SSRIs Part 1

Firsthand 1, SSRIs Part 1: My name is Will, and my experience with SSRIs and SNRIs started when I was in pharmacy school, actually. I was diagnosed with both anxiety and depression at the same time, which, uh, was a lot of fun, um, especially when I was in a doctorate program. And my doctor started me on escitalopram, on Lexapro. It worked fairly well for a while. Uh, needed a little bit of help from buspirone to get through the anxiety. But I did okay. That said, I still had some breakthrough symptoms and I especially had side effects. I had a lot of the sexual dysfunction side effects and I also gained about 30 pounds.

So I swapped off of that for a while, went on a little bit of a vacation, but then my symptoms started coming back and getting worse. So I got started on Wellbutrin, uh, bupropion, and I did a lot better symptom-wise on it, but again, I had really, really bad side effects and it wasn't so much suicidal ideation as it was just an acute knowledge of my own mortality, which is not great when you have anxiety and depression. So at that point, I had the, the wherewithal because of my education as a pharmacist to ask my doctor to go on and do genetic testing, um, which I'm glad I did because when we got the results back, it turned out that there were only about two antidepressants and a couple of anxiolytics that were on my green is go list, that that is to say, you know, that my, hepatic enzymes could metabolize without giving me too bad side effects.

And that is kind of the journey of how I found Pristiq, desvenlafaxine. That is the miracle drug that worked for me. But I still can't help but wonder how long it would've taken me to find my miracle drug if we did it kind of the old-fashioned way, if I hadn't known to ask for this genetic testing. I could have been trying and failing SSRIs and SNRIs for years before I found the drug that worked for me. So, you know, I, I try and advocate for the genetic testing and for, being your own advocate as a patient whenever I can, because I just, I know that there are a ton of people that don't have the same sort of background as I had the, good fortune of, of having. So, um as a fellow health professional, I definitely tell patients all the time, make sure you're advocating for yourself, even if it's just asking questions.

Firsthand 2, SSRIs Part 1: Taking SSRIs is the best thing I've ever done. I've always had trouble with OCD and general anxiety from a young age, probably as long as I can remember. Um, I would have like a baseline level of anxiety and OCD, and then every so often, I'd have these periods where it got so much worse and it was all-consuming.

I spent all my time in my own head worrying, ruminating, doing mental compulsions. I struggled to eat or sleep or socialize, and it really started to have an effect on my personal life. I managed to get through work and other commitments without most people noticing, but I wasn't present and it was really horrible to endure. I felt like I didn't deserve anything nice or for my family to be even sympathetic to me because of these awful, intrusive thoughts I was having. These periods were so difficult that when they subsided, I was so grateful that I didn't even notice the baseline level of anxiety I had all the time and how much of an impact that was having on my life.

Last October, I had an OCD flare up, and it was the worst it's ever been. I was in a really dark place. My therapist recommended taking fluoxetine, and I was so desperate to feel better, I would've taken anything. Within a few weeks, I started to feel more myself again. The thoughts quietened and I remember getting really emotional because it was so strange for me to feel like that. My mind being quiet for once. I can't emphasize enough how much of a positive impact they've had on my life. It was the first time in my life I'd actually felt content in myself and excited for the future. I'm so much happier now and just enjoying life to the full. I'm so grateful that I don't have to feel that permanent level of anxiety and intrusive thoughts anymore. I've literally never felt like this in my life before, and it really hammered home how much I'd been struggling on a daily basis and didn't even notice. The tablets alongside the therapy were like a helping hand to pull me out of a really dark hole. My only regret is not taking them any sooner.

EW: Thank you so much for providing your firsthand account. That really means it means so much. I know we say it all the time, but it it, it always does. It really does.

EAU: it means so much every single time, honestly. So thank you and thank you to everyone who wrote in. Uh, we really, really do appreciate it.

EW: we do. Hi, I'm Erin Welsh

EAU: And I'm Erin Allmann Updyke.

