Why a third of antidepressants are prescribed for something else

19 December 2017, by Leah Shaffer

It was when he became a father that Michael Briggs resolved to somehow bring his ulcerative colitis under control. He was determined to avoid what many people with the disease end up needing – having part or all of their large intestine removed. A trained scientist, manager of a physics lab at the University of New Hampshire, he began reading medical research papers, looking for anything that might help him.

He knew there wouldn't be just one single cure, just as he knew there was not one single cause behind this inflammatory bowel disease (IBD), which causes gut pain, bleeding and diarrhoea. He had already been on a drug called Remicade (infliximab) for more than five years. This blocks the action of an inflammatory protein called tumour necrosis factor alpha (TNF alpha) in order to stop the immune system from attacking the colon wall. The problem is that drugs like this can have significant side-effects, such as leaving patients more prone to infections and, in rare cases, cancer. Another problem, Briggs tells me, is that the drugs stop working as people's immune systems develop antibodies against them.

Briggs knew he couldn't stay on infliximab for ever and he was tired of dealing with the cycle of flare-up and remission with his disease. Seeking a way to heal following a nasty flare-up during the summer of 2013, he sifted through more than 150 papers on anti-inflammatory supplements, diet and TNF blockers.

Eventually, he stumbled upon research suggesting that an antidepressant called bupropion has an effect on Crohn's disease, another type of IBD where the immune system attacks the lining of the gut. Studies on mice had shown that instead of blocking the action of inflammatory proteins, bupropion appears to lower the production of those proteins in the first place.

Briggs decided to give it a try.

Off-label

It's not unusual for a drug to be prescribed for a disease it hasn't been officially approved to treat. It's certainly not illegal; it's not even that difficult. Doctors all over the world are allowed to prescribe drugs off-label, and antidepressants are used for several conditions and diseases beyond depression, including migraines, hot flashes, attention deficit hyperactivity disorder (ADHD) and disorders of the digestive system.

Off-label use means that more potentially effective treatments have a chance of becoming available in medical practice. But it also means that the drugs haven't been tested in clinical trials or received approval from regulatory agencies for these other uses. The potential downside, in the case of antidepressants, is that doctors won't know about possible risks when these drugs are used by people who are not depressed. Their side-effects include insomnia, decreased libido and suicidal thoughts, but that knowledge has been gleaned from clinical trials with depressed patients. You could assume that the same risks apply to depressed and undepressed patients, but again, that's yet to be extensively tested.

Bupropion has been around for more than 30 years, however, and has a pretty good track record for safety. Even so, aside from a few assertive patients like Briggs, very few people know bupropion might have a double life as an IBD drug.

Within two weeks of starting bupropion, Briggs was bleeding far less and had experienced almost no side-effects. Gradually, all his bleeding stopped. After using bupropion to get his disease under control, he added a variety of anti-inflammatory supplements and changes in diet to keep his ulcerative colitis from flaring up again. He believes he has succeeded in creating a functional cure for his disease – he's remained in remission since starting his 'protocol' in 2013, and he's continued to

research the molecular mechanisms behind colitis so he can fine-tune his regimen.

He's written about his research and experiences to help spread the word to others with colitis. And like any good researcher, he declares his interests: "In research papers, it is typical for the author to disclose any vested interests that might bias their views. In that vein, I want to clarify that I have a vested interest, which is that I hope to never crap blood again."

First-hand experience

I have to declare an interest, too: I also have colitis, and I followed Briggs's lead after he shared his protocol. I first asked my gastroenterologist about trying bupropion, but he waved it off as a mental health matter. (Briggs says it's typical for patients to get bupropion from primary care physicians rather than specialists.) My psychiatrist was justifiably cautious. I was already taking a different type of antidepressant for anxiety and sleep problems, so she wasn't sure about giving me a drug that could cause insomnia. But since I could quickly get off bupropion if its side-effects were intolerable, she was willing to give it a try.

Bupropion wasn't a miracle cure for me, but after taking it, I didn't have to go to the bathroom as many times each day. As for side-effects, I didn't have insomnia, but did feel jittery the first week of taking it. As Briggs had predicted, those side-effects quickly subsided. He estimates that, of the people with IBD who have contacted him about bupropion, 80 per cent have had complete success, while the remaining 20 per cent saw improvement.

