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FORGET WRINKLES. BOTOX IS NOW BEING USED TO TREAT MIGRAINES, DEPRESSION, TWITCHING EYES, OVERACTIVE BLADDERS, SWEATY PALMS AND MORE. SOME CALL IT A MARVEL OF MEDICINE; OTHERS CAUTION THE RISKS ARE STILL UNKNOWN. INSIDE THE EXPLODING BUSINESS AND STRANGE SCIENCE OF BOTOX

BY ALEXANDRA SIFFERLIN

everything

DURING A RECENT THERAPY session, one of Dr. Norman Rosenthal's regulars said he was considering suicide. It wasn't the first time the patient had entertained the thought, and even though he was on antidepressants and always kept up with his appointments, Rosenthal, a licensed psychiatrist with a private practice in North Bethesda, Md., wanted to offer his patient something else.

"I think you should get Botox," Rosenthal told him. "You should schedule an appointment on your way home."

It was peculiar advice coming from a shrink, but not without precedent. In 2014, Rosenthal, a clinical professor of psychiatry at Georgetown University School of Medicine, and Dr. Eric Finzi, an assistant professor of psychiatry at George Washington School of Medicine, published a study showing that when people with major depression got Botox, they reported fewer symptoms six weeks later than people who had been given placebo injections. "I'm always on the lookout for things that are unusual and interesting for depression," says Rosenthal, who is widely considered an expert on the condition. "I've found Botox to be helpful, but it's still not mainstream."

It's also not approved by the U.S. Food and Drug Administration (FDA) for depression, not that that stops doctors from prescribing it that way. Such off-label use of Botox, like that of any FDA-approved drug, is legal in the U.S. That's because once a drug has been approved by the FDA for a condition, licensed physicians are legally allowed to prescribe it for any medical issue they think it could benefit, regardless of whether

'I meet with physicians who are using the toxin everywhere—for diseases you would never know about.'

MIN DONG,
Harvard Medical School

it's been proved to work for that condition.

Now, thanks in large part to off-label use, Botox—the wrinkle smoother that exploded as a cultural phenomenon and medical triumph—is increasingly being drafted for problems that go far beyond the cosmetic. The depression suffered by Rosenthal's patient is just one example on a list that includes everything from excessive sweating and neck spasms to leaky bladders, premature ejaculation, migraines, cold hands and even the dangerous cardiac condition of atrial fibrillation after heart surgery, among others. The range of conditions for which doctors are now using Botox is dizzying, reflecting the drug's unique characteristics as much as the drug industry's unique strategies for creating a blockbuster.

Botox is a neurotoxin derived from the bacterium *Clostridium botulinum*. Ingested in contaminated food, it can interfere with key muscles in the body, causing paralysis and even death. But when injected in tiny doses into targeted areas, it can block signals between nerves and muscles, causing the muscles to relax. That's how it smooths wrinkles: when you immobilize the muscles that surround fine lines, those lines are less likely to move—making them less noticeable. It's also why it's FDA-approved to treat an overactive bladder: Botox can prevent involuntary muscle contractions that can cause people to feel like they have to pee even when they don't.

In 2015, Botox, produced by pharmaceutical maker Allergan, generated global revenue of \$2.45 billion—more than half of which came from therapeutic rather than cosmetic uses. That noncosmetic revenue is likely to balloon in the years ahead as doctors try out

Botox for even more off-label uses and as Allergan conducts studies of its own.

"In the majority of these cases, it's the doctors at the front line who start using Botox off-label, and then we see the treatment of things we never expected the toxin to work for," says Min Dong, a researcher at Harvard Medical School who studies botulinum toxins in the lab and has no financial ties to Allergan. "I meet with physicians who are using the toxin everywhere—for diseases you would never know about."

The potential of the drug is enormous, but it isn't without risks. Most of the experts I spoke with agree that in small doses, Botox is safe when administered by a licensed professional, but not everyone agrees that its safety extends to all of its newer off-label uses.

In recent years, a number of high-profile lawsuits have been brought against Allergan in which plaintiffs claimed that off-label uses—for ailments including a child's cerebral-palsy symptoms, for instance, or an adult's hand tremors—resulted in lasting deleterious side effects. Still, the drug's acceptance in a growing number of doctors' offices worldwide, and its revenue growth, show no signs of slowing.

