Botulinum Neurotoxin

Your Questions Answered
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Disclaimer
This information is not intended to take the place of professional medical advice. If you are a patient currently being treated and have questions or if you think you have a movement disorder that has not been diagnosed, please seek the advice of your medical professional. This information does not replace and does not obviate the need for consultation with your physician.
Clostridium botulinum is a type of bacteria that produces spores. These spores are everywhere in our environment—in the soil and on the ocean floor, on fruits and vegetables, and on seafood. These tiny spores aren’t visible to the human eye and, in the right conditions, they produce a poisonous protein, called a toxin. Because this toxin affects the nervous system, it’s called a neurotoxin.

What Is Botulinum Neurotoxin?

If you eat even a small amount of botulinum neurotoxin (BoNT), you may develop botulism, a severe and sometimes fatal form of food poisoning. Many years ago, botulism was more common. Now, however, we know to cook our foods at high temperatures and store them properly, to wash our fruits and vegetables before eating them, to never eat food from a can that is bulging, and to carefully control the way we can foods at home.

Botulinum spores can also infect an open sore and release toxins, again causing botulism. Babies develop a specific kind of botulism in which they actually ingest the spores, which then break down in the babies’ intestines and produce toxin. Babies who have infantile botulism don’t feed well, have a weak cry and lax muscles, and seem to be very tired.

BoNT—a Substance That Can Improve Quality of Life

In the 1950s, scientists discovered that injecting tiny amounts of purified BoNT into the neuromuscular junction causes the muscle to not be able to move. That is, it paralyzes the muscle. In the 1970s, a scientist experimented with BoNT type-A (see a later section for more information on the different types of BoNT) in animals and, in 1980, used a form of BoNT type-A for the first time to treat crossed eyes (strabismus) in a person. After scientists completed more research, the US Food and Drug Administration (FDA) approved the use of one form of BoNT type-A, originally called Oculinum (this same substance is now called onabotulinumtoxinA or Botox) for the treatment of strabismus and blepharospasm in 1989. The FDA also approved the use of onabotulinumtoxinA for the treatment of cervical dystonia in 2000, and for the treatment of spasticity in the flexor muscles of the elbow, wrist, and fingers in 2010.
In 2000, the FDA approved the use of a form of BoNT type-B as rimabotulinumtoxinB (or Myobloc) for the treatment of cervical dystonia. Since then, the FDA has approved two other forms of BoNT type-A. AbobotulinumtoxinA, or Dysport, was approved in 2009 for the treatment of cervical dystonia. And, in 2010, the FDA approved the use of incobotulinumtoxinA, or Xeomin, for the treatment of cervical dystonia and blepharospasm.

Although the FDA has not approved the use of BoNT for the treatment of other movement disorders, doctors often use BoNT to treat muscle overactivity in patients with

- Limb dystonia (such as dystonia of the hand or foot)
- Spasmodic dysphonia (dystonia in the vocal cords)
- Spasticity related to stroke, cerebral palsy, traumatic brain injury, spinal cord injury, or multiple sclerosis in areas of the body other than the elbow, wrist, and fingers.

**How Does BoNT Work in Movement Disorders?**

**Normal Muscle Contraction**

Nerve cells (or neurons) and muscle cells come close together and communicate at sites called neuromuscular junctions. A very small space or gap (called the synapse or synaptic cleft) separates the endings of neurons (called terminals) and muscles cells at the neuromuscular junction. To relay their signal—telling the muscle to move or contract—neurons produce messages in the form of special chemicals to “jump” that gap. These special chemicals are called neurotransmitters.

Nerve terminals contain small pouches (or vesicles) filled with a specific neurotransmitter, acetylcholine. To move these tiny acetylcholine-filled vesicles from inside the neuron into the synapse, a very complicated process takes place that is controlled by three proteins that make up the SNARE protein complex. This complex acts as a “hook” to snatch the vesicles and pull them close to the cell wall, where the vesicles “dock” and blend or fuse with the cell wall. To understand this a little more clearly, picture a bubble rising from beneath the surface of a pot of boiling water. The bubble rises up, fuses with the surface of the water, pushes through to the surface, and eventually pops. In this same way, the acetylcholine-filled vesicle fuses with the surface of the cell wall of the neuron, becomes incorporated into the cell wall, and then “pops out” the other side into the synapse. Once the acetylcholine is released from the neuron, it crosses the synapse and binds to an acetylcholine receptor on the muscle. The acetylcholine attaches to the receptor, and a series of chemical reactions take place that cause the muscle to contract.