I still take bupropion – it improved my colitis symptoms, and my psychiatrist believes it can be complementary to the other antidepressant I take because different antidepressants affect different chemical messengers in the brain, called neurotransmitters. The bupropion frees up more dopamine and norepinephrine, while the other, escitalopram, is a selective serotonin reuptake inhibitor (SSRI) that frees up more serotonin. All this appears to decrease my anxiety.

It seems surprising that antidepressants should work on other diseases, but perhaps it's time to stop thinking of these drugs as 'antidepressants' and admit that they are not one-trick ponies, but jacks of all trades. Antidepressants can all help relieve depression, but they do this in many different ways, acting on different chemical messengers in the brain and nervous system. Those same neurotransmitters have roles in controlling what happens in other organs and systems, so it's no wonder that antidepressants have other effects. Some are unwanted, which we call side-effects, and others are useful, which may be why almost a third of antidepressant prescriptions are off-label.

But the very nature of how we regulate and produce drugs means there are many obstacles to understanding everything that a drug might be capable of. And that means patients could be missing out on potentially beneficial treatments.

A little bit of luck

The research that persuaded Briggs to try bupropion was published by an unorthodox Vermont psychiatrist named Richard Kast. Kast has made a career of seeking new uses for old drugs, often doing research during his free time while running his clinic.

In 1999, Kast had started treating a woman with Crohn's disease for depression. When he switched the woman from fluoxetine, an antidepressant that increases serotonin availability, to bupropion, something entirely unexpected occurred. Her Crohn's went into remission.

It was remarkable because, despite the powerful anti-inflammatories she was taking, she had had chronic abdominal pain, blood in her stool and frequent bouts of diarrhoea until she started bupropion. Kast increased her dose of bupropion and her Crohn's symptoms decreased further, to the point where she had normal bowel movements once a day and no pain. On occasions when she stopped taking bupropion, the blood and abdominal pain returned until she started taking the drug again.

In 2001, Kast and neuroscientist Eric Altschuler wrote the case up for a scientific journal, alongside

another case they'd found of a middle-aged man who had suffered from Crohn's for 20 years but went into remission when he started taking bupropion. They followed this up with a couple more papers exploring the mechanisms behind how bupropion might work to treat IBD. It sounded promising, but they didn't think they could drum up the interest or funds to do clinical trials.

Science is littered with these kinds of stories. Case studies offer intriguing results, there are small studies with mice that seem promising, but then it fizzles out. To truly vet a treatment, it must undergo multiple phases of randomised, double-blinded clinical trials of hundreds of patients, which can cost millions of dollars. With a drug like bupropion, one that's already been through trials for one indication, and which might not be particularly profitable any more, there isn't much incentive for pharmaceutical companies to invest in additional large clinical trials – and there's no guarantee the process will go smoothly, as one manufacturer has found out in recent years.

A cautionary tale

In the late 1990s, breast cancer survivors with depression started reporting anecdotally that their prescribed antidepressants also helped alleviate menopausal hot flashes. Women with a history of breast cancer were advised not to take hormonal replacement therapy (HRT) during the menopause because it could increase the risk of breast cancer recurring, so it was promising to have found something else that might help.

Then, in 2003, results from the Women's Health Initiative study in the USA and the UK's Million Women Study suggested that hormone therapy might increase the risk of cancers and stroke more generally, alarming both physicians and patients. More than a decade later, hormone therapy is making a comeback for some women, as researchers have concluded that the risks to middle-aged women just starting the menopause were overhyped following those studies. But when the studies came out, many more women became interested in avoiding hormones, and researchers started seriously testing the efficacy of using antidepressants for hot flashes.

Hadine Joffe has worked on a number of such studies for a project called MsFLASH, including a three-armed study comparing the effects on hot flashes of a placebo, low-dose oestrogen or an antidepressant. Both oestrogen and the antidepressant were better at relieving symptoms of hot flashes compared to placebo. There was maybe a small advantage to oestrogen, but it was not meaningfully different, Joffe says.

In 2013, the US Food and Drug Administration (FDA) approved Brisdelle, a low-dose version of an antidepressant called paroxetine, created specifically for relieving hot flashes. But the decision came despite a recommendation against approval from the FDA's own advisory committee – something that happens only rarely.

The Reproductive Health Drugs Advisory Committee's disapproval was not to do with safety. Joffe says there are plenty of trials showing the safety of antidepressants, although others might not agree that this data is applicable to women who are not depressed. But the clinical trials for Brisdelle did not show any more adverse reactions compared with placebo.

