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In the 2002 movie “My Big, Fat Greek Wedding,” the bride’s father is said to believe that Windex cleaning fluid can cure “every ailment from psoriasis to poison ivy.” Half a dozen years later, Botox seems to have become the new Windex, touted as a “cure-all” for everything from wrinkles and excessive perspiration to chronic pain, asthma, and migraine.

Botox has become one of the most popular medications on the market, attracting the attention of patients and the medical community alike. A recent New York Times article noted that doctors performed more than 4.6 million Botox treatments last year, nearly a 500 percent increase over 2000 (“Dr. A-List Can See You Now,” New York Times, June 19, 2008).

Botox is a trade name of botulinum neurotoxin (BoNT) type A, which belongs to the group of neurotoxins produced by the bacterium *clostridium botulinum*. BoNTs are highly purified, naturally occurring proteins that have the ability to relax the muscles and block the release of different bioactive substances responsible for pain and inflammation. Though highly toxic, BoNTs in small doses are

Botox comes of age

New applications, but experience is key

By Elena Polukhin, MD, PhD

highly effective and safe in medications and as cosmetic agents.

From sausage to medical use

Around 1820, German physician Justinus Kerner described botulinum toxin as “sausage poison” because the bacterium grew in poorly stored or mishandled meat products, causing poisoning. He was the first physician who realized a possible therapeutic use of botulinum toxin. In 1870, Hans Muller, another German physician, coined the name “botulism,” from the Latin word *botulus*, meaning sausage.

In the 1940s, scientists cultured *clostridium botulinum* and isolated the toxin, ushering in decades of extensive studies to clarify the exact mechanism of action and clinical applications of botulinum neurotoxins. Around 1950, researchers discovered that injecting overactive muscles with minute quantities of botulinum toxin type A decreased muscle contraction by blocking the release of acetylcholine at the neuromuscular

junction, rendering the muscle unable to contract for a period of four to six months. Later investigations demonstrated that botulinum neurotoxins are able to block the release of not only muscle movement mediators, but also pain hormones and other substances responsible for excessive sweating, skin oiliness, and even depression.

Current medical applications

In December 1989, the U.S. Food and Drug Administration (FDA) approved Botox exclusively for treatment of conditions such as strabismus (crossed eyes), blepharospasm (uncontrollable blinking), and hemifacial spasm in patients over 12 years of age. Since then, Botox injection has become an almost routine procedure in ophthalmologic offices around the country.

Soon after, Botox began to be used to relieve excessive muscle tone in patients with neurological disorders such as stroke, cerebral palsy, and multiple sclerosis. Today, Botox injections may

be recommended for a variety of additional medical conditions, including excessive underarm sweating, muscle spasms, pain disorders, headaches (including migraine), prostatic symptoms, asthma, obesity, and arthritis.

In addition, Botox is used for cosmetic purposes. The cosmetic effects of BoNT have been observed concurrently by a number of independent groups. As a result of these studies, on April 15, 2002, the FDA approved the use of botulinum toxin type A (Botox Cosmetic) to temporarily improve the appearance of moderate-to-severe frown lines between the eyebrows (glabellar lines).

Today, it is generally agreed in the medical community that Botox remains the gold standard for smoothing wrinkles and fine lines. Many doctors prefer to start in-office cosmetic practice with Botox, a simple procedure that is highly effective and not overly expensive (approximately \$200–\$500, depending on the amount of medication injected).

Botox is manufactured by U.S.-based Allergan, Inc., for both therapeutic and cosmetic use. Dysport, a therapeutic formulation of the type A toxin that was developed and is manufactured in Ireland, is licensed for the

treatment of focal dystonias and certain cosmetic uses in many countries worldwide. However, Dysport is not licensed in the United States. Neuronox, a new type A toxin manufactured by Medy-Tox Inc., in South Korea, is approved for use in the U.S. The only type B BoNT, Myobloc, has a slightly different molecular structure; it is produced by U.S. pharmaceutical company Solstice.

How BoNT injections work

Regardless of the serotype or manufacturer, all BoNTs have a similar mechanism of action: They block the release of chemical mediators responsible for muscle movements and temporarily paralyze muscles. The words "paralysis" and "toxins" have caused misunderstanding and fears about BoNT products. Scientific research and everyday clinic practice have shown that BoNTs are safe and effective medications in experienced hands. Doses used for cosmetic and medical procedures are extremely minute. In fact, the dosage is so limited that the possibility of poisoning does not exist.