It's a remarkable arc for a drug that only a few years ago was associated with Hollywood cocktail parties where guests came for Bellinis and left with a forehead full of Botox injections. It highlights the advances that can occur when physicians, seeking new therapies for their patients, explore creative new uses for approved drugs—basically, real-world experiments that take place largely beyond the reach of federal regulators. That, in turn, raises questions about the risks of deploying medicines in ways that have not been fully vetted. But it happens all the time.

THE DRUG HAS COME A LONG WAY since its ability to smooth facial wrinkles was first discovered, by accident. In the 1970s, ophthalmologist Dr. Alan B. Scott started studying the toxin as a therapy for people with a medical condition that rendered them cross-eyed. "Some of these patients that would come would kind of joke and say, 'Oh, Doctor, I've come to get the lines out.' And I would laugh, but I really wasn't tuned in to the practical, and valuable, aspect of that," Scott told CBS in 2012. Scott named the drug Oculinum and formed a company of the same name in 1978. In 1989 he received FDA approval for the treatment of strabismus (the crossed-eye disorder) and abnormal eyelid spasms.

BOTOX BY THE NUMBERS

In the 28 years since Botox was approved, the drug's popularity—and the number of ailments it treats—has skyrocketed

12.2 billion

Number of Botox doses administered in the past quarter-century

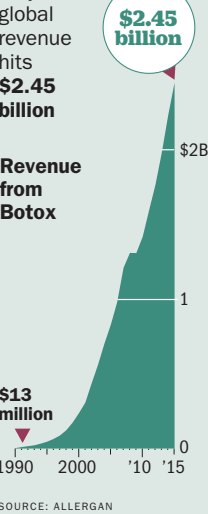
800

Number of patents held by Allergan for current and potential Botox applications

► In 1991, Allergan paid **\$9 million** for a small company that made Botox

► In 1998, Botox global revenue was **\$125 million**

► By 2015 global revenue hits **\$2.45 billion**



Two years later, Allergan bought Oculinum for \$9 million and changed the drug's name to Botox. At the time, Allergan was primarily an ocular-care company that sold products like contact-lens cleaners and prescription solutions for dry eyes, bringing in about \$500 million in annual sales. Allergan says it saw Botox as a drug for a niche population: it's estimated that 4% of people in the U.S. have crossed eyes, for which the drug was initially approved, and Allergan made about \$13 million in sales from the drug by the end of 1991.

In 1998, David E.I. Pyott became CEO of Allergan. He was enthusiastic about Botox's wrinkle-reducing potential, he says, and pushed the company to conduct a series of studies on the matter. In 2002, Botox earned FDA approval for so-called frown lines—wrinkles between eyebrows—marking the first time a pharmaceutical drug was given the green light for a strictly cosmetic purpose. In 2001, the year before Botox was approved for wrinkles, it generated about \$310 million in sales. By 2013, the year it was approved for overactive bladder, Allergan reported nearly \$2 billion in revenue from Botox.

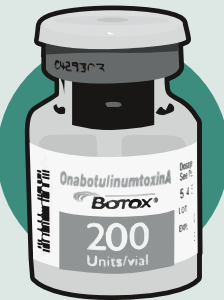
In just over a decade, the number of people in the U.S. receiving cosmetic botulinum toxin type A injections—mostly from Botox but also from another brand called Dysport, which commands less than 10% of the market—exploded. From 2000 to 2015, use of the toxins for wrinkles increased 759%. It became a cultural phenomenon too, spawning Botox parties, *Simpsons* jokes, even greeting cards. In 2008, *Sex and the City* character Samantha famously quipped, "I don't really believe in marriage. Now Botox, on the other hand, that works every time."

But today it's the medical uses of the drug that are the great moneymaker, in part because doctors are getting a better handle on how to use it. Botulinum toxin type A is one of seven neurotoxins produced from *Clostridium botulinum*. Contracting botulism is bad news: it can cause blurred vision, persistent trouble swallowing and worse. In one recent case, close to 30 people were hospitalized in Ohio in 2015 after attending a church potluck. One person died. The outbreak was ultimately attributed to a potato salad made from improperly home-canned potatoes that were harboring the bacteria. Given its level of toxicity, some countries have even explored its potential use as a bioweapon.

With Botox, however, the dose makes

Botox FAQ

Botox was invented as a drug to treat crossed eyes. Today it's used on a wide range of disorders—some approved, some not. Here's what to know:



1

WHAT IS BOTOX?