**The Effects of BoNT on Muscle Contraction**

BoNT binds to the wall of the nerve terminal at the neuromuscular junction and is incorporated into the neuron—the reverse of the way in which the acetylcholine is released. The “bubble” of BoNT fuses with the cell wall and “pops” through the wall into the neuron. This is true not only in
botulism, but also when doctors inject tiny doses of purified BoNT into the neuromuscular junction to treat the overactive muscles of a movement disorder. Once the toxin enters the neuron, it blocks the release of acetylcholine from the neuron by interfering with one of the three SNARE proteins that is involved with the fusion process. Without the release of the acetylcholine, the signal is blocked between the neuron and the muscle, and the muscle cannot contract—it is paralyzed. By cutting or cleaving a protein product, the BoNT enzyme interferes with the building of the SNARE protein complex. Without the SNARE protein complex, there’s no hook to “grab” the acetylcholine, the acetylcholine can’t fuse with the wall of the neuron, and thus, the acetylcholine isn’t released into the synaptic cleft. Without a signal from the neuron, the muscle is paralyzed.

In the case of injection of an overactive muscle of a person with a movement disorder, this paralysis usually begins about two to four weeks after the BoNT injection takes place. In about three months, the normal release of acetylcholine begins to return, with the muscle beginning to return to its previous activity level. This return to previous activity is usually complete in about six months.

**Are There Different Types of BoNT?**

The different serotypes of BoNT contain enzymes that are specific to that type of BoNT. The enzymes act on one of the three proteins that make up the SNARE complex. Only a few of these strains of BoNT have been purified and are being used for medical treatments. As mentioned previously, in the US, the FDA has approved the use of only abobotulinumtoxinA, incobotulinumtoxinA, onabotulinumtoxinA, and rimabotulinumtoxinB.

**What Are the Differences Between the Various Types of BoNT?**

The different forms of commercially available BoNT are not interchangeable. This is a very important statement to understand. The dose units and the amount of toxin are different in each of these products. This means that one unit of abobotulinumtoxinA is not the same as one unit of onabotulinumtoxinA or rimabotulinumtoxinB and vice versa.

BoNT acts on not only the communication between nerve and muscle cells, but also on the cholinergic neurons of the autonomic nervous system. The targets of cholinergic neurons in the autonomic nervous system include the heart, smooth muscle (such as the bladder, intestine, and others) and glands (including glands that make sweat, saliva, and tears and the adrenal glands). The effects of cholinergic stimulation on these various sites account for the paralysis associated with exposure to BoNT—either accidentally through botulism or purposefully with injections of purified BoNT. The effects also include a slowing of the heart rate, decrease in the movement of food through the intestines, dry eyes and mouth, blurred and double vision, and swallowing difficulty, among others. Some of the differences in the types of BoNT may be related to their effects on the autonomic nervous system.
Are BoNT Injections Safe?
Many thousands if not millions of people worldwide have been safely treated with BoNT injections in the past 20 years since BoNT was first approved for use in medical conditions. In 2008, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology reviewed all of the published studies on the use of BoNT in patients with movement disorders and spasticity and determined that BoNT is safe and effective in the treatment of spasticity in children and adults and the treatment of cervical dystonia in adults. In addition, the Subcommittee found that BoNT injections are probably effective in the treatment of blepharospasm, adductor-type spasmodic dysphonia, and essential tremor and possibly effective in treating hemifacial spasm and motor tics. They did not have enough evidence to draw a conclusion regarding abductor-type spasmodic dysphonia or focal limb dystonia. The Subcommittee did not comment on the different serotypes or formulations of BoNT.