EW: This is, This Podcast Will Kill You

EAU: And today we're talking about SSRIs,

EW: SSRIs, and next week we're talking about

EAU: SSRI.

EW: Yeah, I mean it really does warrant at least two full episodes. Like there's so much there, uh, in the history, in the biology and sort of the, the current

EAU: discourse.

EW: Jinx. We did not plan

EAU: No, we didn't.

EW: God. That's thrilling. Just shows that we're best friends,

EAU: Yeah. And we spent way too much time like thinking about this too.

EW: and with each other. Yeah. Yeah.

EAU: But yeah. So we're gonna do a two-parter. Um, this week. Erin Welsh's gonna tell me all about the history because I don't know it other than like, we had MAOIs and then TCAs and now SSRIs. That's what I

EW: Done. Next episode.

EAU: Uh, and then next week I'll get into what we think we know about how SSRIs actually work in their mechanism. And then, yeah. I'm excited to tell you what I know. Uh, and then some of the, yeah, the current discourse. We'll say

EW: Uh, but before we get into all of that, it is of course quarantini

EAU: time or should we say placeborita time this week?

EW: We've been like mixing it up and every now and then it's like, what do you, what do you feel like doing? Oh, placeborita this

EAU: We'll do This one.

EW: yeah. Uh, this week is the Serotonin Spritz.

EAU: Be anything else. It could have been actually, we thought about other

EW: Yeah. We had other names and we were like, this is as bad as it is. It's the best we can do. Serotonin spritz. It's pretty simple. It's um, it's got soda water, hence the spritz. It's got sparkling apple cider and some pineapple juice and it's tasty. It's simple. It's refreshing.

EAU: Yeah. Nice. For a, a warm or a cold day. Right.

EW: Um, yeah,

EAU: Yeah, sure.

EW: Jack of all trades. Anyway.

EAU: the full recipe on our website. This podcast will kill you.com and our socials, are you following us there? Because you could and should be. We're on Instagram, TikTok, the Facebook Blue Sky. We are also online on a website called This podcast Will Kill you.com. Have you checked it out yet? Because if you haven't, what a wealth of things you'll find there.

EW: Many things.

EAU: bookshop.org affiliate, A list account that we have. Um, a good read,

EW: You're doing

EAU: a thank you. A good reads list. Uh, transcripts. We've got, um, blood mobile. We've got sources from every single one of our episodes, including this one. Um, what else?

EW: Is now on Instagram, so

EAU: Oh, really? That's exciting.

EW: Check him out. Check him out.

EAU: We've got merch, we've got a link to our Patreon account. Um, if you haven't yet dropped a, what do you call it? Rate and review and subscribe. I'm trying to do too much.

EW: sure to do that.

EAU: Do it. Okay. We're on YouTube.

EW: we go. I was just trying to take a little off your plate,

EAU: Thank you. My plate is done. The end.

EW: end and the beginning. Uh, let's take a quick break and get started.

EAU: I can't wait.

EW: In December, 1987, the FDA approved Prozac for treatment of depression and it became the first SSRI to hit the US market the following January.

EAU: Okay.

EW: Within two years, pharmacies were filing 1 million prescriptions each month.

EAU: Wow.

EW: Yeah.

EAU: In the us

EW: the us. Mm-hmm.

EAU: Wow.

EW: Today global numbers are hard to pin down. I'm sure you'll do some error errand math maybe, but,

EAU: No, no, I won't. Sorry.

EW: Well, they're really hard to find. I mean, I Googled for like five minutes and no, it was longer than that. It was,

EAU: I believe it was substantially longer than that.

EW: But I did find one estimate from the CDC in from 2018 where they suggested that 13% of people in the US are on antidepressants, which comes out

to around 42 million people. And this is likely an underestimate since prescriptions have increased in recent years

EAU: Okay.