Instead, the committee's recommendation was about efficacy. To be approved by regulators, studies should ideally show a drug is both safe and more effective than placebo – which sounds reasonable until you find that, when studying antidepressants, there is generally a very high placebo response.

Analysis of many depression studies has found that more than 80 per cent of antidepressants' effects could be attributed to placebo response. In the studies of Brisdelle, 48 per cent of the participants saw their hot flash symptoms reduced by at least half. Sounds good, but in the placebo group, 36 per cent also saw a 50 per cent reduction in symptoms. Not a huge difference.

That means "you have to be very cautious in assuming that the numbers you get from a study are significant," says Julia Johnson, a gynaecologist at the University of Massachusetts. She was chair of the Reproductive Health Drugs Advisory Committee at the time that Brisdelle came

through for a decision. She adds that off-label use alone cannot provide evidence that a drug should be FDA-approved for a new indication. The data must be "very, very strong that this has benefits that outweigh its risks".

So why did Brisdelle end up getting approved? It boiled down to the fact that having one non-hormonal treatment for hot flashes was better than nothing. Since then, however, off-label use of other antidepressants for menopausal women remains common.

When Susan Grier's doctor wanted to take her off oestrogen last year, they suggested an antidepressant, though not Brisdelle. Instead, 60-year-old Grier, from New Jersey, has been taking venlafaxine, a type of serotonin and norepinephrine reuptake inhibitor. She hasn't experienced any side-effects.

"I've found it has reduced my hot flashes, although I still get them," she says. "I didn't really believe an antidepressant would be of any assistance. I had a few days where I didn't have my medication with me and the hot flashes substantially increased."

Because doctors have been able to prescribe other antidepressants off-label and reduce hot flash symptoms, FDA approval likely hasn't yet translated into huge profits for Brisdelle's manufacturer. "It's not like everyone rushed to use Brisdelle," says Joffe, noting that insurance companies might be more likely to pay for a generic antidepressant than for a new brand-name drug (generic paroxetine costs $10 a month compared to $200 a month for Brisdelle). And because of that, there is less incentive for drug companies to pay for clinical trials, as it's less likely they'll profit from them. So do we need new ways to explore different uses for licensed prescription drugs?

Building the evidence base

For Jenna Wong, a researcher at McGill University in Montreal who studies off-label use of antidepressants, the future doesn't necessarily lie in dragging old drugs through the regulatory approval process again. Instead, she thinks doctors need to get better at tracking drug indications in the first place.

In many places around the world, a prescription for an antidepressant doesn't list whether it's actually used for depression or not. France is one of the few countries to set up a system of evaluating drug indications by requiring drug companies to track off-label use. There, companies have a three-year window to evaluate unlicensed use of their drugs and attain additional licensing. But setting up a similar system large-scale would be difficult.

Wong is able to track and study off-label use because her lab's lead investigator, working with physicians in Quebec, has set up a database that includes the specific indications for their prescriptions. Wong says we need accessible databases that compile the evidence for or against off-label uses.

It's not that off-label use is bad, she says, it's just when doctors find these extra uses, they should be able to back that up with plenty of evidence. "When I talk to a lot of physicians, they didn't know certain uses were not approved," she explains. Often they also don't know which uses are based on sufficient evidence. "The off-label uses without evidence, that's what we're concerned about."

But it takes time to track down that evidence, and there can be contradictory results. For example, a couple of studies suggest that use of bupropion is associated with a lower risk of glaucoma, but a few others show an increased risk. Without further research, what's a doctor to make of it?

Pick your poison

The story of how doctors discover new uses for antidepressants is usually the same, according to Jeffrey Jackson, professor of internal medicine at the Medical College of Wisconsin. Patients report to their doctors that more than just their depression has improved after taking a drug. This has happened in cases of people with dyspepsia, irritable bowel syndrome, chronic pelvic pain, chronic prostatitis, fibromyalgia, headaches and more.

A few antidepressants do have multiple indications,

meaning they are approved for purposes besides mental health. Duloxetine (Cymbalta), a serotonin and norepinephrine reuptake inhibitor, has indications for mental health disorders and also nerve pain such as fibromyalgia, or even osteoarthritis. But the complexities of how patients respond to pain mean that one drug or treatment doesn't work for everyone. So other antidepressants are also often used off-label to treat pain. They have proved effective at preventing migraines and reducing the severity of chronic back pain and gastrointestinal pain, according to Jackson's research.

