The Essential Guide for Clinicians Who Prescribe and Inject BoNTs

This is a detailed and practical guide to botulinum neurotoxin therapy (BoNT) and the wide range of applications for neurological and pain disorders. A unique reference source for new injectors and experienced clinicians alike, this indispensable manual provides information on dose, dilution, and indications for all four FDA-approved toxins in one handy text.

Following a brief review of relevant pharmacology, the book provides product information and comparative distinctions between the four FDA-approved toxins (Botox®, Myobloc®, Xeomin®, and Dysport®), along with guidance techniques and common and emerging clinical applications. The heart of the book is an injection manual, organized anatomically and by condition and covering all applications for medical treatment. For each condition or disorder, information pertinent to the relevant muscles involved, dosing guidelines and dilution for the applicable toxins, number of injection sites, and potential risks and benefits. Targeting techniques are organized in table format for quick retrieval. Anatomic illustrations and cross-sections are provided to orient injectors and help identify optimal insertion points. An appendix with useful clinical rating scales is also included.

Key Features:
- Presents state-of-the-art information about current indications for all four FDA-approved botulinum neurotoxins
- Compares and contrasts the four toxins along with common and emerging clinical applications
- Provides dosing guidelines for various indications and injection sites for each muscle
- Includes anatomic drawings and cross-sections to illustrate muscle relationships and insertion points
- Serves as a practical, portable, how-to guide for new and experienced clinicians

Recommended Shelving Category: Neurology, Physical Medicine & Rehabilitation

KATHARINE E. ALTER
NICOLE A. WILSON

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Botulinum Neurotoxin Injection Manual

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Dedicated to our patients, from whom we receive daily inspiration. To Terry for his encouragement and heroic efforts in making this text as close to perfect as we could hope and to Foster for his unending patience and the reminder that “all work and no play make Katharine and Nicole dull girls.”
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Preface

The past two decades have seen an almost exponential increase in the number of approved, accepted, and investigational uses of botulinum neurotoxins (BoNTs) in clinical practice. At the same time, the number of FDA-approved BoNTs has expanded from a single serotype A toxin to three serotype A toxins and one serotype B toxin. Clinicians who prescribe and inject BoNTs must be familiar with an ever-expanding list of clinical applications and with the unique properties of each of the available BoNT products, including a thorough understanding of the approved and unapproved indications and differences in the preparation/dosing for each of the commercially available BoNT products. Clinicians must also be aware of the potential risks and benefits of BoNT therapy, be skilled in various guidance techniques (e.g., imaging, electromyography), and be aware of strategies that are used when performing BoNT therapy. The purpose of this handbook is to provide a concise overview of the currently approved BoNTs and their use for specific clinical conditions, including the approved and published dosage ranges for the BoNT products (where available). Anatomic illustrations are provided to enhance localization of muscles and other target structures. We hope this information will be useful for clinicians and will ultimately enhance patient care.

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Nicole A. Wilson, PhD, MD
Section One

Botulinum Neurotoxin: Basic Science and Reconstitution
Pharmacology of Botulinum Neurotoxins

Katharine E. Alter, MD
Fatta B. Nahab, MD
Barbara I. Karp, MD

Botulinum neurotoxins (BoNTs) are biological products produced by various strains of Clostridium botulinum, which are gram-positive, obligate anaerobic bacteria. BoNTs are widely recognized as the most potent toxin known to man. It is somewhat surprising that BoNTs are also used in clinical practice for an ever-expanding list of approved and off-label indications. Despite their deadly nature, BoNTs have an excellent safety profile when used in minute quantities by experienced clinicians. This chapter provides a review of the pharmacology of BoNTs, an understanding of which is essential for clinicians who use these agents to treat patients (1, 2).

