



Botox Update: Emerging FDA Approved Indications and Off-Label Uses

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Botulinum Toxin

- Once mainly known as the source of botulism food poisoning
 - A natural poison found from the soil in decomposing food
 - Produced by the bacterium *Clostridium botulinum*
- 40 million times more power than cyanide
 - Paralyzes muscles throughout body if ingested
 - Causes controlled weakening of the muscles to produce desirable cosmetic and medical effects when injected in tiny doses

Botulinum Toxin

- Commonly recognized as Botox today
 - Best known for its cosmetic indication to diminish frown lines; FDA approved for a number of medical indications
 - Cosmetic and medical indications rely on its ability to block muscle contractions

Botox: An Overview

- Manufactured from type A strain of *Clostridium botulinum*
 - Most researched out of seven different strains (A, B, C, D, E, F, and G)
 - Contains tiny amounts of highly purified botulinum toxin protein refined from the bacterium
- Small injections reduce specific muscle activity by blocking the overactive nerve impulses that trigger excessive muscle contractions or glandular activity

Botox: History and Development Highlights

- **1989:** Originally approved by the FDA for the treatment of strabismus (eye muscle problems) and blepharospasm (abnormal spasm of the eyelids)
- **2002:** Approved for first, and currently only, cosmetic indication—treatment of moderate to severe frown lines between the eyebrows
 - Marketed as Botox cosmetic, with indication-specific dosing
- **2010:** Most recently approved for the prophylaxis of headaches in adults with chronic migraines
- **2011 and beyond:** Studies underway for potential new indications, including treatment of overactive bladder and benign prostatic hyperplasia

Botox: FDA Approved Indications

- **Botox is approved for:**
 - Prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting ≥ 4 hours a day)
 - Treatment of increased muscle stiffness in elbow, wrist, and finger muscles with upper limb spasticity in people ≥ 18 years
 - Treatment of abnormal head position and neck pain that happens with cervical dystonia in people ≥ 16 years
 - Treatment of strabismus or blepharospasm in people ≥ 12 years
 - Treatment of the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when topical medicines do not work well enough in people ≥ 18 years

Botox: FDA Approved Indications

- Botox Cosmetic is approved to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in people 18 to 65 years of age for a short period of time (temporary)

Botox: Not A Permanent Solution

- Whether Botox is used for medical or cosmetic purposes, its effects wear off in a few months
- Repeat injections are an expected part of therapy
- Doses are adjusted according to the patient's weight, the severity of pain, and the amount of muscle being injected
- With regular injections, the muscle may atrophy and lose some of its function, allowing greater time between treatments
- The effects of Botox reverse once injections stop
- Excessive injections may lead to early development of antibodies, making the injections ineffective

Botox: Common Side Effects

- Most common problem: bruising and discomfort
- Other potential side effects include:
 - Itchy rash
 - Swelling
 - Shortness of breath
 - Dry mouth
 - Discomfort or pain at the injection site
 - Tiredness
 - Headache
 - Neck pain
 - Eye problems (double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of eyelids, dry eyes)

Botox: Potentially Serious Side Effects

- Serious, potentially fatal, side effects such as respiratory failure can develop if Botox spreads to other parts of the body from the injection site
 - These are unlikely when Botox is used to treat migraines, blepharospasm or strabismus, frown lines, or severe underarm sweating
- Certain muscle or nerve conditions (ALS, myasthenia gravis, or Lambert-Eaton syndrome) may put patients at increased risk of serious side effects, including severe dysphagia (difficulty swallowing) and respiratory compromise (difficulty breathing), from typical doses of Botox

Off-Label Uses: Definition

- Physicians can prescribe drugs such as Botox for uses other than those approved by the FDA
- Unapproved uses are referred to as “off-label” uses

Off-Label Use of Botox: **Common Unapproved Uses**

- Common off-label uses for Botox include treatment of:
 - Facial tics (dystonia and hemifacial spasms), voice disorders (spasmodic dysphonia, a type of focal dystonia, and stuttering), urinary incontinence, piriformis syndrome, thoracic outlet syndrome, Parkinson's disease, myofascial pain syndrome, ischemic digits
- Botox is also widely prescribed for off-label treatment of cerebral palsy in children and cramping and muscle spasm in adults
 - Doses hundreds of times greater than the approved doses are injected into the body to control involuntary muscle movements

Off-Label Use of Botox Cosmetic: Common Unapproved Uses

- Off-label uses of Botox Cosmetic include injection on:
 - Wrinkled forehead
 - Crow's feet
 - Lip area
 - Bands in the neck
- These applications expose patients to higher doses of the drug than those in the studies that led to FDA approval