EW: as antidepressant use has grown, so has the controversy surrounding these medications. RFK Junior, the [00:05:00] secretary of the US Department of Health and Human Services, despite having zero medical training, has made claims that SSRIs are more harmful and addictive than heroin. These are claims not supported by any data and has proposed limiting their use instead sending people to quote unquote, wellness farms. I mean, we could do an entire,

EAU: I am sorry. It's just so unserious, but it's very serious because he is very much in charge of everything right now. Um, but it's, it's one of those, you laugh or you just break down and give up on everything.

EW: it is. I mean, I'm scared every day and it feels surreal every day and Yep. Yep. I mean, this is like, wellness farms are not a new concept and uh, it's never been a good concept. We could do an entire episode in the dark history of wellness farms, or the ones similar to the ones that he presumably has in mind. That's my guess. And how ableist and racist and sexist and classist they are. Uh, it's dark.

EAU: It's dark.

EW: It's dark, but this controversy extends beyond conspiracy theories and conspiracy theorists like RFK Jr, with some psychiatrists and researchers expressing reservations about the way that we use or think about antidepressants and mental health disorders. Prompting the popular media to release articles, exploring this controversy with headlines like the risks and rewards of antidepressants, and do antidepressants work better than placebo?

EAU: Mm.

EW: Despite all the progress that has been made in raising awareness and being open about mental illness, it is still a taboo subject in many ways.

EAU: Very much so.

EW: Acknowledging that you struggle and seeking help because of that is perceived by some as or by many as a weakness. Oh, we all get a little blue here and there. You don't need meds. Just think on the bright side. Go get some fresh

air. Just take a walk, take a, take a nice little stroll. Or, yeah, I get anxious too. Sometimes you just, I just try not to think about it. Just kind of put it in a box, put it away. Don't just, just stop.

EAU: Yeah. Just stop.

EW: Just stop.

EAU: Just stop being anxious and depressed.

EW: Easy, it's easy. Uh, the, the stigma surrounding mental health disorders also extends to the treatments that people seek, whether that's an SSRI or therapy. And it, the stigma, no doubt, contributes to the constant questioning of antidepressants by the general public. However, the skepticism that some researchers or healthcare practitioners express towards SSRIs, while likely influenced by this overarching doubt, is also informed by the gaps in our scientific knowledge about the causes of mental illness and the mechanisms by which SSRIs may work to improve symptoms. So, in other words, like what do these medications do and how do they do it?

EAU: Mm-hmm.

EW: next week, Erin, I know that you're gonna take us through the long answers to these questions, but the short answer is that we don't really know.

EAU: Yeah, that, I mean, that's the conclusion of next week's episode.

EW: Yeah. Well, I mean, we have some ideas and those ideas have changed over the decades, but we don't know for certain how these medications work, and that's partly because we don't understand the underpinnings of depression, of anxiety, of obsessive compulsive disorder and of other mental health disorders.

EAU: Yeah.

EW: And at first glance, that maybe that sounds a little strange. Like what do you mean we use these antidepressants, but we don't quite know how they work,

EAU: It doesn't sound strange if you work in medicine, Erin,

EW: I was gonna say there are still, there's so many medications that are also mysterious. There's acetaminophen, paracetamol, uh, we don't know why or how it reduces pain and fever. Metformin is still a bit of a black box. Even a few of our general anesthetics hold some mystery.

EAU: There is probably more medicines that we do not fully understand. Not, and I don't just mean like how they work, like a, a lot of things we know, like it binds to this receptor and this mechanism happens. That does not mean that we understand how, like why do they improve the things that they improve? Because we use a lot of medicines for a whole bunch of different stuff. Like I'm gonna get into it next week more as well too. Like this concept and the way that we talk about these medicines for depression versus other medicines that we don't understand. But yeah, it's, it is not just SSRIs.

EW: not. It's not. And I think that this speaks to how our approach to drug development is not always guided by a find the specific problem engineer, the targeted solution mindset. Like that's just not the way that drug development often works. And maybe, maybe that's the ideal way, [00:10:00] but like that rarely, rarely happens or it doesn't happen. And we, we think that we found the solution, but it's like, well, we didn't quite understand the problem in the first place.