Wong's study found that the tricyclic antidepressant amitriptyline, which is only approved for depression, was almost always prescribed for off-label indications, mostly pain, insomnia and migraine. Another antidepressant called trazodone is almost exclusively used off-label for insomnia.

Jackson has written several reviews of the efficacy of antidepressants in chronic pain relief. They can have a fairly modest effect, he says: "If your pain was 8 out of 10, it would probably reduce you to 5 [or] 6 out of 10." But that can make a big difference to someone's quality of life.

It's a bell curve, he adds. Some patients have a more dramatic response, some don't respond, but the average patient's response is modest. There is some evidence that the tricyclic antidepressants are marginally more effective at controlling pain, but they also have more side-effects, so it's a 'pick your poison' situation. "It can be a difficult choice for patients."

That's why Jackson will try out different medications to see what works. "I try and figure out which ones work for them and also which ones don't have crazy side-effects," he says.

It doesn't help that most people don't really know what antidepressants do. Some assume they will have a profound effect on their mood, or will drug them up. "I try to emphasise: your basic personality doesn't change," says Jackson.

People who have suffered from pain for many years can also be defensive if doctors suggest an antidepressant – they don't want to be told the pain is all in their head. "I will say, 'Listen, everything in the universe is in your head, pain is perceived in your brain.'"

Indeed, a growing body of evidence suggests that one of the more effective treatments for pain is cognitive behavioural therapy (CBT) – changing the way people think about pain to change the way it feels. Jackson's argument to persuade patients is that antidepressants can work directly on their physical symptoms, but it will also help the depression that comes with physical misery.

Because pain and depression go together, researchers have been careful to screen out depressed patients when studying the effects of antidepressants on pain. This is to make sure any improvement in symptoms is not just from depression relief. From such studies, it appears that the effect of antidepressants, specifically the tricyclic antidepressants, was independent of the effect on depression, says Jackson. There was some overlap, "but there does seem to be an effect that was separate from that".

Yes, your mood is improved, but the antidepressant appears to also impact how your body processes pain signals.

And it does not take as much of a dose to improve pain compared to relieving depression. In Jackson's clinic, he'll slowly work his clients up to higher levels of an antidepressant until their symptoms improve. For example, if he's using the tricyclic antidepressant amitriptyline, doses can go up to 300 mg a day for people with depression. But for pain symptoms, he starts as low as 10 mg and increases the dose slowly until the patient feels better.

He not expecting to cure disease. "But if I can make [people] more functional and feel better, that's a win."

Houston, we have an opportunity

Richard Kast, who studied bupropion for Crohn's, continues to seek new uses for old drugs. His quest has taken him to research areas well beyond

behavioural science – as well as IBD, he's delved into treatments for brain cancer, often through off-label use of antidepressants.

There is a growing movement to repurpose old drugs, he says, but it's still not a common practice. "The normal thing is to get a bazillion dollars from some drug company or some funding agency and then explore new molecules."

Instead, Kast likens his work to the scene in Apollo 13 where engineers try to figure out how to fix the space shuttle by using the ordinary objects found within it. Researchers have this box of approved drugs, he explains: "That's what we have to work with. Now what can we see in the pile of drugs, what is there that we can potentially use to do what we want?"

Recently, he has been working on setting up trials of drug regimens for recurrent glioblastoma, a type of brain cancer that is very difficult to treat. One of the regimens is called CUSP9 and includes nine repurposed drugs, including the antidepressant sertraline. None of these drugs is indicated for cancer treatment, yet together they're intended to block pathways for tumour growth. And, although nine seems like a lot of medications, all the drugs are well-tolerated and affordable, which is unusual for cancer treatments.

Kast is fine with continuing to mine potential drugs off-label. Just because a drug has been labelled an antidepressant, that doesn't mean it can't help treat other conditions. And they are so often used off-label that the label 'antidepressant' may now be a complete misnomer.

"That's a name we use, but they're not really 'antidepressants'," he says. "They block a certain neurotransmitter pump." Whatever we call it – a serotonin agent, clog for neurotransmitter pumps, something entirely different – "the drug is doing what it's supposed to do in the brain."

He offers another example of how antidepressants might help supplement cancer treatment: the antidepressant mirtazapine can dramatically increase appetite in people with cancer, and prevent the appetite suppression associated with the disease treatment. But like many insights from off-label prescribing, the idea remains intriguing and, for the moment, obscure.

"No one is going to fund research like the kind I do," says a resigned Kast. "It's not what people expect. It's not what you're supposed to do."

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