Off-Label Use of Drugs: Scientific Evidence Is Limited

- Some drugs have solid scientific evidence to support off-label uses, but the majority do not
- Available data are usually placebo-controlled or case series data; not from trials with active comparators
- Without adequate safety and efficacy data, there is risk for adverse outcomes that could result in devastating complications and legal action
- Physicians must explain and document:
 - The rationale for the therapy
 - The risk that patients are taking of unknown and unanticipated side effects
 - The lack of proven efficacy data for the off-label uses

Off-Label Use of Botox: Potential Risks to Patients

- Off-label use of Botox in the treatment of spasticity associated with cerebral palsy in children has been linked to serious medical problems, including hospitalization and death
- Problems can arise when high doses of Botox move from the injection site and affect other areas of the body, causing interference with vital bodily functions such as breathing and swallowing (similar to botulism poisoning)
- The spread of toxin to other body sites is not a danger when Botox is used at approved doses for cosmetic purposes

Botox: Black Box Warning

- Many adults and children who received off-label Botox treatments suffered from debilitating complications and death
- The FDA now requires black box labeling on Botox and similar products
 - The warning highlights the risks of Botox side effects causing respiratory failure and even death
- A black box warning is the strongest warning issued by the FDA

Off-Label Use of Drugs: Legal Issues

- Off-label prescribing is not restricted by law and is supported by the American Medical Association
- About 20% of all medications prescribed for adults are for off-label purposes
- Off-label use of prescriptions for children is closer to 50% to 97%
- FDA guidelines allow pharmaceutical companies to tell doctors about unapproved uses of their medicines and to distribute copies of medical journal articles that describe unapproved uses
- Drug companies cannot legally market unapproved uses of medications

Radley et al. *Arch Intern Med.* 2006;166:1021-1026.
Roberts et al. *JAMA.* 2003;290:905-911.

Company Promoted Off-Label Use of Botox: \$600 Million Settlement Reached in 2010

- Several whistleblower suits were filed against Allergan alleging that its promotion of off-label drug uses caused false claims to be submitted to government healthcare programs
- The company reached a \$600 million settlement with the U.S. Department of Justice (DOJ) to settle charges that it illegally promoted off-label uses for Botox
- The company agreed to admit that between 2000 to 2005, it marketed Botox for the therapeutic treatment of headache, pain, spasticity, and juvenile cerebral palsy, which were not among the FDA's approved uses for the drug

Man Suffers Brain Damage After Off-Label Use of Botox: **Awarded \$212 Million in 2011**

- The patient, who received off-label Botox treatments for hand tremors and writer's cramp, alleged that:
 - Botox treatments triggered an autoimmune disease that ultimately led to permanent brain damage
 - Allergan failed to adequately warn his physician about the potential risks of Botox for off-label use
- A Virginia federal jury awarded him \$212 million
 - \$12 million in compensatory damages and \$200 million in punitive damages
 - Largest penalty ever in a Botox injury case

Independent Medical Review: **Facilitates Determination of Medical Necessity**

- The versatility of Botox for both cosmetic and medical conditions complicates the process of establishing evidence-based criteria for practice guidelines and reimbursement for treatment
- Independent medical review looks at whether or not a specific procedure was medically necessary

Botox Plan Exclusions:

Cosmetic vs. Medically Necessary Treatment

- Most healthcare plans will not pay reimbursement for uses not approved by the FDA
- Insurance coverage varies for Botox injections, depending largely on the medical necessity that the patient's condition presents
- Botox is generally not covered by insurance when used for cosmetic purposes

The Role of Independent Medical Review in Determining Medical Necessity

- Allows access to a range of board-certified physician specialists who keep up-to-date with the latest medical research literature and with the latest standard of care
- Provides specialty match to allow healthcare plans to ensure that the requested treatment falls under the medical necessity requirements before approving a course of treatment
 - Reviewers stay on top of treatments as they are studied more extensively and potentially accepted into clinical guidelines
- Avoids conflicts of interest, which can relate to economics, lack of specialists to review cases, or having the same doctor who denied a case review an appeal

The Specialty Match: **Critical for Evaluating Off-Label Drug Use**

- Assesses the potential risks, complications, and contraindications of a treatment
- Investigates the acceptance of a proposed off-label use within the medical community
- Determines whether the off-label use meets the latest standard of care

Conclusions

- Botox is probably best known for its cosmetic indication, but it is also approved for numerous medical conditions
- Botox is often prescribed for off-label uses
- Healthcare plans face the challenge of keeping up with emerging data, indications, and standard of care
- External independent medical review:
 - Provides ready access to board-certified specialists, which healthcare plans may lack internally
 - Allows timely unbiased determinations of whether the requested treatment falls under medical necessity guidelines
 - Facilitates safe and effective use of Botox

Questions and Answers

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