Biotech Company Offers Neurotoxin Alternative for Opioid Pain Management

By Monica J. Smith

Surgeons are well aware that opioid dependency is a huge problem in the United States; it results in 80 to 90 overdose-related deaths every day, 40% of which are associated with prescription medications. But a product created by Bonti, a small biotech company in Newport Beach, Calif., could have the potential to reduce the use of opioids by providing another option for pain management.

EB-001, a serotype E botulinum neurotoxin (BoNT-E), has a mechanism of action similar to that of serotype A botulinum neurotoxin (BoNT-A), for example, Botox (onabotulinumtoxinA, Allergan). EB-001, however, achieves efficacy faster—within 24 hours—and lasts for only about a month. The fast onset makes EB-001 well suited for postoperative and other types of focal musculoskeletal pain management.

"Through focus groups with clinical experts and patients, we realized something that worked fast with limited duration would be ideal because you address the pain quickly, but it doesn't last long enough to cause muscle atrophy," said neurologist Susan Abushakra, MD, chief medical officer and cofounder of the company.

"Right now, most postoperative and other musculoskeletal pain is treated with nonsteroidal anti-inflammatories, muscle relaxants or narcotic medications (opioids), which all have side effects—gastrointestinal upset, constipation, sedation and, of course, the risk of addiction," she said.

Many of the individuals who make up Bonti's team worked together at Allergan, where they investigated potential uses for BoNT-A. With that background, they started thinking about other serotypes similar to type A, but with some protein changes and different clinical profiles.

"We decided to work on a serotype that nobody had put to clinical use, type E," Dr. Abushakra said. "This type of botulism, which causes generalized muscle weakness, was known from food poisoning around seaports, where people ate bad fish. But it would set in quickly and last a short amount of time, while classic botulism usually starts after several days and can last for weeks."

When low doses of a BoNT are *injected* into a muscle, however, they produce focal targeted relaxation of that muscle, thus their benefit as treatments for focal muscle hyperactivity and/or spasticity, she explained.

Like BoNT-A serotypes, BoNT-E blocks neuromuscular transmission and, depending on the dose, relaxes or paralyzes muscles. "Botox was initially introduced as a neurotoxin for treating spasticity; it morphed into an enormous industry for cosmetic purposes, where its duration is advantageous," said Terry Whipple, MD, an orthopedic surgeon practicing in Richmond, Va., who has been serving as an advisor to Bonti. "But EB-001 has really unveiled the stage for pain management with a neurotoxin."

Most pain management relies on masking the perception of pain, tricking or dulling the brain with some sort of drug. But EB-001 addresses the *cause* of musculoskeletal pain, Dr. Whipple said, explaining how pain itself is a symptom of an injury to the muscle or tendons, even a surgical dissection or stretch injury.

"If a skeletal or nonskeletal muscle is in spasm, that muscle will choke off its oxygen supply and exhaust its ATP [adenosine triphosphate] chemical content, and those muscle cells will begin to starve for nutrients and oxygen."

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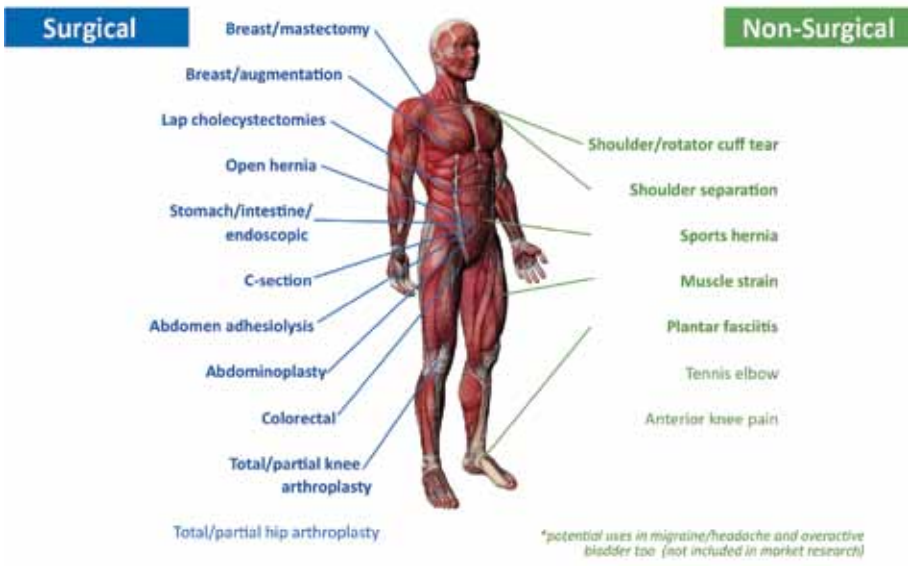
—Steve Yoelin, MD