Normal Neurotransmitter Release

At presynaptic nerve terminals (NTs), neurotransmitters (NrTrs) (e.g., acetylcholine) are stored in synaptic vesicles (SVs). The arrival of an action potential at NTs leads to the mobilization of SVs through exocytosis, resulting in the release of a quanta of NrTrs contained within the SV (3). The release of NrTrs through exocytosis is a multistep process that includes binding and fusion of the SV with the neuronal membrane, followed by the release of NrTrs into the synaptic cleft (Figure 1.1). This process of binding and exocytosis requires the interaction of a suite of intracellular polypeptides, the soluble N-ethylmaleimide-sensitive receptor (SNARE) proteins. Different SNARE proteins are located in the cytosol, on the SV, and on the presynaptic membrane of NTs. Membrane-associated SNARE proteins include SNAP25 and syntaxin. Vesicle-associated SNARE proteins include synaptobrevin (also known as vesicle-associated membrane protein [VAMP]) and synaptotagmin. Following exocytosis, the NrTrs diffuse across the synaptic cleft and bind to the specific postsynaptic receptors. Postsynaptic activation of target structures results in the activation of target structures,
including muscle contraction at neuromuscular junctions (NMJs), glandular secretion (e.g., eccrine and salivary), and other sites (4).

**BoNTs Synthesis and Structure**

BoNTs are synthesized as inactive, single 150-kDa polypeptide chains that are released, along with nontoxic proteins, from the cytosol from *Clostridium* bacterium following bacterial autolysis (1). Different strains of *Clostridium* produce different BoNT serotypes A to G, which vary in amino acid sequence. There are also amino acid variations within serotypes, creating subtypes within a given serotype (e.g., serotypes A1 and A2) (5).

The active BoNT molecule is composed of a 50-kDa light chain (LC) and a 100-kDa heavy chain (HC) linked by a disulfide bond. BoNTs are activated, or “nicked,” by proteolytic cleavage to create the active disulfide chain molecule. The HC is responsible for receptor-mediated binding and membrane translocation. The LC, the catalytic domain, is responsible for blocking the action of BoNT at the synapse (6). BoNTs have a complex three-dimensional (3D) conformation that is required for site-specific binding and other actions of BoNTs (Figures 1.2A and B).
BoNTs, in their natural state, are associated with various nonhemagglutinating and hemagglutinating proteins, called complexing proteins (CPs). CPs increase the overall size of the neurotoxin complex to 300 to 900 kDa. Although little is known about the biological function of CPs, they are believed to protect or stabilize BoNT following ingestion and to prevent degradation following exposure to gastric proteases in the mammalian stomach (5, 7).
BoNT Binding/Blocking

At cholinergic NTs, SNARE proteins are the intracellular targets of BoNTs. These intracellular nanomachines are involved in the intracellular transport and release of acetylcholine and other NrTrs (2, 7–11). The action of BoNT at presynaptic cholinergic NTs has been studied extensively and is understood in some detail. BoNTs, like other bacterial exotoxins, block their intracellular targets in a complex, multistep process. Step one of this process is uptake of the toxin into the presynaptic NT via site-specific binding of the HC-binding domain to a receptor on the presynaptic membrane. Following binding, the toxin is internalized by the process of receptor-mediated endocytosis. The LC is then cleaved from the HC by a process that has yet to be identified. To reach the SNARE targets in the cytosol of the neuron, the LC must then exit the endosome.

There are at least two proposed mechanisms for how the LC exits or translocates the endosome and both implicate the HC in this process. The translocation domain of the HC may act as a chaperone for the LC, facilitating its movement through the lipid bilayer. The other prevailing theory is that the HC creates a membrane pore through which the LC exits the endosome (12, 13). In this pore theory, conformational changes in the shape of the globular BoNT LC are required to allow it to exit the endosome. Under the influence of the acidic pH of the endosome, the LC unfolds and exits the endosome though the pore. Once in the cytosol, the LC must again refold into its original 3D conformation to allow it to bind to its SNARE target (13). This process of unfolding and refolding is influenced by a pH differential between the endosome (acidic) and the cytosol (neutral).

