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THE NEUROTOXIN REVOLUTION

WITH A CLUTCH OF TRAILBLAZING TOXINS IN THE PIPELINE AND A
LITANY OF PROMISING NEW USES COMING TO LIGHT, BOTOX AND CO.
ARE POISED TO REVOLUTIONIZE THE WELLNESS REALM

BY JOLENE EDGAR

Born of the bacterium *Clostridium botulinum*, the botulinum neurotoxin is a protein, exerting its influence by cutting communication between nerves and muscles to immobilize its target. In its raw form, it's one of the deadliest substances known to man, but when purified, heavily diluted, and expertly injected in tiny doses, it can harness its powers for good. The type-A toxin activating FDA-approved neurotoxins Botox Cosmetic, Dysport and Xeomin has been shown to ameliorate everything from crow's-feet and muscle spasms to chronic migraines and urinary incontinence. Fully defying its vanity-drug stigma, "more than half of the botulinum toxin now used in the world is for medical purposes," says New York dermatologist Paul Jarrod Frank, MD. Aiming to add to its repertoire, Botox is currently being investigated as a treatment for depression, a host of pain disorders, even atrial fibrillation in cardiac patients—earning itself a reputation as "the product that keeps on giving," says Chicago facial plastic surgeon Steven Dayan, MD.

Botulinum toxin first proved its medical value in the 1970s, correcting ophthalmological conditions like strabismus (crossed eyes) and blepharospasm (marked by uncontrollable blinking). In 1987, the story goes, Vancouver-based ophthalmologist Jean Carruthers, MD, wife of world-renowned dermatologist Alastair Carruthers, MD, discovered a happy side effect of treating such eye issues with toxins: a softening of the lines between patients' brows. The drug, which came to be known as Botox, was approved for therapeutic use in 1989, and as a fix for frown lines in 2002.

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Since then, Botox's myriad talents have shined in more than 500 peer-reviewed articles. And newer brands of toxin, like Dysport and Xeomin, have emerged as worthy competitors. The category as a whole has become an

unrelenting tour de force, with doctors administering over 5 million neurotoxin injections worldwide in 2017, according to the International Society of Aesthetic Plastic Surgery (ISAPS).

With a Taylor Swift-caliber fan club, Botox Cosmetic has become a household name—the Kleenex of toxins—and its manufacturer, pharmaceutical goliath Allergan, bears the bottomless pockets needed to keep the brand on the forefront of groundbreaking research. Still, the majority of injectors artfully use all three muscle relaxers in practice, appreciating their subtle differences and finessing them to beautiful effect. The doctors we spoke with also expect to welcome into their armamentaria several new neurotoxins in the near future, each poised to offer its own breakthrough advantages once greenlighted by the FDA.

Over the next few pages, we'll share all we know about the neurotoxins of today and tomorrow—fascinating theories on how they may squelch sadness; the science behind their ability to improve scars, refine pores, prolong blowouts, and out-contour the Kardashians; and why, despite prevailing no-big-deal notions, one should never underestimate the gravity and complexity of these "miracle poisons."

THE BIG THREE: WHICH WRINKLE-BUSTER IS RIGHT FOR YOU?

While Botox Cosmetic may be the most famous of the bunch, Dysport and Xeomin contain the same type of toxin, and work by identical means—blocking the release of a chemical messenger called acetylcholine to lessen muscle contractions for three to four months in most cases. “The overall gestalt of neurotoxins is that there is no one best—they all fill different niches,” says Dr. Frank, due to slight distinctions between final formulations.

Beyond an unrivaled track record—“it is the most tried-and-true,” says New York dermatologist Macrene Alexiades, MD—**Botox Cosmetic** is famous for its potency. “Patients with very strong muscles, and those wanting a complete block, tend to prefer it because it really gives a precise and powerful correction,” says Philadelphia plastic surgeon Ivona Percec, MD, PhD. **Dysport** reportedly kicks in faster than its competitors—within a couple days opposed to a week. It also “diffuses a bit more into its

surroundings, making it ideal for treating a high forehead or a long stretch of crow’s-feet, or for softening the bands of the neck,” says New York dermatologist Heidi Waldorf, MD. Injectors commonly describe its effect as softer and smoother, “theoretically due to the diffusion,” notes Dr. Percec, “but the data isn’t definitive.” **Xeomin** is also known for its mild manner, but more so for its peerless purity, as it omits the complexing proteins present in other neurotoxins, “which may play a role in immunogenicity, or the fact that a small percentage of patients don’t respond as well to Botox [and Dysport] after many years of use,” explains Dr. Alexiades. The purpose of the proteins is debatable, but they’re thought to help stabilize the drugs. “While there’s very little evidence of immunogenicity in cosmetic doses, I have had a handful of patients—very few in more than 30,000 treatments—who’ve become inexplicably unresponsive to Botox,” says Dr. Dayan. In those cases, switching them to Xeomin

“usually remedies the problem.” Still, he adds, “it’s hard to say definitively if Xeomin is successful because of the lack of proteins, but some speculate it may be.”