EAU: That's the thing. You have to know the problem very clearly to be able to do that kind of targeted development. So we have that for some situations, right? For some cancers, for example, like, but not for a lot of other disorders that are more nebulous, that have multiple factors that contribute to their development.

EW: I mean, it's kind of, it's kind of amazing. Like it, and just, just how much serendipity can play a huge role in bridging these gaps of like, we, here's this problem. What's the solution? We don't have the information, but then something comes along and it's like, Hey, that seems to work. How does it work? We'll figure that out later. Right now we know that it works.

EAU: Mm-hmm. It's what is it doing first and then how does it work? And we don't have the, how does it work for a lot of

EW: Yes. Yeah. And so what I wanna do in this episode is take us through the story of SSRIs, starting with serotonin itself and how the first antidepressants were developed, and then ultimately ending with. Kind of a small reflection of how these medications have led a revolution in our understanding and

perception of mental illness. That's the good, the bad, and everything in between.

EAU: I can't

EW: So let's start at the beginning with serotonin. The neurotransmitter and cellular messenger. That's the star of this episode,

EAU: I can't wait.

EW: which, um, to do this means that we have to start pretty far back, like billions of years

EAU: You know I love it when you go deep time, Erin.

EW: I mean, I'm not gonna stay deep for very long, but

EAU: okay.

EW: it is, I was so surprised to learn how ancient serotonin is,

EAU: Hmm.

EW: I mean, two to 3 billion years ago.

EAU: Wow.

EW: It can basically be found in all walks of life from bacteria to protozoans, leeches, worms, fishes, birds, plants. Did you know that plants make serotonin.

EAU: No, but that makes me so happy.

EW: Know, I, I don't know. Dogs, humans, I mean, basically, yeah, I mean, dogs make sense. Plants is a little more like what?

EAU: It's a little what?

EW: But basically everything, it exists in all the organs of the human body, which is pretty fascinating, but not as fascinating as the fact that it's found in basically every living organism on this planet.

EAU: Wow.

EW: So what does this tell us? Like, it's so widespread and so ancient that it means that A, this serotonin is gotta be really important, super important, and b, just how many ways it is important, like the varied roles that it can play.

EAU: It's obviously not just doing one thing.

EW: It's not just, oh, this is the depression neurotransmitter in humans only.

EW: Right? Like, I mean, and, and we tend to think of and describe serotonin as a neurotransmitter, which it is, but it also existed before neurons did.

EAU: Oh my gosh. Stop.

EW: Isn't that wild?

EAU: ' cause if you're talking about bacteria have serotonin, I didn't know that.

EW: yeah, yeah,

EAU: don't have neurons.

EW: Exactly.

EAU: One cell.

EW: Neurotransmitter existed before it could be transmitted by neurons. Like, what? Isn't that so cool? It's so cool.

EAU: What it do? We know what that does in bacteria

EW: Uh, I'm not sure. A lot of it is like, uh, energy capture or regulation or management. Sometimes there's like, um, intercellular or like a signaling between different

EAU: So still a signaling molecule, which is what it is for us. Okay. Okay. Yeah.

EW: I mean it is involved, like these are just some of the things that it's involved in just across life, which is regulating cell activity and signaling, um, development and plasticity plays a huge role.

EAU: Ooh.

EW: energy consumption, metamorphosis, embryogenesis, digestion, feeding behaviors, motor activities, sleep regulation, neurological development, decision making, stress responses, mood, behavior, social dynamics, anxiety, learning and memory. Just to name a few, really.

EAU: name a few.

EW: to name a few. It's everywhere. Does everything. Yeah. And so Erin, I know that next week you'll tell us more about what Serotonin's role is thought to be in humans or like, at least some of the things that we know it does. But I wanted to share just a couple of fun tidbits that I discovered in researching for this. Like in not on the non-human side of things.