In addition, studies have shown that the neuroblock muscle immobilization is temporary and reversible. The usual action of Botox or other BoNTs lasts for only a few months and is reversible. There is no permanent damage to the skin or muscle as a result of Botox injections. Patients can stop Botox treatments at any time and be confident that they will gradually return to pre-treatment appearance.

Injection procedure.

Technically, Botox injections have limited FDA approval, but most doctors use it off-label, i.e., without FDA approval for a particular condition. Each injection depends on the type of procedure. For example, for treatment of spastic muscles,

BoNT is injected inside the muscle with guidance from an electrostimulating device. It is important that the physician inject medications inside the most spastic muscles and not inside the fat tissue.

There are several injection techniques for treatment of chronic headaches and facial wrinkles. Most clinicians inject Botox in the forehead and around the eyes. However, this technique frequently causes face distortion and uneven light reflection, resulting in distortion in facial expressions.

In my practice, using relatively small doses of Botox (not more than 30 units at once) diluted in 2–4 cc of Lidocaine, I inject the whole face and neck, not only the separate parts of the face. This technique is not overly expensive, never causes eyebrow droop, and creates a diffuse skin glow all over the face and neck. In addition, this technique can lead to better headache control, mood stabilization, improved sleep, and neck muscle relaxation. No sedation is required, so patients are able to continue with all usual activities immediately after treatment.

Length of procedure.

The BoNT injection procedure is relatively short and simple; the whole procedure, including skin cleansing and numbing, takes about 10 to 15 minutes. The treated muscles usually start to relax within a day or two and reach the maximum degree of relaxation within seven to 14 days. However, most patients experience the benefit of BoNT immediately after the procedure. The effect of Botox starts to wear off after approximately 12 to 14 weeks; patients can return to the clinic for a second injection before the Botox has completely worn off.

Common side effects.

Broadly speaking, there are

two major types of side effects: paralysis of the wrong muscle group and allergic reaction. After the treatment, the patient might complain of inappropriate facial expression, such as a drooping eyelid, uneven smile, or inability to close an eye. These side effects wear off in about six weeks. Bruising at the site of injection is another, rather rare side effect, usually a result of inexperienced injectors. Clinicians can prevent this side effect by applying pressure to the injection site. Bruising usually lasts about seven to 10 days. In addition, some patients experience difficult chewing and dry mouth. This occurs as a result of injecting the masseter muscle of the jaw and usually requires no treatment. The effect may last as long as six weeks. Other reported adverse effects from cosmetic injection include headaches, temporary facial paralysis, muscle weakness, difficulty swallowing, flu-like symptoms, and allergic reactions.

How safe is BoNT treatment?

In September 2005, a study published in the *Journal of the American Academy of Dermatology* quoted an FDA analysis that the use of Botox had resulted in 28 deaths between 1989 and 2003; none were attributed to cosmetic use. In February 2008, the FDA announced that Botox had "been linked in some cases to adverse reactions, including respiratory failure and death, following treatment of a variety of conditions using a wide range of doses," due to its ability to spread to areas distant to the site of the injection. The non-profit consumer advocacy group Public Citizen has petitioned the FDA requesting regulatory action concerning the possible spread of botulinum toxin (Botox,

Myobloc) from the site of injection to other parts of the body (HRG Publication #1834, Public Citizen).

Based on careful analysis of the reported cases and my personal experience of nearly 20 years, I consider BoNT to be one of the safest and most reliable medications when applied by experienced hands. Though BoNT is a powerful weapon in the physician's armamentarium, using it well requires many years of training and education. Once a qualified physician understands the intricacies of the procedure and the need for extreme precision, the procedure is easy, quick, and, most importantly, beneficial to the patient.

This is not to say that medical concerns over Botox use are without merit. Indeed, we have seen a recent trend in trained medical professionals, or even individuals without any medical background, injecting Botox in spas and tanning salons, leading to horrific results. These unacceptable and dangerous procedures have created public fears and physician frustration, and have led to defamation of an excellent medication. Patients planning to undergo a professional Botox injection need to make sure that their physician has adequate experience and expertise in this procedure.

After many years of clinical and academic practice trying different medications for pain control and in-office cosmetics, I believe that we are at the beginning of a new era of BoNT use. Further research and safety precautions are required, but the potential future applications look very promising. ❑

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