Such nuances are largely anecdotal, we should note, and experienced injectors say they can achieve similar results with all three toxins—essentially leveling the playing field between brands. Much comes down to individualized injection technique (a point of pride among doctors) and a little thing called reconstitution—the act of restoring these powdered toxins back to liquid form with saline prior to injection. “This step can differ among injectors, changing clinical outcomes,” says Miami dermatologist Joely Kaufman, MD. A high dilution can beget a quicker onset and more spread—across the board. Boosting the dose of any will give a stronger, more lasting effect. The bottom line: Find a doctor proficient in all toxins, not just one, who can handily manipulate them to suit your unique anatomy and aesthetic goals.

BEFORE



AFTER

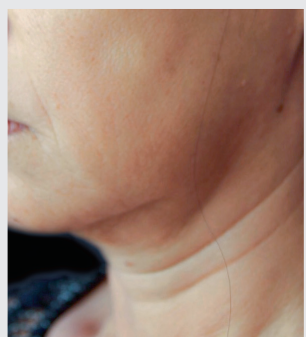


Aiming to improve the look of fine lines and wrinkles across this 47-year-old patient’s upper face, Birmingham, AL dermatologist Corey L. Hartman, MD injected the forehead, glabella (between the brows), bunny lines (on the sides of the nose), and crow’s-feet with Xeomin, tailoring the dose to maintain the patient’s ability to make expressions. The “after” photo was taken two weeks post-treatment.

BEFORE



AFTER



New York facial plastic surgeon Jennifer Levine, MD addressed this 60-year-old patient’s platysmal bands and neck lines by injecting 100 units of Dysport. “The platysma is a depressor of the lower face, so injecting a neurotoxin causes lifting. The muscle contracts and attenuates over time; neurotoxins help soften bands, lines and wrinkles,” she says. The “after” photo was taken two weeks later.

BEAUTY AND BEYOND: POPULAR USES FOR NEUROTOXINS

The list of FDA-sanctioned (on-label) uses for botulinum toxins is concise, but doctors routinely inject them experimentally (off-label) to address countless other beauty and wellness concerns. (FYI: “Botox Cosmetic” and “Botox,” the therapeutic version, are the same drug vetted in different studies.)

FINE LINES Botox Cosmetic, Dysport and Xeomin are approved to treat frown lines; the big B is also cleared for forehead lines and crow’s-feet. “The upper face was the original gold-standard aesthetic use for toxins,” says Dr. Percec. Injecting the lower face was initially considered controversial due to its more intricate anatomy. (An errant needle stick or overdose around the mouth could leave one unable to formulate words or control drooling.) Over time, however, doctors found the drug’s benefits outweighed the risks in these areas. “Muscle strain increases the most around the mouth with age, and as women lose bony mass, our tooth position changes,” explains Dr. Percec. But, neurotoxins can help remedy the repercussions of these shifts: “We’ve now learned to treat lip pursing, the turned-down corners of the mouth, puckering of the chin—all of which are strain-related,” she says. Delicate areas, like the upper lip and neck, demand dilute microdoses of toxin (often combined with filler) for the most discreet effect, and require frequent touch-ups, because small doses lack durability.

GUMMY SMILES Injecting minute amounts under and on the sides of the nose will reduce the extreme pull on the upper lip, helping it rest in a more

pleasing position. According to Birmingham, AL dermatologist Corey L. Hartman, MD, this area requires the precise placement of Botox Cosmetic or Xeomin. And, fair warning, with this treatment “you’re changing the quality of your smile—yes, you’ll show less gum, but the corners of the mouth may go up higher than they normally would, so small test doses are key,” says Dr. Frank.

