Non-cosmetic uses of botulinum neurotoxin (BoNT) have been FDA-approved for a growing number of spastic neuromuscular conditions, headaches, and secretory conditions (see Fast Fact #299). While supporting evidence is limited for many indications and expense can be a barrier, this Fast Fact will review potential BoNT uses for seriously ill patients when traditional treatment modalities have failed.

Pharmacology  BoNTs are a metabolic waste product of the bacteria *Clostridium botulinum*. In large quantities, BoNTs cause botulism, a rare but potentially lethal illness resulting from muscle paralysis. In minute quantities, the toxin can be therapeutic for overactive muscle conditions via reversible inhibition of presynaptic acetylcholine release at the neuromuscular junction. They are also known to inhibit gland secretion via parasympathetic effects. At least one of the seven antigenically different serotypes (A) may have direct analgesic effects (1).

Practical Aspects  Treatment with BoNTs involves direct, localized injection of a saline solution containing the diluted toxin at the site of intended action (intramuscular or subcutaneous). It is usually an office-based procedure. Procedural specialists often provide this service, but other clinicians could become certified after training and demonstrating proficiency, depending on individual institutional regulations. Onset of action is generally within 3-4 days. The toxins’ effects can last 3-4 months for striated muscle and 6-9 months for autonomic neurons.

Specific Palliative Indications  

**Spasticity**  Controlled studies suggest BoNTs can be particularly useful for short-lived spasmodic pain that may be difficult to target with systemic analgesics. Serotype A is FDA-approved to treat spasticity of the upper and lower extremities in adults. In children, different BoNT formulations are used off-label to treat many muscle groups; the only FDA-approved pediatric indication is cervical dystonia in patients over age 16. Available data suggests BoNT A is safe and improves function, self-worth, and parental/caregiver perception of care for cerebral palsy (CP)-related spasticity in children when used as an adjunct to traditional therapies (2). Other evidence suggests BoNTs may have a role in:

- Stroke-related spasticity and pain (3-5)
- Non-malignant chronic neck pain (6)
- Pain and spasticity in head and neck cancer patients (7-9).

**Neuropathic pain syndromes**  Case reports and case series suggest BoNTs may reduce neuropathic pain and reduce opioid use from post-mastectomy and post-thoracotomy pain syndromes (10-12). A randomized controlled trial (RCT) suggested that BoNT reduces pain severity and attack frequency in trigeminal neuralgia (13) and should be considered for patients who cannot tolerate other standard treatments due to toxicities. RCTs also show BoNT can improve pain scores, reduce recovery time, and decrease opioid use in post-herpetic neuralgia (14-15).

**Sialorrhea**  Randomized trials show BoNT injections into salivary glands are beneficial for sialorrhea from many neurologic conditions (CP, amyotrophic lateral sclerosis, Parkinson’s disease, multiple system atrophy, corticobasal degeneration), with results lasting several months (16-18).

**Depression**  Psychotherapy and anti-depressant medications remain the mainstay of depression treatment (see Fast Fact #309), but BoNTs show promise in patients with limited prognoses. Single glabellar region BoNT injections show anti-depressant effects within 2 weeks and lasting 4 months, as demonstrated by several RCTs (19-21).

**Other Uses**  Anecdotally, BoNTs have been used for radiation proctitis pain, chronic pelvic pain, phantom limb pain, chronic regional pain syndrome, multiple sclerosis tremors or spasticity, chronic low back pain, neurogenic bladder, diabetic neuropathy, and speech failure following laryngectomy.
Financial Issues  Cost and insurance coverage can be significant barriers. Medicare often covers BoNTs for non-cosmetic indications with a small co-payment. Private insurance coverage can be variable, leading some patients to require prior authorization and others to pay entirely out of pocket. Depending on the supplier and pharmacy, a single vial of BoNT can cost over $800, which may limit its use in hospice patients.

Risks and Limitations  The diminishing effect of BoTN over months can require repeat injections over time. Depending on injection site, patient age, and tolerance of the procedure, sedation or even general anesthesia may be required, introducing additional risks. Furthermore, there is a lack of large randomized controlled trials for many indications. Although the side effect profile is felt to be low if injected correctly, clinicians should be aware of the following potential adverse reactions, most of which occur within hours to days of the injection, and usually subside after several days (22-24):

- Anaphylaxis or botulism-like systemic reactions: most have occurred in off-label use in children; consequently, the FDA issued a black box warning for all BoNT products in 2009.
- Bruising, edema or pain at the injection site (2-3%)
- Flu-like symptoms (1.7-20%)
- Ptosis or diplopia (2-13%)
- Dry mouth, dysarthria, or dysphagia (2-10%)

References:
23. Keuhn, B. FDA Requires Black Box Warnings on Labeling for Botulinum Toxin Products. JAMA 2009; 301(22):2316.

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