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
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 psychologist 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, 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, nor 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 it’s been proved to work for that condition.

Now, thanks to one of Dr. Rosenthal’s 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 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.

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Botox and Dystonia

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“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 the Chicago Tribune in 2012. Scott named the drug Oculinum and formed a company of the same name in 1978. In 1995 he received FDA approval for the treatment of strabismus (the crossed-eye disorder) and abnormal eyelid spams.

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:

WHAT IS BOTOX?

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

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.

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 patients are not informed about possible side effects. Still, serious side effects have been reported.

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 Botox and potential Botox applications

$12.5 billion

In 1998, Botox global revenue was $12.5 billion. By 2015 global revenue hit $2.45 billion.

$2.45 billion

Revenue from Botox

513 million

In 1991, Allergan paid $9 million for a small company that sold Botox.

$9 million

“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.

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WHAT BOTOX IS USED FOR

Best known for reducing facial wrinkles, Botox is approved by the FDA for the conditions below. The drug now brings in significantly more revenue for its noncosmetic uses.

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<th>FDA-APPROVED Uses (off-label trials were required before Botox was determined to be safe and effective for these uses):</th>
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<td>Strabismus (crossed eyes)</td>
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BOTOX IS USED FOR

- Reduced facial wrinkles
- Overactive bladder
- Cervical dystonia
- Severe underarm sweating
- Upper-limb spasticity
- Chronic-migraine prevention
- Overactive bladder
- Lower-limb spasticity
- Some facial wrinkles

That’s why for any off-label uses that Allergan wants to market to doctors and the public—depression, cold hands, ataxial 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 Finzi’s Brin. “It still has many different, exciting, meaningful opportunities for patients.”

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

SARAH PEDDICORD, FDA

In 2010, the FDA approved Botox for migraines, with severe underarm sweating, facial spasticity and juvenile cerebral palsy. But even then, the FDA was warning that the drug’s off-label use was causing “significant and sometimes severe” side effects, more common in women. Now Allergan is pushing to expand the drug’s off-label uses even further, sometimes with controversial treatments.

On December 30, 2015, the FDA announced that it was warning Allergan about the drug’s off-label uses. Over the past five years, the FDA had received reports about off-label use of Botox. But the agency had not conducted a comprehensive review of the drug’s safety and efficacy for off-label uses. The FDA had also not issued any formal guidance to doctors about the drug’s off-label uses.

The FDA is currently conducting a review of Botox’s safety and efficacy. The agency is also considering whether to issue a warning about the drug’s off-label uses. The FDA has not yet announced any changes to its guidance for doctors.

In the meantime, doctors are using Botox for off-label uses on a daily basis. Some doctors are using the drug to treat conditions that have not been approved by the FDA. Some doctors are using the drug to treat conditions that have been approved by the FDA but are not approved by the FDA in the way the doctors are using it. Some doctors are using the drug in ways that have not been approved by the FDA.

In the case of the drug Botox, the question of whether the benefits of the drug outweigh the risks is a question that has been debated for years. The drug is approved by the FDA for a number of conditions, including overactive bladder, cervical dystonia, and spasticity. But the drug is also used off-label for a number of conditions, including headaches, migraines, and pain. The question of whether the benefits of the drug outweigh the risks is a question that has not been answered by the FDA.

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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.