LARGE PORES “Micro-sized injections of toxin into the dermis target the arrector pili muscles, which control pore size,” says Dr. Hartman. Relaxing these muscles causes pores to shrink up a bit and secrete less oil. Some doctors inject toxin as part of an AquaGold treatment, during which a small stamping-type tool with hollow needles delivers actives into the skin; others apply toxin directly to the skin’s surface and then press it in with a microneedling pen.

CONTOURING “By carefully injecting the muscles that pull the neck down, and purposefully not injecting those that lift the mouth, we can reshape the jawline,” says Dr. Kaufman.

TIP FLIP Injecting toxin at the base of the nose “relaxes the muscle responsible for dragging its tip down with age, temporarily raising it back up,” Dr. Hartman says. It’s very important to limit the spread of toxin here, he notes, to prevent slurred speech and an inability to purse the lips or open the mouth.

SLIMMING THE JAWLINE Injected into the masseters, or jaw muscles, “toxins can narrow the lower face and make it look more feminine,” says Dr. Dayan. The change comes on gradually

over several weeks. A high dose is needed to shrink them, but “results usually last at least six months, and sometimes longer,” notes Dr. Kaufman.

CLENCHING AND GRINDING Lifelong teeth grinding can make masseters bulky. By weakening these muscles with toxin, says Dr. Percec, “it not only softens and slims the face, but also alleviates functional problems, like jaw clenching and teeth grinding.” It’s such a powerful fix, adds Dr. Alexiades, that “many of my patients have stopped wearing night guards.”

EXCESSIVE SWEATING The sympathetic nervous system rules our sweat glands by pumping out acetylcholine. When toxins block the chemical, glands can’t contract, and perspiration subsides. “This is where Dysport shines for its ability to diffuse and capture as many sweat glands as possible,” explains Dr. Hartman. Toxins typically take aim at underarms, palms and soles, but can help in less obvious areas, too, like the folds beneath the breasts where sweat tends to pool, sometimes causing rashes and infections. Neurotoxins can stymie sweat on the scalp as well—the hairline, the crown and the nape of the neck—keeping strands clean between blowouts, says Boston dermatologist Papri Sarkar, MD. Results last up to six months.

SCARS “Tension is the worst thing for a fresh scar, but when underlying muscles move, the skin stretches,” says New York plastic surgeon Alan Matarasso, MD. “By freezing the area with Botox [an off-label use], we remove the tension and get a better scar.” (Think of it as

a chemical cast.) Studies show Botox may also modify wound healing by other means, tamping down inflammation along with growth factors known to promote keloid scarring, says Dr. Frank.

MIGRAINES Botulinum toxins are now a standard treatment for migraines that don’t respond to traditional oral medications. “With Botox [the first brand FDA-approved for migraines], we usually see about a 50 percent improvement in the frequency of migraines, and most patients say they’re better able to control, or abort, oncoming migraines with prescription triptan drugs,” says Boston anesthesiologist Edgar L. Ross, MD. “There’s evidence that botulinum toxins can affect pain-modulating molecules, like neuropeptides, all along the pain pathway, as well as prevent the release of pain molecules like substance P,” says Bethesda, MD neurologist Barbara Karp, MD. “There is also evidence that botulinum toxins can help suppress inflammation.”

PAIN DISORDERS Neurologists are using toxins (off-label) to treat all kinds of aches, typically as part of comprehensive pain-management regimens. Of their many advantages, botulinum toxins “can be safely combined with other treatments, and have very few interactions with medications,” says Dr. Karp, adding that some users are even able to curb their reliance on opioids. “In a study of botulinum toxin for the chronic pelvic pain of endometriosis, we’ve seen women decrease their daily use of analgesics and better tolerate pelvic floor physical therapy after injections,” she adds.

Botox Seeks FDA Approval for Major Depressive Disorder

Since the mid aughts, Botox has been moonlighting as an antidepressant, starring in a cache of small mental-health studies, and turning out remarkably consistent results: a 50 to 60 percent response rate; a 45 to 55 percent reduction in depressive symptoms; and a remission rate of approximately one-third, notes Chevy Chase, MD dermatologist Eric Finzi, MD, PhD, in an article published in *Dermatologic Surgery* in 2018. “People diagnosed with depression are reporting improvements in mood following treatment of facial wrinkling with botulinum toxin,” says Philadelphia psychologist David B. Sarwer, PhD. “These observations have grabbed the attention of both the doctors who offer these injections, as well as mental health professionals seeking alternative therapies for depression.”