EAU: Okay.

EW: So we love leeches.

EAU: Ahuh, we do,

EW: And we, um, love kissing bugs is, love is not the right word, but we are intrigued by kissing

EAU: Uh, appreciate their, they are interesting creatures.

EW: Yes. Um, and we have episodes that feature both of

EAU: Mm-hmm.

EW: [00:15:00] creatures in, in these two in medicinal leches and kissing bugs. Serotonin acts as a signal to expand their, so that they can eat many, many, many more times their body size

EAU: It's what lets them just suck all of our blood.

EW: Yep. Yep. Just expand. Expand. It also seems to help, uh, leeches swim.

EAU: Oh.

EW: In some species of worms, it stimulates development and egg laying

EAU: Oh.

EW: in certain marine mollusks, environmental serotonin is needed to induce metamorphosis from the larval to the adult stage. And so it's thought that the serotonin is produced by algae, which the mollusks feed on. And so if you are detecting not high enough levels of serotonin and you're a mollusk and you're like, wait, where's the serotonin in the environment? And it's a little low, that could signal a resource poor area. So it's like, don't metamorphos here. You won't get enough to eat

EAU: What?

EW: serotonin.

EAU: Serotonin.

EW: It's, it's incredible. I mean, and we could spend forever talking about what serotonin does in different species or tissues or organs, but do you know what else is fascinating about serotonin?

EAU: I, I want to,

EW: How it was discovered?

EAU: Okay.

EW: Okay. I was surprised at of how much serotonin history. I was like, okay, I, I gotta start at the beginning. What's the, what's the story of serotonin? And then I was like, actually, this is fascinating. I've never thought about serotonin in isolation. Like I've always thought about it in the context of SSRIs or in mental health disorders and like, what does it do in humans without thinking of it as a broader picture. Yeah.

EAU: Yeah.

EW: Okay. So serotonin discovery, the early decades of the 20th century were an exciting time to be a molecular biologist, uh, because what they found was

that in these increasingly sensitive bioassays, allowed them to tease apart the functions of the tiny compounds that are constantly flitting around within the bodies of animals, humans, and other animals. Things like hormones or antibodies, uh, vitamins, and of course neurotransmitters. What do these different molecules do? How do they interact with one another? What happens if things go awry and how can we use all this knowledge to develop medications to treat certain conditions? These were the types of questions that motivated many researchers in the 1930s among them an Italian physiologist and pharmacologist named Vittorio Erspamer Yeah, Erspamer. Anyway, we will try that. I say his name a bunch more times. So great. Um, but Erspamer had a particular interest in deriving pharmacologically active substances from nature to use in medications. 'cause he, so he would be like, what is this plant alkaloid? Can we use this as a medication? What does it do? These sorts of things. Um, it was a very hot time for that. If you think also of things like willow and aspirin and you think of, um, quinine, malaria, that sort of thing. Anyway, so his work, Erspamer's work centered around the smooth muscle of animals and trying to figure out which substances caused it to constrict or contract. So he looked at the skins and intestines of rabbits, of molls, of mollusks, it's a hard word to say, and of frogs to name a few. And one substance found in a certain type of cells in the gut caught his eye. When he isolated it and tested it out, he observed that it caused smooth muscle contraction and it didn't seem to be any of the recently discovered usual suspects. It was something completely undescribed at that point. And so he named it enteramine in his 1937 paper.

EAU: Okay.

EW: Yeah. In the subsequent years, he found the substance in many other organisms and tissues, uh, mollusk heart, octopus, salivary glands. Like he, I guess, had a particular bent towards,

EAU: Ocean

EW: yeah, marine creatures. And he seemed quite enamored with it in a, in a letter that he wrote at 89 years old. So way, way later he described it as quote unquote, my firstborn daughter.

EAU: Oh, okay.

