

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

For Health Plans, Medical Management Organizations and TPAs

Executive Summary

Botox belongs to a class of drugs called botulinum toxins, which are derived from the bacterium *Clostridium botulinum*. Although there are seven different types of botulinum toxin, most research has focused on type A, which is manufactured as Botox.

Since 1989, the U.S. Food and Drug Administration (FDA) has approved Botox for a number of medical indications, such as treatment of strabismus and blepharoplasty. The most recent approval, in 2010, was for prophylaxis of headaches in adults with chronic migraine. The only approved cosmetic use of Botox is for treatment of moderate to severe frown lines between the eyebrows.

Although Botox is also widely used off label to treat conditions other than those it was approved for by the FDA, it has been linked to serious medical problems, including hospitalization and death. These serious side effects are unlikely to occur when Botox is used for FDA approved indications.

Healthcare plans, which generally do not cover off-label and cosmetic uses of Botox, face the challenge of keeping up with emerging data and indications, as well as the latest standard of care.

The FDA has approved Botox for a wide range of indications since its introduction in 1989, when it was originally approved for the treatment of strabismus (eye muscle problems) and blepharospasm (abnormal spasm of the eyelids).

Independent medical review facilitates the evaluation of medical need for Botox treatment by providing ready access to specialists who have an in-depth understanding of the variety of applications for the drug, the potential risks and complications, the status of current indications and off-label uses, the latest medical research literature, and the most current standard of care.

Introduction

Botulinum toxin was once mainly known as the source of botulism food poisoning. Produced by the bacterium *Clostridium botulinum*, the toxin is a natural poison from the soil found in decomposing food and is 40 million times more powerful than cyanide. If ingested, it can paralyze muscles throughout the body, including those that control breathing. However, when injected in tiny doses, it can cause controlled weakening of the muscles to produce desirable cosmetic and medical effects.

Today, botulinum toxin is commonly recognized as Botox, which is probably best known for its cosmetic indication to diminish frown lines. However, the U.S. Food and Drug Administration (FDA) has also approved it for a number of medical indications. Both its cosmetic and medical uses rely on Botox's ability to block muscle contractions.

Botox Overview

History and Development

Out of seven different types of botulinum toxin produced by different strains of the *Clostridium botulinum* (A, B, C, D, E, F, and G), most research has focused on type A, which is manufactured as Botox. Botox contains tiny amounts of the highly purified botulinum toxin protein refined from the bacterium. The product is administered in small injections to reduce specific muscle activity by blocking the overactive nerve impulses that trigger excessive muscle contractions or glandular activity.

The FDA has approved Botox for a wide range of indications since its introduction in 1989, when it was originally approved for the treatment of strabismus (eye muscle problems) and blepharospasm (abnormal spasm of the eyelids). In 2002, it was approved for cosmetic treatment of moderate to severe frown lines between the eyebrows (glabellar lines) and marketed as Botox Cosmetic for this use, with dosing specific to treat frown lines. The most recent indication for Botox was announced in late 2010, when the FDA approved Botox for the prophylaxis of headaches in adults with chronic migraine.

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A number of studies are underway for potential new indications, including treatment of overactive bladder and benign prostatic hyperplasia.

FDA Approved Indications

Botox is a prescription medicine that is injected into muscles. The FDA has approved it for:

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

Botox Cosmetic is a prescription medicine that is injected into muscles and used 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).

Whether Botox is used for medical or cosmetic purposes, its effects usually wear off in a few months, making repeat injections 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, so the time between treatments may increase. The effects of Botox reverse once the injections stop, but excessive injections may lead to early development of antibodies and make the injections ineffective.

Potential Side Effects

If Botox is injected and spreads to other parts of the body, it can cause serious, possibly fatal, side effects, such as respi-

ratory failure. However, such serious side effects are very unlikely when Botox is used to treat migraines, blepharospasm or strabismus, frown lines, or severe underarm sweating.

The most common problem is bruising and discomfort for a few days. Other potential side effects include itchy rash, swelling, shortness of breath, dry mouth, discomfort or pain at the injection site, tiredness, headache, neck pain, and eye problems (double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of eyelids, and dry eyes)

Certain muscle or nerve conditions, such as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), 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 Use of Botox

Common Unapproved Uses

Physicians can prescribe drugs such as Botox for uses other than those approved by the FDA; these unapproved uses are referred to as "off-label" 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, tremor, Parkinson's disease, myofascial pain syndrome, and ischemic digits.