Botox will soon be entering phase three clinical trials for major depressive disorder, yet scientists still can’t say for sure how the drug works to combat the disease. “We do know that improvement in mood is not related to improvement in wrinkles, because if we treat someone young, who has no lines at rest, their depression can still improve,” says Dr. Finzi. The most probable explanation for the drug’s psychological success, he adds, is the facial feedback hypothesis, or the idea that our expressions can influence our emotions. “Many studies have shown that the mere act of frowning leads subjects to have a more negative appraisal of whatever they’re evaluating—a

story, a cartoon, a photograph. Subjects have also reported feeling sadder right after frowning,” Dr. Finzi explains.

It seems the muscles responsible for our angry frowns may play a role in regulating our mindset, not just revealing it. “There’s something unique about the glabella [area between the brows],” says New York psychiatrist Sudeepa Varma, MD. In fact, she notes, studies show through brain imaging that “by quieting the glabellar muscles, we can reduce neural messages sent to the amygdala, or the fear center of the brain, which is known to be overactive in depression and anxiety.”

Now, the glabella is arguably the most common injection site for anyone seeking smoother skin. And the doses used in depression studies are roughly equivalent to those used to minimize wrinkles. But according to Dr. Varma, that doesn’t necessarily mean every between-the-brow shot comes with a side of joy, as studies investigating Botox’s mood-altering prowess have looked only at individuals with depression. For that select set, however, “it’s reasonable to see if botulinum toxin treatment of the frown can help, as we know it’s safe, and doesn’t have the side effects of other medications for depression,” notes Dr. Finzi. But not every shrink is boarding the Botox bandwagon just yet. “While it’s fascinating to think botulinum toxins could be an accepted treatment for depression,” says Dr. Sarwer, “we need more research—large, randomized, controlled trials comparing toxins to placebo injections—before recommending them to patients suffering from major depression.”

New Toxins in the Pipeline

Coming soon to a doctor’s office near you? A squad of new botulinum toxins, each with its own designer appeal. For the Bo-phobe or neophyte looking for a test run, there’s an innovative **botulinum toxin type E from Allergan** that works on demand (within 24 hours) and **wears off in two to four weeks**. The drug has been tested in frown lines and Mohs surgical scars (resulting from skin-cancer removal). It’s also being investigated for its painkilling and spasm-quelling properties when injected into affected muscles during breast augmentation and abdominoplasty surgeries. “Much of the discomfort following these procedures results from the muscle work we do—lifting up the chest muscles when placing breast implants, or putting hundreds of stitches into the abdominals to tighten them,” says Dr. Matarasso. This short-acting shot “could be good, because some people are still sore a couple weeks later.” Doctors anticipate it gaining approval around 2025.

Nearer on the horizon is a **neurotoxin from Revance Therapeutics** shown to outperform all current options: “In many studies, we’re seeing it **last seven to nine months**,” says Dr. Carruthers, a lead investigator on the trials. The product contains the same active component as Botox Cosmetic, but adds a proprietary peptide thought to prolong the toxin’s reign. “We compared 20, 40 and 60 units of the Revance product to 20 units of Botox, and also to placebo, and the longevity was just spectacularly better with the Revance groups,” says Dr. Carruthers, noting that the 40-unit dose offered the best balance of longevity, natural appearance and lack of complications. “Subjects were thrilled with how they were looking at every single visit.” There were a few cases

of mild and transient eyelid drooping, Dr. Carruthers notes, which resolved before the drug wore off. “You’d think that if a product lasted twice as long [as Botox Cosmetic] that the complications would, too, but somehow that didn’t seem to be the case.”

Attempting to measure up, **Botox Cosmetic is being tested at higher doses** (40, 60 and 80 units), and proving a link between quantity and longevity. But bigger isn’t always better. “I don’t advocate the higher dose, as it can lead to a more frozen look and I want patients to retain some muscle action,” says New York facial plastic surgeon Jennifer Levine, MD. On the flipside, Dr. Alexiades says she’s already giving patients five to six months of smoother skin—without sacrificing expression—by injecting larger doses of Botox Cosmetic over two sessions, so as not to “overdose on the first.” Dr. Carruthers also uses generous doses in practice when treating athletes and certain men with outsize facial muscles, but says “in a delicately muscled person, I certainly wouldn’t do this because it wouldn’t provide a natural look.”