Botox comes from a bacterium called *Clostridium botulinum* that can cause severe food poisoning if eaten. When the drug is injected, it delivers a tiny dose of toxin that blocks communication between nerves and muscles.

2

DOES INSURANCE COVER IT?

Not for wrinkles. Some companies will cover it for FDA-approved medical uses if other therapies have not worked. Out of pocket, it can cost \$350 to \$500 per injection. Most treatments require multiple shots.

3

IS IT SAFE?

The FDA requires Botox to bear a black-box warning—an alert that the drug may come with major risks—but most experts agree it's safe when used correctly for approved conditions. Still, serious side effects have been reported.

the poison. In medicine, it’s used in such small amounts that most experts deem it safe. “It’s fascinating,” says Dong, the Harvard researcher. “These are the most toxic substances known to man, and they are also the most useful toxins used in medicine right now.”

Botox works by temporarily immobilizing muscle activity. It does this by blocking nerve-muscle communication, which makes the injected muscles unable to contract. Paralyzing muscle activity is how Botox can steady a straying gaze, eliminate an eyelid spasm or stop signaling from nerves that stimulate sweat in a person’s armpit.

Botox has also been shown to prevent chronic migraines, but there, it’s unclear exactly why Botox works. (For doctors, reaching a firm understanding of how Botox prevents migraines will be tricky, since they don’t know for certain what causes the severe headaches in the first place.) “There were multiple clinical trials for migraines, and most of them failed,” says Dr. Mitchell Brin, senior vice president of drug development at Allergan and chief scientific officer for Botox. “It took a long time to figure out where to inject and how much.” Today people who receive Botox for migraine prevention get 31 injections in different spots on their head and neck. The effects of Botox can last about three to six months depending on the condition.

The use of Botox for migraines was, like many other new applications for the drug, a kind of happy accident. A Beverly Hills plastic surgeon observed that people who got Botox for wrinkles were reporting fewer headaches, paving the way for studies about migraines. Similarly, doctors in Europe were intrigued when they noticed that their patients who got Botox for facial spasms were sweating less than usual.

“It’s pure serendipity,” says Brin.

THOUGH PEOPLE OFTEN ASSOCIATE pharmaceutical discovery with giant industrial laboratories and expansive, rigorous clinical trials, the mission creep for Botox—as with many other drugs that have received government approval for one specific use—has been driven by off-label use.

In the case of Botox, doctors who experiment off-label say they do so because they’re looking for better treatment options for their patients. “In my 30 years of medical practice, Botox is one of the most impactful treatments I had ever seen,” says Dr. Linda Brubaker,

dean and chief diversity officer of the Loyola University Chicago Stritch School of Medicine, who independently studied Botox for overactive bladder before the FDA approved it for that condition in 2013.

Many of the women she saw in her practice didn’t want to take drugs for the disorder over the long term. Brubaker found that about 70% of women she treated with Botox reported an average of three leaks a day, compared with the average of five leaks a day at the start of the study. “It’s a very rewarding option for them,” she says.

It’s true that Botox’s ever expanding uses have been largely physician-driven. But drugmakers are also often aware of off-label uses long before those uses are officially recognized by the FDA; that’s how Botox ended up being approved for wrinkles, after all.

Some industry insiders say it’s not unusual, if still legally murky, for drug-company representatives and doctors to share information with one another about the different ways an approved drug may be used. If a doctor notices that, say, a treatment for crossed eyes also “takes the lines out,” he may mention it to the representative from whom he buys the drugs. That rep may share that with another of his clients, and so on.

U.S. pharmaceutical companies are prohibited from marketing a drug for unapproved purposes until they’ve submitted proof to the FDA of its efficacy and gotten the agency’s green light. If they skip that step, they’re breaking the law, and the penalties can be steep.

In 2010, Allergan pleaded guilty and agreed to pay \$600 million to resolve allegations that it unlawfully promoted Botox for conditions—including headaches, pain, spasticity and juvenile cerebral palsy—that at the time were not approved by the FDA. In one of the complaints, prosecutors said that Allergan “illegally, vigorously and without any thought to the possible negative health effects to which it subjected patients, promoted off-label uses of Botox.” The U.S. Department of Justice also argued that Allergan exploited on-label uses for cervical dystonia—a disorder characterized by extreme neck-muscle contractions—to “grow off-label pain and headache sales.” Prosecutors also argued that Allergan paid doctors to give presentations and trainings to other physicians about Botox uses that at the time were off-label.