This activates sensory nerves that transmit pain signals to the brain. "The brain receives this pain stimulus and says, 'There must be something wrong in that muscle area.' But if you can paralyze the muscle so that it isn't trying to contract, then it won't hurt," Dr. Whipple said.

"If you're not asking that muscle to work, there is no pain stimulus, no demand for nutrients or oxygen." During its month of paralysis, the muscle injury heals, but it is not inactive long enough to atrophy or require rehabilitation.

Bonti's initial clinical trial investigation of EB-001 was in the treatment of glabellar frown lines, to establish safety and provide proof of concept. "The reason we started with that is that it's easy to see the effect: Relaxing the glabellar muscles eases the frown lines in that area. Once we got to the dose that showed efficacy, a woman who had the injection early Monday morning found her wrinkles were gone when she woke up Tuesday," Dr. Abushakra said. "She was very excited. She had immediate feedback on what the cosmetic effect would look like and became interested in further treatment."



EB-001, a serotype E botulinum, has the potential to provide effective non-narcotic relief for postoperative and nonsurgical pain.

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The company is now planning a trial to investigate the agent's potential for pain management, starting with mammoplasty. "In breast reconstruction or augmentation, the implant is placed underneath the pectoral muscle and stretches it, which hurts like crazy," Dr. Whipple said. "But if we can paralyze the muscle, it shouldn't be so painful postoperatively." Enrollment in this trial was expected to begin in late summer 2017.

Should the findings of the mammoplasty trial suggest EB-001 is indeed well suited for postsurgical pain relief in that setting, the agent may have potential to provide pain management in a host of other situations, such as hernia repair.

"We have found papers describing the use of Botox for chemical component separation, where the muscle becomes longer and thinner, which helps with reconstruction of the abdominal wall," Dr. Abushakra said. A recent meta-analysis identified 12 papers supporting the potential of BoNT injections for the management of ventral hernias (*J Plast Surg Hand Surg* 2017 Feb 20. [Epub ahead of print]).

"With EB-001, you could inject it under ultrasound to prepare the abdominal wall for reconstruction, but without having to wait a week for the agent to take full effect."

The company also envisions EB-001 being used in nonsurgical situations to manage musculoskeletal pain, such as torn rotator cuff and plantar fasciitis. Studies in the above conditions would allow development of EB-001 for broad use in the management of focal musculoskeletal pain.

Steve Yoelin, MD, a Newport Beach ophthalmologist experienced in the injection of neurotoxins and principal investigator in the glabellar frown lines trial, sees EB-001 as a potential new tool in the pain management armamentarium. "It's quick-onset profile lends itself to pain management for quicker pain relief. The first EB-001 human trial did not show any adverse events related to pain management, which is another reassuring sign that EB-001 can play a pain management role in the population at large," he said.

He pointed out, however, that several patients in the glabellar frown line trial were uneasy about being injected with a toxin; their fears were allayed by the positive results. "It could be helpful to share that information with future toxin-naive patients," he said.

"Clearly, the U.S. has a huge, unfortunate problem with prescription pain medications, and I think we can improve management of postoperative pain in certain cases. Society would likely benefit from a pain management alternative. We as physicians have more work to do, but it's a good sign that there's something exciting on the horizon."

Assuming everything goes well with clinical trials and the FDA approval process, Bonti estimates EB-001 could be commercially available in 2020.

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Neither *General Surgery News* nor Dr. Goldfarb has any financial relationship with Bonti.