Injectable and topical neurotoxins in dermatology

Indications, adverse events, and controversies

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Learning objectives
After completing this learning activity participants should be able to compare and contrast botulinum toxin with emerging products not yet on the market; discuss appropriate off-label uses for neurotoxins; list noncosmetic usages of neurotoxins in other medical specialties; and describe how to combine neurotoxin treatment with toxins, lasers, and fillers safely and effectively, while minimizing complications.

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The use of neuromodulators for therapeutic and cosmetic indications has proven to be remarkably safe. While aesthetic and functional adverse events are uncommon, each anatomic region has its own set of risks of which the physician and patient must be aware before treatment. The therapeutic usages of botulinum toxins now include multiple specialties and multiple indications. New aesthetic indications have also developed, and there has been an increased utilization of combination therapies to combat the effects of global aging. In the second article in this continuing medical education series, we review the prevention and treatment of adverse events, therapeutic and novel aesthetic indications, controversies, and a brief overview of combination therapies. (J Am Acad Dermatol 2017;76:1027-42.)

Key words: abobotulinum; adverse events; botulinum toxin; controversies; cosmetic uses; incobotulinum; neuromodulator; neurotoxin; onabotulinum; therapeutic uses.

THERAPEUTIC INDICATIONS

Key points

- **The therapeutic use of botulinum toxin has spanned across multiple specialties**
- **Disorders of sweating, flushing, and scar prevention are some of the dermatologic therapeutic usages of neuromodulators**
- **Other specialties highlighting the use of neuromodulators for therapeutic purposes include psychiatry, neurology, ophthalmology, gastroenterology, and urology/gynecology**
- **Off-label usages are common, and new usages are continuously under investigation**
- **Hypersensitivity reactions to the product and infection at the site of injection are the only absolute contraindications**
- **There is a black box warning with the use of neuromodulators regarding the potential spread of toxin and associated adverse events**

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Since the discovery of botulinum toxin, indications have rapidly expanded across multiple specialties, including neurology, ophthalmology, dermatology, gastroenterology, psychiatry, and urology.[1] Table I and Figs 1 and 2 show nondermatologic indications for botulinum toxin and ongoing investigations. Many dermatologic indications are reviewed below for each of the botulinum toxin type A agents. Of note, there is a paucity of comparative trials for incobotulinum toxin; therefore, data for each indication are limited.

Indications approved by the US Food and Drug Administration

Botulinum toxin is approved by the US Food and Drug Administration (FDA) for use in the treatment of axillary hyperhidrosis, glabellar lines, and lateral canthal lines.

Hyperhidrosis. Botulinum toxin is widely used for the treatment of localized hyperhidrosis and is approved by the FDA for the treatment of severe axillary hyperhidrosis that is unresponsive to topical therapies. The procedure has minimal patient discomfort and has proven to be of great clinical success, with improvement in patient quality of life.[16-18] The average dose is 50 units of onabotulinumtoxin per axillae.[16,17,19] The duration of effect is variable, reported from 2 to 24 months; however, recent data suggest an increase in the duration of efficacy with increasing repetition of botulinum toxin injections. The median duration of effect from the first injection was 5.5 months compared to the last injection, which was 8.5 months (mean, 4 injection series).[20] Axillary osmidrosis (foul odor) has also been successfully treated with injectable toxin, but the effect is also transient.[21]

Palmar hyperhidrosis is a common off-label site for treatment.[22] The therapeutic effect is less than that seen with axillary treatment.[23-30] In thick acral skin, pain upon botulinum toxin injection can be a significant limiting factor.[22] Pretreatment with ice/cold, vibration, topical anesthetics, nerve blocks (eg, Bier block), and frequent needle change can reduce patient discomfort.[31] On average, the duration of response is 6 months,[32,33] but there may be an increase in the duration of response with repeated treatments.[34,35] Dosages vary between studies, with many showing adequate results with onabotulinum and incobotulinum doses of 50 to 100 units per hand and 100 to 240 units of abobotulinum toxin per hand.[24,36-38] Mild reversible hand grip weakness has been reported; however, there was no alteration in sensation.[39]

Successful treatment with botulinum toxin has been reported in other disorders of sweating, including Hailey–Hailey disease,[40] the face and back, where compensatory hyperhidrosis tends to occur after thoracic sympathectomy,[41-44] and there have been reports of successful treatment associated with Frey syndrome (sweating on the cheek during chewing as a result of parotid gland injury),[45] granulosis rubra nasi (nasal sweating),[46] and chromhidrosis (colored facial sweat).[47]

Glabella/lateral canthal lines. The first cosmetic use approved by the FDA for botulinum toxin in the United States was for the treatment of glabellar lines in 2002.[48] Since that time, the treatment of lateral canthal lines is the only other cosmetic indication to achieve approval despite the widespread clinical use for multiple other indications, which will be separately reviewed. Abobotulinumtoxin and incobotulinumtoxin have also achieved approval for the treatment of glabellar lines, and while lateral canthal lines are not yet approved for these products, treatment of this area has demonstrated similar efficacy to onabotulinumtoxin.[49-52] The average dose for glabellar lines is about 10 to 40 units total of onabotulinumtoxin/incobotulinumtoxin (50-80 units of abobotulinumtoxin), but treatment must be individualized to the anatomy, muscle mass, and sex of the patient.[53,54] Lateral canthal lines generally require 10 to 30 units total of onabotulinumtoxin/incobotulinumtoxin (20-60 units of abobotulinumtoxin), with individual variation in number and location of injection points based on the degree of the wrinkle fanning.[54,55] As with many other facial cosmetic regions, treatment lasts approximately 4 months; however, there are data to suggest that an increased number of treatments over time leads to a greater interval of time between repeat treatments.[49,56] Patient satisfaction with treatment of these areas remains exceptionally high.[54]

Indications not approved by the US Food and Drug Administration

Nondermatologic approved uses include strabismus, blepharospasm, cervical dystonia, upper limb spasticity, chronic migraine, overactive bladder, and urinary incontinence. Off-label uses in aesthetic medicine include brow lift,[57,58] eye widening,[59] jaw sculpting,[60] minimization of surgical scars,[61] platysmal band reduction,[62] perioral lines, masseter reduction, and palmar hyperhidrosis.[22] A few of the more pertinent dermatologic usages are discussed below.

Chemical brow lift. Glabellar injections alone lead to an immediate lateral eyebrow elevation followed by a central and medial brow elevation 12 weeks posttreatment.[58] The mechanism of action