Side effects associated with the use of BoNT injections may occur within hours or may not appear until weeks later. It’s important for you to keep in mind the possible side effects. If you develop muscle weakness, blurred vision, or drooping eyelids, you should not drive a car or operate any other motor vehicle, and you should avoid engaging in any other potentially hazardous activities.

In patients treated with BoNT for cervical dystonia, additional side effects include hoarseness, difficulty swallowing, and aspiration (food or liquids that enter the lungs instead of the stomach). In patients treated with BoNT for spasmodic dysphonia, the most commonly reported side effects are breathiness, trouble swallowing, stridor, and aspiration for a few days to weeks after the injection. In patients treated with BoNT for spasticity, additional side effects may include fever and difficulty controlling the bladder.

In 2009, the FDA began requiring a warning on all BoNT products sold in the US. This warning says, “The effects of all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.”

The FDA encourages everyone who receives BoNT injections or who provides care for someone who receives BoNT injections to do the following:

- Review the Medication Guide accompanying BoNT products.
- Discuss any concerns you may have about the risks and benefits of these products with a healthcare professional.
- Pay close attention for the development of any side effects. Seek immediate medical attention if you have unexpected difficulty swallowing or talking, trouble breathing, or muscle weakness following treatment with a BoNT product.

Common Side Effects Associated with the Use of BoNT

- Pain or bruising at the injection site
- Dry mouth
- Blurred or double vision
- Droopy eyelids
- Flu-like symptoms
- Muscle weakness in nontargeted muscles
- More than the desired amount of weakness in the targeted muscles
In addition, the FDA requires that all manufacturers of BoNT products have in place a Risk Evaluation and Mitigation Strategy (REMS). A REMS is a type of safety plan that is required when the FDA approves certain potentially dangerous drugs or biologic products or when new information becomes available about drugs or biologic products that have been previously approved. These drugs or biologic products can offer great benefit, but their use may be associated with known or potential serious risks. This safety plan is put in place to help guarantee that healthcare professionals prescribe the drug safely and that patients use it safely or, in the case of BoNT, that physicians use the toxin appropriately.

**How Long Do the Effects of BoNT Treatment Last?**

Injections of BoNT typically last from eight to 12 weeks, depending on the type of movement disorder that is being treated, the muscle that is injected, and the amount of BoNT that is injected. The injections may last slightly longer or shorter. Researchers and clinicians have found that repeated BoNT treatment remains effective in most people for many years.

**What Is the Role of Antibodies in BoNT Treatment?**

Some individuals treated with BoNT may develop antibodies, which bind to the toxin and inactivate it. Your body recognizes anything that’s not a part of itself as a foreign substance, or antigen, and tries to isolate or expel the antigen. Every day, your body launches immune responses many, many times to protect you from these antigens—bacteria, viruses, toxins, pollen, dander, parasites, molds, mildew, and other foreign substances that are constantly bombarding you.

Because your body recognizes anything that is not a part of itself as an antigen, it views BoNT that you receive as injections for the treatment of a movement disorder as an antigen. You may develop antibodies to the neurotoxin. Some, but not all, antibodies render the BoNT incapable of accomplishing its intended task—to relieve the tight muscles of your blepharospasm, dystonia, spasticity, spasmodic dysphonia, or other movement disorder. These antibodies are called neutralizing antibodies, and the phenomenon is known as immunoresistance.

Recent studies have shown that fewer than 1% of people treated with onabotulinumtoxinA will develop neutralizing antibodies; the rate of immunoresistance in people treated with rimabotulinumtoxinB or abobotulinumtoxinA is unknown. The rate of immunoresistance is higher in people whose treatment requires the injection of larger muscles, for example, those with cervical dystonia, as opposed to people with blepharospasm or spasmodic dysphonia, which involves injection of very small muscles.
How likely you are to develop immunoresistance depends on a number of factors, including

- The type and purity of the BoNT
- The cumulative dose of BoNT, that is the total amount of BoNT that you have ever received
- How often you receive BoNT injections
- Your genetic make-up
- Whether you have developed immunoresistance to another serotype of BoNT

To test for immunoresistance, your doctor can send a sample of your blood to a laboratory to be tested for blocking antibodies. Another option is to inject BoNT into a muscle in your one side of your forehead or neck or into one arm. If, within one to two weeks, there is no difference between the side that was injected with BoNT and the side that was not injected, you likely have developed immunoresistance.