Some researchers debate whether these conformational changes are required (12). Recent studies have revealed additional details about the HC and LC structure, including specialized regions of the HC. These specialized regions include a binding domain, translocation domain, and a belt region. The belt region surrounds the catalytic domain of the LC, which is buried deep in a cleft within the BoNT molecule. The belt region may serve to protect the LC catalytic moiety, although its exact function has yet to be elucidated (1).

After entering the cytosol of presynaptic neurons, the LCs of the various BoNT serotypes exert their action by blocking their respective SNARE proteins (Table 1.1). Once the LC binds to its SNARE protein target, the SNARE protein can no longer

<table>
<thead>
<tr>
<th>Serotype</th>
<th>SNARE Protein Target</th>
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<tbody>
<tr>
<td>A</td>
<td>SNAP25</td>
</tr>
<tr>
<td>B</td>
<td>Synaptobrevin</td>
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<tr>
<td>C1</td>
<td>Syntaxin</td>
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<tr>
<td>D</td>
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function to release vesicular NrTrs. The action of that SNARE protein is permanently blocked. Although this blocking process is permanent and the poisoned nerve terminus degenerates, the toxin does not kill the neuron (1). The chemodenervation effects of BoNT are temporary because, eventually, the internalized BoNT is metabolized and the SNARE proteins and effected NTs regenerate. Once this process is complete, the function at the NT is restored, neural transmission resumes, and the function of the end organ is restored. This process of NT regeneration typically takes several months (2, 5).

**BoNT Potency and Dosing**

BoNTs, being biological agents and not drugs, are measured in units of bioactivity, not by weight, mass, or volume. BoNT is measured and dosed in mouse units (MU or U), where 1 MU or U equals the median lethal dose (LD 50) for an intraperitoneal injection in a particular size, sex, and breed of mouse. For example, the MU of onabotulinumtoxinA is based on lethality in a 30-g female Swiss Webster mouse, following intraperitoneal injection of the neurotoxin. The potency, and therefore the recommended dose in units, for each serotype and each commercially available BoNT product is unique. Further differences among the products accrue from variances in the strain of *Clostridium* used to manufacture the toxin, as well as proprietary manufacturing practices. Therefore, these products are not interchangeable. This topic will be covered in detail in Chapter 2.

**Clinical Implications of BoNT Pharmacology**

As noted earlier, BoNTs inhibit the release of NrTrs by blocking the action of one or more SNARE proteins required for NrTr vesicle exocytosis. Although the action of BoNTs at cholinergic NMJs was identified decades ago, their action is not limited to the NMJ. BoNTs also affect neuroglandular junctions, pain signaling, and other sites (2). BoNTs produce a sustained blockade of NrTr release, which at cholinergic NTs leads to chemodenervation. In clinical use, physicians exploit the effects of the chemodenervation produced by BoNTs through injection into specific muscles, glands, or other sites to selectively decrease the output of overactive neurons. The resultant decrease in neuronal activity thereby reduces overactivity in the target end-organ, such as muscle contraction, gland secretion, pain signaling, or others. By careful manipulation of the injected dose of BoNT, physicians can effectively titrate the extent of BoNT blockade on a specific target.

The uptake of BoNT is reportedly higher at active NTs. Hence, NTs that are pathologically overactive (i.e., those most active in the condition being treated) may have the highest uptake of BoNT and thereby be preferentially affected by the toxin. This bias toward a BoNT effect in overactive structures is potentially beneficial for patients and useful for clinicians in maximizing efficacy and minimizing side effects (14).

Following injection of BoNT for hypersecretion, pain, or muscle overcontraction, the clinical effects are typically first apparent within a few days and peak between 4 and 6 weeks after injection. The duration of effect may be influenced by the dose, target end-organ, severity of the condition being treated, and individual patient factors,
but generally lasts 10 to 12 weeks. Although the duration of effect in aesthetic uses is generally 10 to 12 weeks, the response of overactive bladder to BoNT may last as long as 5 to 6 months (15, 16). Currently, most expert clinicians recommend re-injection when the patient’s symptoms return, but no more frequently than every 12 weeks (15, 17). The limitation on the frequency of injections arises from concerns about the potential for antigenicity and antibody formation.