As part of the settlement, Allergan agreed to plead guilty to one criminal misdemeanor

misbranding charge and pay \$375 million. The company acknowledged that its marketing of Botox led to off-label uses of the drug. Allergan also agreed to pay \$225 million to resolve civil charges alleging that the marketing of Botox had caused doctors to file false reimbursement claims, though Allergan denied wrongdoing. The company said in a statement that the settlement was in the best interest of its stockholders because it avoided litigation costs and “permits us to focus our time and resources on . . . developing new treatments.”

As with any drug, Allergan is legally required to make known Botox’s most severe potential side effects, and in 2009 the FDA required Botox to bear a black-box warning—the strongest type of warning label given to any drug—cautioning that there was evidence the drug had been linked to serious side effects. With Botox, this includes effects spreading from the injection site to other parts of the body, causing muscle weakness, double vision and drooping eyelids.

In physicians’ offices—where patients typically don’t see the box the vials are packed in and therefore may be unaware of the black-box warning—the onus is on doctors to outline the potential risks with any patient choosing to try Botox for any condition, FDA-approved or not.

Ray Chester, an attorney in Austin who has represented several plaintiffs in lawsuits against Allergan, says that just about all the cases he has handled involved off-label use of the drug. In 2014 a New York couple argued that Botox, which they chose to try off-label to treat their son’s cerebral-palsy symptoms, caused life-threatening complications. The family was awarded \$6.75 million by a jury. Allergan, which initially planned to appeal, ended up privately settling the case with the family, and the terms of the settlement have been kept confidential.

Though the off-label use of drugs makes many experts—including some at the FDA—uncomfortable, the practice is de rigueur in medicine. It’s how doctors learned that Lyr-ica, which is approved to treat nerve pain, can treat anxiety, and how they learned that finasteride, a drug that treats enlarged prostates, can reduce male baldness.

“A separate balancing of risks and benefits is necessary for each intended use of a drug, even once it is approved, to ensure the benefits of using the product to treat a particular disease or condition outweigh the risks,” says FDA press officer Sarah Peddicord.

OFF-LABEL

Once a drug has been approved for one condition, doctors can use it for any disorder they think it can help. Here are just a few uses doctors have embraced:

■ **Severely cold hands**

■ **Lockjaw**

■ **Back pain**

■ **Cleft-lip scars**

■ **Painful sex**

■ **Depression**

■ **Premature ejaculation**

■ **Parkinson’s-disease symptoms**

■ **Anal fissures**

■ **Drooling**

■ **Teeth grinding**

A balancing of risks and benefits is necessary for each intended use of a drug, even once it is approved.

SARAH PEDDICORD, FDA

That’s why for any off-label uses that Allergan wants to market to doctors and the public—depression, cold hands, atrial fibrillation in heart-surgery patients—the company must conduct its own clinical trials to show its efficacy and safety.

Allergan does not disclose its research-and-development budget for Botox specifically, but the company’s annual R&D budget is about \$1.5 billion. “This drug is not done in terms of its different applications,” says Allergan’s Brin. “It still has many different, exciting, meaningful opportunities for patients.”

THE STUDIES USING BOTOX for depression, like other research into Botox’s off-label potential, were so encouraging that they caught the attention of Allergan. In Rosenthal and Finzi’s research, 74 people with major depressive disorder were randomly assigned to receive Botox injections or a placebo. Six weeks later, 52% of the people who received Botox experienced a drop in reported symptoms, compared with 15% of the people given a placebo. “Over 50% of people responding is a high number,” says Finzi. “These are people who have already tried other treatments, and they are significantly depressed.”

Now Allergan hopes to replicate the findings on a larger scale, and the company is currently running its own Phase 2 clinical trial. If its results are in line with Rosenthal and Finzi’s, it would be huge, paving the way for Botox to obtain official approval for the drug as a depression treatment. That wouldn’t change anything for doctors, of course—they can already prescribe it off-label, and some do, with great results—but it would allow Allergan to begin marketing Botox for depression, a change that could dramatically increase its adoption and sales.

