with insufficient detrusor function and increased residual urine who for other reasons cannot use intermittent catheterization, BoNT-A injection into the external sphincter is a possible alternative [208, 209]. A so-called quadrant injection of the external sphincter is recommended using a paraurethral route for female patients, if possible with EMG guidance, and endoscopically guided transurethral injection for male patients. [209-212]

Authors' comments
In DSD, intermittent self-catheterization with single-use catheters is always the first choice option for symptomatic treatment. In cases with reasons against catheterization, treatment with BoNT may be considered.

NEUROGENIC DETRUSOR HYPERACTIVITY

Evidence
Involuntary detrusor contractions (detrusor hyperreflexia) due to suprasacral spinal cord or suprapontine neural network lesions are characteristic for the neurogenic detrusor hyperactivity syndrome. The clinical symptoms are neurogenic bladder dysfunction with incontinence. For patients not responding to or with poor tolerability of anticholinergic therapy, BoNT injection into the detrusor offers an alternative treatment option. It leads to the desired increase in

residual urine without increasing bladder pressure and lowers the incidence of micturition caused by hyperreflexive detrusor contractions. [213] Injections are administered with the help of transurethral cystoscopy, taking care to avoid the trigone. [214] Depending on the patient's bladder sensitivity, apply local, regional or general anesthesia. [215-217]

Authors' comments
Especially for patients unable to use regular self-catheterization, this is a useful treatment option to restore continence unaided by any devices.

PROTECTIVE PTOSIS

Evidence
Incomplete eyelid closure, or lagophthalmos, can be due to a number of different reasons. A common consequence is insufficient corneal lubrication and impaired protective reflex with increased risk of corneal injury and infection. Intervention with BoNT-A aims to restore complete lid closure. [218, 219]. There were reports of persisting hypotropias after the treatment. [220]

Authors' comments
In cases where a protracted course of lagophthalmos is expected, BoNT injection of the upper eyelid levator muscle offers a good alternative to surgical tarsorrhaphy (suturing together of upper and lower eyelids) or the care-intensive watch-glass eye dressing.

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