EW: loved enteramine. Yeah. But where Erspamer was actively looking for this stuff, another research group, uh, which was comprised of, uh, researchers Maurice Rapport, uh, Arda Green and Irvine Page, they were looking for how to get rid of it.

EAU: Hmm.

EW: So since 1948, they had been investigating the cause of hypertension in the hopes of developing a drug. And Kept coming across the substance in their clotted blood samples where it seemed to act as a vasoconstrictor.

EAU: Interesting. Erin.

EW: Yeah. And so they were like, gosh, like this is like one collaborator later said, yeah, the group just kind of thought of it as a contaminant, and [00:20:00] they were like, how can we identify this so that we can get rid of it? We can get it out of our samples. I mean, and that might be underestimating their interest or understating their interest because they ended up isolating, synthesizing, and then producing an elemental analysis of this serum vasoconstrictor, which they named Serotonin in 1948, not knowing that it already had a name. Yeah.

EAU: But so they won out.

EW: They, yeah, they won out. I mean, and I, I think they won out because, um. It was the serum part. The pharmaceutical company liked the names Sero, like SERO, to indicate that it was found in the serum.

EAU: Oh, okay.

EW: First they named it. Yeah. Five hydroxy tryptamine. But the pharmaceutical company, yeah. They were like serotonin.

EAU: I mean, that is still what it is called. That's like

EW: five hydroxy. Yeah. Five ht.

EAU: Yeah. Five ht

EW: Um, yes. But they, yeah, they wanted a catchier,

EAU: name, of course.

EW: I appreciate. I five hydroxy tryptamine is a hard, is a harder one to say for sure. Um, so, but within a few years, this research group realized that, oh, wait a second. This thing already, like, has been described. And so enteramine and serotonin actually the same thing. And then they published this in a paper

saying like, Hey, these, these two things are the same. And this kind of like expanded the interest and sort of the, the, the knowledge base of what this thing does.

EAU: Right.

EW: But at the time it was still thought of as primarily a vasoconstrictor and involved in smooth muscle contraction. Its role as a neurotransmitter had not yet been uncovered,

EAU: Hmm.

EW: and when it was, it would launch serotonin out of the realm of like, oh, cool. Physiological things like, this is neat. Maybe this does something in mollusks and into the burgeoning field of brain chemistry.

EAU: Hmm

EW: There was a researcher named Betty Twarog who had been interested in understanding a phenomenon in the muscles of mussels. Um, yeah, the

EAU: the Bivalve.

EW: bival. Mm-hmm. And she had identified serotonin as a likely candidate for the mystery neurotransmitter that she had sub, that she had suspected of playing a role. The structures seemed to match and analyses confirmed her hypothesis making serotonin a neurotransmitter. But this landmark finding had trouble getting published because the editor of the journal that she submitted it to sat on it for two years because he was like, this is not worthy of review. Two years. And he only sent it out for review after her advisor was like, Hey man, like what's the deal? Can you please review this? This might be a pretty huge finding. Um. And it was, it didn't get a ton of traction. It's funny because it came out, I think after another paper that got a lot more traction, which makes sense. But, but anyway, so Twarog didn't stop there with just this, like, this is a neurotransmitter. She reasoned that if serotonin was an important neurotransmitter in invertebrates like mussels, it was probably in vertebrates too. One of her advisors was like, I don't think so. I think this is just a, this is

EAU: Just an invert

EW: yeah, just an invert thing. Just like a very, um, you know, like primitive neurotransmitter, right? Yeah. Uh, but she got the last laugh because she

isolated serotonin not only from mussel nervous tissue, like in the, the bivalve, but from mammalian brain as well. And her resulting 1953 publications started a new chapter, or even a new book, really, on serotonin in brain function and mental illness. Okay. So that is, that is how serotonin was like discovered and then discovered to be a neurotransmitter in the, in the mammalian brain.

EAU: right. Something that was in the mammalian brain that potentially was having effects in the mammalian

EW: What do we do with this? Yeah. So, okay. Since the 1940s, LSD fascinated those who knew about it,

EAU: Of course it did.