A third newcomer, **Jeuneau** from aesthetics company Evolus, won FDA approval for frown lines in February. The toxin hails from Korea where “it’s been used safely and effectively for years,” says Dr. Carruthers. As for its onset, duration, efficacy and risk profile, “it appears to have similar clinical properties to Botox Cosmetic,” she adds. Jeuneau’s edge will likely be its **lower price point**—a perk stemming from the fact that “the drug will only be used in aesthetics, thereby decreasing the amount of money spent on research studies,” says Dr. Kaufman. What’s more, adds Dr. Percec, with no therapeutic counterpart, its price won’t be swayed by insurance companies, which is ordinarily the case with toxins that work in both worlds.

MYTH VS. FACT

Given their origin story, is it any wonder neurotoxins are steeped in confusion? Here, top doctors demystify their superpowers.

Myth:
Toxins will leave me forever frozen.

Fact:
Neurotoxins’ line-limiting triumphs are only temporary, and again, the drugs can be finagled to grant more or less of an effect. “In the early stages of Botox, everyone wanted to skate off their foreheads,” recalls Dr. Frank. “Now, that is out of vogue and ill-advised because that sort of complete and chronic paralysis can negatively affect the way you age, making the brow feel heavy and eyes look smaller.” Baby Botox has become the new standard of care: conservative doses that maintain movement and expression.

Myth:
A shot of toxin can fully erase every wrinkle.

Fact:
Botox Cosmetic isn’t an anti-aging everything. Deep glabellar grooves and etched-in lip lines, for instance, won’t disappear with toxin alone. “As we age, keeping it natural generally requires combination therapy with toxins, fillers, resurfacing and tightening devices,” notes Dr. Waldorf. Plastic surgery, too, some would argue. Toxins may slow the descent of the brow or jawline to an extent, but “they’re not going to give you what a facelift does,” says Dr. Matarasso.

Myth:
Neurotoxins can travel throughout the body.

Fact:
While the very idea of a paralytic going rogue inside your body is, indeed, alarming, doctors say the risk is exceedingly rare: “With high-volume toxins, like those used to treat medical conditions, such as cerebral palsy spasticity, this can potentially be a problem,” says Montclair, NJ dermatologist Jeanine Downie, MD. “But in all of the patients I’ve injected with standard cosmetic doses of Botox since 1994, I’ve never had an issue with a toxin spreading beyond the injection site.”

NEWBEAUTY
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DOCTOR
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WHY IT PAYS TO SEE A DOCTOR FOR BOTOX

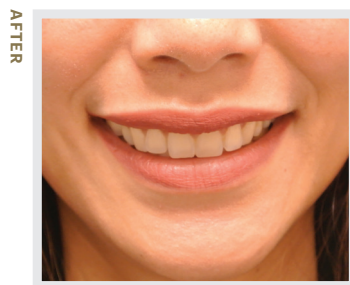
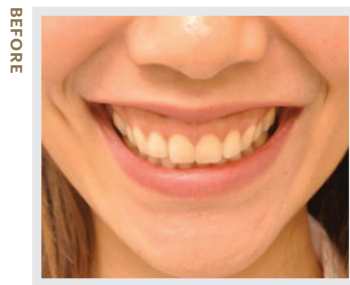
Pedaled at house parties like burp-able storage containers, and teased on placards fronting stripmall spas, “Botox is quickly losing credence as a real medical procedure,” laments Dr. Downie. In truth, neurotoxins are prescription drugs intended to be injected in sterile environments by experienced practitioners who not only know their way around a syringe, but also have the chops to handle any complication. If you haven’t yet pledged allegiance to an MD injector, consider these reasons for doing so.

NEUROTOXINS AREN’T WITHOUT RISK.

Pain, swelling and bruising are common and fleeting, but “when the product goes outside of the intended muscle, one may experience droopy eyelids, dropped eyebrows, crooked smiles, drooling, and excessive tearing or dry eyes,” says Dr. Hartman. And because there’s no undo button for Botox, such effects can linger for months. Getting injected by a board-certified dermatologist or plastic surgeon is the best way to sidestep would-be problems.

DOCTORS ARE ANATOMY EXPERTS.

Anyone can push a needle, but MDs are versed in muscular interplay and anatomical nuances, and can better tailor treatments. A prime example: Everyone’s



This 35-year-old patient was bothered by her gummy smile. Philadelphia dermatologist Nazanin Saedi, MD treated her with Botox Cosmetic, injecting a total of six units to target the levator labii superioris alaeque nasi muscles, which lift the upper lip and dilate the nostrils. The dose was divided into two injections at the base of the nose. The “before” photo features the patient’s original smile; the “after” photo was taken two weeks post-treatment.