To decrease the likelihood that you will develop immunoresistance, your doctor will want to

- Use the smallest possible effective dose of BoNT
- Extend the time between injections sessions to at least three months if possible
- Avoid the use of booster injections (which are small injections given earlier than 3 months)

**What Should I Tell My Doctor When I Have BoNT Injections?**

Tell your doctor if you

- Have had a change or worsening of your movement disorder since your last visit.
- Think you are allergic to any of the ingredients contained in the form of BoNT that you will be receiving.
- Have had any unusual reactions such as skin rash or flu-like symptoms to any injections of BoNT in the past.
- Have a history of bronchitis, pneumonia, or breathing problems
- Have ever had any prolonged periods of muscle weakness for any reason.

If you receive or a family member receives BoNT injections and begins having problems with speech, swallowing, or breathing, contact your doctor immediately or go to the closest emergency department.
GLOSSARY

Acetylcholine: Acetylcholine is a neurotransmitter that is present at neuromuscular junction cells and various sites of the central nervous system. Primary functions of acetylcholine include regulating the delivery of messages from neurons to skeletal muscle fibers, smooth (involuntary) muscle fibers, and organs and glands, as well as between nerve cells in the brain and spinal cord. Acetylcholine also dilates blood vessels and triggers certain actions such as lowering blood pressure and slowing heart and breathing rates.

Antibodies: Antibodies are proteins in the blood or other bodily fluids that the immune system uses to identify and dispose of foreign substances, such as viruses, bacteria, toxins, or other substances, that enter the body.

Antigen: An antigen is a substance that prompts the generation of antibodies and can cause an immune response.

Autonomic nervous system: The autonomic nervous system controls most of the involuntary reflexive activities of the human body. The system is constantly working to regulate the glands and many of the smooth muscles of the body through the release or uptake of the neurotransmitters acetylcholine and norepinephrine.

The autonomic nervous system is made up of two primary parts: the sympathetic and parasympathetic systems. The sympathetic nervous system prepares the body for emergencies or times of stress and is responsible for the body's "fight or flight" response when faced with a dangerous situation. During this response, the heart rate and blood pressure increase, the pupils of the eye dilate, and the digestive system slows down. The parasympathetic nervous system helps the body's functions return to normal after they have been stimulated by the sympathetic nervous system and also has some responsibility for keeping the body's immune system properly functioning.

Blepharospasm: Blepharospasm is a type of dystonia that causes involuntary spasms and closure of the eyelid.

Botulism: Botulism comes from the Latin word for sausage. This is because, in the 1800s, scientists discovered that an often-fatal form of food poisoning was caused by tainted blood sausages. We now know that botulism, which is caused by Clostridium botulinum, can also be caused by infection of open wounds or in babies who swallow botulinum spores. Botulism causes paralysis, speech and swallowing problems, and vision disturbances.

Cervical dystonia: Cervical dystonia is the most common form of focal dystonia. It is characterized by abnormal tightening and twisting of muscles in the head and neck. These ongoing muscle contractions result in abnormal positions or posturing. Almost all of the movements share a directional quality. Movements may be prolonged or occur in an instant.

Cholinergic neurons: Cholinergic neurons are nerve cells in which acetylcholine is the neurotransmitter responsible for sending information between nerve cells, between nerves and muscles, or between nerves and glands.
**Dystonia**: Dystonia is a neurologic movement disorder characterized by sustained muscle contractions, resulting in repetitive, involuntary, twisting or writhing movements and unusual postures or positioning. Dystonia may be limited to specific muscle groups (focal dystonia), such as dystonia affecting muscles of the neck (cervical dystonia) or the eyes, resulting in closure of the eyelids (blepharospasm). Dystonia is associated with certain underlying genetic disorders, such as dystonia musculorum deformans, dopa-responsive dystonia, and paroxysmal kinesigenic and paroxysmal non-kinesigenic dystonic choreathetosis. The condition may also result from the use of certain medications, lack of oxygen during or immediately after birth, or other causes of brain trauma.