EW: who also wandered at its psychedelic properties. So a couple of these researchers, Dilworth Woolley and Elliot Shaw followed these developments on serotonin with great interest because the neurotransmitter was structurally very similar to LSD. So when they, like, when that, when that chemical structure was published by that first group, they were like, this is, this is really interesting.

EAU: Hmm.

EW: And they thought, okay, maybe, um. Because it's so structurally similar to LSD, does this mean that LSD could act as a block, like fitting into serotonin's receptors and preventing it from working?

EAU: Okay.

EW: And this concept of like a lock and key for neurotransmitters would form the basis for understanding how drugs could act [00:25:00] as either mimicking a natural substance like a neurotransmitter or a hormone, or blocking its action like LSD did to serotonin. So it was like, what does this do? Can this either, um, flood the brain with more of the same and then there are all the receptors are filled in the way that it normally and things continue to act the way they would, but maybe like kind

EAU: elevated kind of, yeah.

EW: or would it block

EAU: Block the action. Yeah.

EW: Yeah. And so sure enough, when it came to LSD that is exactly what happened. When someone tried it out, it, it blocked serotonin. For receptors. Mm-hmm. And so for Wooly and Shaw, this raised the question of whether serotonin could play a role in mental illness

EAU: Hmm.

EW: because they had observed that people who were on LSD could experience mental disturbances that looked very similar to something like schizophrenia, for example.

EW: And so what if those disturbances were the result of the drug blocking serotonin?

EAU: Right.

EW: So maybe to extend this even further, they thought, okay, maybe it's not just about someone on LSD and these disturbances, but what if mental illnesses, mental health disorders, like schizophrenia are actually some sort of mismatch or decrease in serotonin?

EW: Yeah. And so subsequent experiments and closer scrutiny in, in this idea showed that it didn't quite work out that way as particularly when it came to schizophrenia. But there was something to the idea. And researchers began testing other drugs that could either deplete or replenish stores of serotonin.

EAU: Okay.

EW: One of these serotonin depleters was reserpine.

EAU: Mm-hmm.

EW: Does this sound familiar? Okay.

EAU: Did we talk about it on the podcast or did

EW: have, we've talked about it on the podcast. Yeah. So, 'cause I was like, this sounds familiar. So I did a control F of our, um, transcripts. Sure enough. And yes, so Reserpine is an alkaloid from the snake wood plant, uh, Rauwolfia serpentina.

EW: And it was examined as a possible treatment for hypertension. Uh,

EAU: Ah,

EW: and then, but this is not, this is not when we. I'll tell you about it in a second. Yeah, yeah,

EAU: Okay.

EW: Okay. First I'm gonna get to like the serotonin part. So researchers found that people were given reserpine, uh, and then they tended to become depressed, which was resolved if treatment stopped. And so they were like, what is Reserpine doing that is causing these symptoms of depression? And it seems very clearly reserpine because it stops with where the stopping treatment. Yeah. And so in tests carried out on rabbits, reserpine was found not only to deplete stores of serotonin, which um, was the big contender, but also norepinephrine and a newly discovered neurotransmitter called dopamine. Yes. So we talked about this in our Parkinson's episode. This is how L-DOPA was found because they, they found that when you, when you gave rabbits high doses of reserpine, they tended to exhibit some of, um, like paralysis symptoms similar to Parkinson's. Mm-hmm. And then they added l-dopa, and that sort of snapped him out of it, ultimately leading the researchers to discover dopamine,

EAU: Oh, wow.

EW: Okay. But what does this all mean for depression and under and other mental health disorders? Like I've talked about Parkinson's, I've talked about hypertension, I've talked about schizophrenia. We haven't really talked about depression yet. Okay. The precise mechanism wasn't clear. Researchers hypothesized that maybe it was depletion of serotonin, dopamine, and norepinephrine that underlaid the development of depression. And that excesses might also lead to psychosis, especially when it came to dopamine. So in other words, mental illness might be a result not of psychological imbalances, but rather chemical ones. And so this is really when like the imbalance sort of notion of mental health illnesses began

EAU: And specifically imbalances of those three, like mono means.