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Botox is also now widely prescribed for off-label treatment of cerebral palsy in children and cramping and muscle spasms in adults. Doses of Botox hundreds of times greater than the approved doses are injected into the body to control involuntary muscle movements in cerebral palsy patients and individuals suffering from cramping and muscle spasms.

Off-label uses of Botox Cosmetic include injection on the wrinkled forehead, crow's feet, the lip area, and bands in the neck. These applications expose patients to higher doses of the drug than those in the studies that led to FDA approval

Scientific Evidence to Support Off-Label Use Is Limited

Although some drugs have solid scientific evidence to support off-label uses, the majority of them do not. When data are available, they are usually placebo-controlled or case series data and 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. Therefore, physicians must explain and document the rationale for the therapy, the risk that patients are taking of unknown and unanticipated side effects, and the lack of proven efficacy data for the off-label uses.

Potential Risks to Patients

Off-label use of Botox in the treatment of limb 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, including the lungs, throat, and even the brain. Side effects from the spread of Botox throughout the body can cause interference with vital bodily functions, including breathing

and swallowing. These Botox side effects are 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.

The FDA now requires black box labeling on Botox and similar products after receiving many reports of adults and children who received off-label Botox treatments suffering from debilitating complications and death. 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.

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.

Legal Issues

Off-label prescribing is not restricted by law and is supported by the American Medical Association. According to research from Stanford University and the Institute of Medicine, about 20% of all medications prescribed for adults are for off-label purposes. The Institute also estimates that the off-label use of prescriptions for children is closer to 50% to 75%.

Under FDA guidelines, pharmaceutical companies can tell doctors about unapproved uses of their medicines and can distribute copies of medical journal articles that describe unapproved uses. However, drug companies cannot legally market unapproved uses of medications.

In 2010, Allergan 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 settlement resolves a DOJ investigation of Allergan's marketing practices after several whistleblower suits were filed against the company alleging that its promotion of off-label drug uses caused false claims to be submitted to government healthcare programs. Allergan 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.

Earlier this year, a Virginia federal jury awarded \$212 million to a man who alleged that Botox treatments triggered an autoimmune disease that ultimately led to permanent brain damage and that Allergan failed to adequately warn his physician about the potential risks of Botox for off-label use. The man had received off-label Botox treatments for hand tremors and writer's cramp, and is now unable to care for himself independently. The verdict awarded the man \$12 million in compensatory damages and \$200 million in punitive damages, the largest penalty ever in a Botox injury case.

Role of External Independent Medical Review

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. An independent medical review, which is normally used by healthcare payers, looks at whether or not a specific procedure was medically necessary.

The board-certified physician specialists who work with independent review organizations keep up-to-date with the latest medical research literature and with the latest standard of care. These specialists allow healthcare plans to make sure that the requested procedures fall under the medical necessity requirements before approving a course of treat-

ment.

Physicians who review cases for independent review organizations stay on top of treatments as they are studied more extensively and potentially accepted into clinical guidelines. The specialty match that independent review organizations provide is especially important in: assessing the potential risks, complications, and contraindications of a treatment; investigating the acceptance of a proposed off-label use within the medical community; and determining whether the off-label use meets the latest standard of care.

Independent medical review also 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.

Conclusions

Botox is probably best known for its cosmetic indication to diminish frown lines, but the FDA has also approved it for numerous other indications, most recently for prophylaxis of headaches in adults with chronic migraine. Although drug manufacturers cannot legally market a drug's unapproved, or off-label, uses, Botox is often prescribed for uses that are not approved by the FDA. Since most healthcare plans do not reimburse for off-label use of Botox, they face the challenge of keeping up with emerging data and indications, as well as the latest standard of care for patients who seek treatment with Botox.

External independent medical review facilitates safe and effective use of Botox by providing unbiased evaluation of the appropriate use of the drug, which has numerous cosmetic and medical applications and clinical trials underway for potential new indications. Independent medical review also provides ready access to specialists, which healthcare plans may lack internally, allowing for timely determination of whether the requested treatment falls under medical necessity guidelines.

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