**Antigenicity, Antibody Formation, and Nonresponsiveness to BoNT**

Some individuals or conditions do not respond well to BoNT (i.e., they have limited benefit or effect following BoNT injection). If there is no response to the first injection of BoNT, the patient is deemed a primary nonresponder. Primary nonresponse may be due to a variety of factors, either alone or in combination, including failure to properly target or inject the intended muscle/structure, selecting the wrong target or muscles, insufficient dosing, or injection of limbs with fixed contracture or other deformities that are not amenable to treatment with BoNT (17, 18).

Following injection, BoNTs, being foreign proteins, may induce neutralizing antibody formation rendering the toxin ineffective, which is called secondary nonresponse. Secondary nonresponse occurs rarely with current BoNT formulations. The presence of antibodies to BoNT can reduce or eliminate responsivity to BoNT injection. Although antibodies may form against either the toxin polypeptide itself or the accompanying CPs, it is likely that only some of these antibodies are neutralizing antibodies that contribute to reduced efficacy. Nonneutralizing antibodies may be present, but probably do not reduce the activity or clinical efficacy of BoNT (19).

Although BoNTs can induce an antibody response, they are only weakly antigenic in comparison to other biological toxins. When BoNT was first developed for clinical use, it was common for patients to receive an initial injection followed by “booster injections” every 2 to 4 weeks until response was achieved. Such booster injections, however, may foster the development of antibodies. To minimize the likelihood of antibody production and subsequent loss of clinical response, the practice of “booster injections” is now generally not advised. This recommendation is strengthened by early analyses showing that antibody formation was more likely in patients receiving high doses of BoNT or in those receiving injections more frequently than every 12 weeks (20). The initial reports on antigenicity were based on observations with an early preparation of onabotulinumtoxinA (1979 Botox®) that reported an antibody rate of 4% to 10% in patients being treated for cervical dystonia. The higher protein load of that preparation, compared to that of the currently available toxin (1997 Botox®), may have made it more antigenic. The current incidence of neutralizing antibodies is lower (2). A meta-analysis in 2000 revealed an overall antibody incidence of 0.49% in 2,240 patients with mixed diagnoses and indications for injection. Only 3 of 11 patients with antibodies were clinically unresponsive (21).

To reduce the risk of immunoresistance, the current expert consensus opinion is to use the smallest effective dose of BoNT, wait as long as possible between injection cycles, and avoid booster dosing (11).
Safety

BoNTs have been used in clinical practice since the 1970s with an excellent safety profile when administered by physicians familiar with the risks and benefits of BoNTs (2, 11, 15, 17). When injected therapeutically in humans, the lethal dose of the various BoNT preparations is not known, and the doses required to cause systemic side effects are difficult to predict. Rare serious generalized adverse events, particularly neuromuscular weakness with respiratory compromise, have been reported following BoNT injections, most commonly with high doses and in compromised pediatric patients. However, similar life-threatening reactions can potentially occur in noncompromised patients at therapeutic doses. The serious nature of the potential risk prompted the Food and Drug Administration to add boxed warnings to all BoNT products in 2009 (Figure 1.3).

**Central Effects of BoNTs**

In addition to local effects in target or distant peripheral structures, there is mounting evidence that BoNTs are transported from peripheral sites into the central nervous system.
system, including spinal motor neurons and the brain. Most of the data on retrograde transport and central effects arise from animal studies on pain reduction (5). Central or retrograde transport of BoNT to pain centers in the brainstem, particularly the trigeminal system, may be partly responsible for the antinociceptive effects of BoNT observed in animal studies and clinical practice.

Summary

The use of BoNTs in clinical practice requires that physicians understand BoNTs mechanism of action to realize the potential benefits and to minimize the risks of these potent biological agents.

BoNTs are complex biologic molecules, and although much is now known about their structure and function, future research is likely to reveal additional information relevant to their clinical use. The versatility of BoNTs is likely to lead to the expansion of their use for as yet unidentified clinical problems and indications.