**Enzyme**: An enzyme is a protein produced by cells that speeds up the rate of or "catalyzes" a specific chemical reaction in the body without being permanently changed in the process. A chemical substance that is acted upon by an enzyme is called a *substrate*. In many cases, enzymes are named by adding the suffix *-ase* to the name of the substrate upon which the enzyme exerts its action.

**Food and Drug Administration**: The United States Food and Drug Administration is a federal agency charged with ensuring that the food supply in the United States is safe and wholesome, that cosmetics are not harmful, and that medicines, medical devices, and radiation-emitting consumer products are safe and effective.

**Hemifacial spasm**: Hemifacial spasm is a neuromuscular disorder characterized by frequent involuntary contractions (spasms) of the muscles on one side (hemi-) of the face (facial). The first symptom is usually an intermittent twitching of the eyelid muscle that can lead to forced closure of the eye. The spasm may then gradually spread to involve the muscles of the lower face, which may cause the mouth to be pulled to one side. Eventually the spasms involve all of the muscles on one side of the face almost continuously. The condition may be caused by a facial nerve injury or a tumor, or it may have no apparent cause. Hemifacial spasm is most often caused by a blood vessel pressing on the facial nerve at the place where it exits the brainstem.

**Immunoresistance**: Immunoresistance is the presence of circulating antibodies that help prevent the body from being “invaded” by certain bacterial or viral diseases.

**Neuromuscular junction**: The neuromuscular junction is the region where the ending of a nerve comes into contact with a muscle fiber.

**Neuron**: Neurons or nerve cells in the body receive and send messages to and from the brain. In the brain, neurons communicate with each other. One end of a neuron receives messages and the other sends the message to the next neuron or to a muscle or gland.

**Neurotoxin**: A neurotoxin is a substance or chemical that causes damage to the nervous system.

**Neurotransmitter**: Neurotransmitters are chemicals that your body produces and that nerve cells use to communicate.

**Serotype**: A serotype is a group of related microorganisms that all contain a common set of antigens.
**SNARE protein complex**: SNARE stands for soluble NSF attachment receptor. SNARE protein complexes are made up of three proteins (syntaxin-1, SNAP-25, and synaptobrevin or vessel-associated membrane protein [VAMP]) anchored in opposing membranes before membrane fusion.

**Spasticity**: The word *spasm* comes from the Greek work, *spasmos*, meaning to pull or drag. *Spasticity* is defined as an involuntary, velocity-dependent, increased resistance to stretch. This definition means that the amount of resistance to stretching is at least partly determined by the speed with which a spastic muscle is stretched. One factor that is thought to be related to spasticity is the stretch reflex. This reflex is important in coordinating normal movements in which muscles are contracted and relaxed and in keeping the muscle from stretching too far. Although the end result of spasticity is problems with the muscles, spasticity is actually caused by an injury to a part of the central nervous system (the brain or spinal cord) that controls voluntary movements. The damage causes a change in the balance of signals between the nervous system and the muscles. This imbalance leads to increased activity (excitability) in the muscles.

**Spasmodic dysphonia**: Spasmodic dysphonia (also sometimes called laryngeal dystonia) is a voice disorder characterized by involuntary movements of one or more muscles of the larynx (vocal folds or voice box) during speech.

**Spore**: Microorganisms develop spores so that they can stay in an inactive form to protect themselves for long periods of time in unfavorable conditions.

**Strabismus**: Strabismus is a medical condition that is caused by a lack of coordination between the eyes. As a result, the eyes look in different directions and do not focus at the same time on a single point.

**Stridor**: Stridor is a harsh high-pitched sound during breathing that is caused by a blockage or narrowing in the voice box (larynx) or windpipe (trachea).

**Terminals**: Axons are relatively slender extensions of nerve cells or neurons that transmit messages away from the bodies of the neurons. The ends of the axons are called terminals. These terminals release neurotransmitters, which allow messages to be sent to other neurons, muscles, or glands.

**Vesicles**: Vesicles are packages or pouches of chemicals, such as acetylcholine or other neurotransmitters. Vesicles store these chemicals and then release them when necessary.