Still, Botox’s use for depression raises a question that confounds some researchers. In some cases, how Botox works is evident: the toxin can block the signals between nerves and muscles, which is why it can help calm an overactive bladder, say, or a twitching eye, or the facial muscles that make wrinkles more apparent. In other cases, however (with migraines as well as with depression), scientists are flummoxed. They may have noticed that the drug works for a given condition, but they aren’t always sure why—in sciencespeak, they don’t know what the mechanism is.

With depression, Rosenthal and Finzi think it may relate to what’s known as

the facial-feedback hypothesis, a theory stemming from research by Charles Darwin and further explored by the American philosopher and psychologist William James. The theory posits that people's facial expressions can influence their mood. Lift your face into a smile and it may just cheer you up; if you can't frown or furrow your brow in worry, perhaps you won't feel so anxious or sad.

But it could be something else altogether. In 2008, Matteo Caleo, a researcher at the Italian National Research Council's Institute of Neuroscience in Pisa, published a controversial study showing that when he injected the muscles of rats with Botox, he found evidence of the drug in the brain stem. He also injected Botox into one side of the brain in mice and found that it spread to the opposite side. That suggested the toxin could access the nervous system and the brain.

"We were very skeptical," says Edwin Chapman, a professor of neuroscience at the University of Wisconsin–Madison, after reading Caleo's study. But in August 2016, Chapman and his graduate student Ewa Bomba-Warczak published a study in the journal *Cell Reports* showing similar spreading effects in animal cells in the lab. For Chapman, it explained what he was hearing anecdotally from doctors: that Botox might be influencing the central nervous system and not just the area where it's being injected.

Ironically, it's the off-target effects of Botox that have some researchers most excited. "Botox may be working in a way that is different from what we think," says Bomba-Warczak. "It may be even more complex."

Chapman and Bomba-Warczak both think Botox is safe when used correctly, but they say their inboxes quickly filled with messages after their study was published. "We were startled by the number of people who feel they were harmed by these toxins," says Chapman. "We feel these were pretty safe agents. Now it seems that for some people, they believe the toxin can sometimes cause something that may be irreversible. And that's a total mystery."

Allergan says Botox is well established as a drug and that the benefits and risks of toxins are well understood. "With more than 25 years of real-world clinical experience ... approximately 3,200 articles in scientific and medical journals, marketing authorizations in more than 90 markets and many different indications, Botox and Botox Cosmetic are [among] the most widely

researched medicines in the world," an Allergan rep wrote in an emailed statement.

Even if Botox's mechanism isn't always well understood and some of its off-label uses are still unproven, interest in the drug isn't likely to wane. "Botox is a big cash cow for the physicians' practices," says Ronny Gal, an investment analyst at Sanford C. Bernstein who has watched the drug closely for more than a decade. "When I talk to physicians, they say, 'Botox is not a problem. It works and gives you the result you want.' If it works for depression and atrial fibrillation, it could be massive."

IN NOVEMBER, the FDA held a two-day hearing asking for expert comment on the agency's rules concerning off-label drug use and marketing. Some said the practice paves the way for scientific progress and gives doctors and their patients much needed alternatives for hard-to-treat medical conditions. Others said that off-label drug use is primarily financially motivated and that it poses a serious threat to public health, particularly when drugs are used experimentally on children.

Off-label use is a topic the FDA has been eyeing for some time. "There have been many instances where unapproved uses of a drug, even when commonly accepted by the medical community, have later been shown to be unsafe or ineffective or both—sometimes with devastating consequences to public health," says the FDA's Peddicord.

It's unclear how the FDA's focus will pivot with the next Administration. President-elect Donald Trump has pledged that in his first 100 days, he would be "cutting the red tape at the FDA," and insiders have speculated that a Trump Administration would loosen the agency's already limited oversight on off-label use.

But even if the laws remain unchanged, as long as off-label uses are permitted by law, expect doctors to keep pushing the boundaries of Botox's applications—sometimes in the name of medical progress and sometimes with remarkable results.

Norman Rosenthal, the Maryland psychiatrist who recommended Botox for his suicidal patient, says he's seen the upside firsthand. The patient, persuaded by Rosenthal, did indeed get Botox shots on his forehead and between his brows. Days later, Rosenthal got an email from the patient. It was a thank-you note. Finally, the patient wrote, he was feeling better. □

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EWA BOMBA-
WARCZAK, University of
Wisconsin–Madison