EW: the, the monoamine or catecholamine hypothesis of depression was essentially born out of these experiments. Yeah. Okay. So I wanna take a second here to ground ourselves in what depression meant at the time this research was happening. This is the 1950s, 1960s or so. It was rarely diagnosed.

It wasn't often even included as a separate category of diagnosis. Like there wasn't really like depression as a diagnosis when patients expressed symptoms that today we would associate with depression. So despondent, low energy, chronically sad, something that would interfere with their everyday life. They were usually ascribed to an expression of [00:30:00] someone's anxiety. So like anxiety was thought to be at the heart of most mental health disorders at the time. Some clinicians felt that depressive symptoms were like a self-defense against anxiety. Oh, I can't worry too much if I just become apathetic. That was sort of like the idea

EAU: Okay. Interesting.

EW: Into. Yeah, it is, it is really interesting, um, especially considering like. Today, sort of the, the lines between anxiety and depression and the Yeah.

EAU: Yeah, I mean there is, there is so much overlap with anxiety, symptoms of anxiety and depression and a lot of times depression is a lot harder to treat if there is an anxiety component versus if there isn't. Um, yeah, so that's really interesting.

EW: It is, it's, um, yeah, the history of, anyway, we could, yeah.

EAU: I know that like the history of psychiatry, Ooh,

EW: Oh,

EAU: that's not this episode.

EW: not, not this episode. Yeah. And so there was a distinct diagnosis for depression, separate from anxiety, but it was reserved for extreme, like really severe cases that involved, uh, psychosis.

EAU: Okay.

EW: And so from the 1952 DSM describing quote unquote psychotic depression reaction quote, "these patients are severely depressed and manifest evidence of gross misinterpretation of reality, including at times delusions and hallucinations". End quote. So it's, it's not, again, it's a very narrow definition that compared to what we

EAU: we have today.

EW: Exactly. Yeah. And things like melancholia or melancholy had also been a popular diagnosis in the late 18 hundreds and into the 19 hundreds. And it was, it was believed to have a biological basis, um, until Freud, that biological basis. And melancholia in general kind of fell out of favor as Freudian theory took over, which held that biology had nothing to do with it.

EAU: Yeah. It was all your mom and stuff.

EW: your mom.

EAU: Yeah. That's the conclusion of Freud.

EW: Yeah.

EAU: The end.

EW: So all of this is to say that in the 1950s and 1960s, depression was not the widespread, broadly defined clinical entity that we think of today. And so it really wasn't seen as a major problem warranting extensive searches for effective treatment or better understanding of its underlying cause.

EAU: Wow.

EW: Of it really prevented interest, I think, and like consideration.

EAU: Hmm.

EW: And some treatments did exist, such as electroconvulsive therapy, which was used for severely depressed patients with psychosis in the 1940s. And it seemed effective in the short term, but no one knew why. And it quickly fell out of favor as long-term negative effects emerged, like extreme memory loss and other things. Amphetamines were prescribed for "the blues" in the 1940s, in the 1950s. Then there were combination amphetamine sedatives to treat anxiety and the depressive symptoms that came with it.

EAU: oh gosh. Okay. Gonna upper and a downer. Mix it all up. Okay, great.

EW: Yep. But again, none of these drugs were antidepressants. They were treating what was understood at the time to be a symptom of anxiety.

EAU: Mm-hmm.

EW: What turned things around was tuberculosis.

EAU: Stop it. Everything is tuberculosis.

EW: Was just, yeah, I have here, John Green was, right. Everything really is tuberculosis.

EAU: Stop it.

EW: Yes. Okay.

EAU: Tell me more.

EW: So as the 1950s rolled around the hunt for an effective tuberculosis treatment had been going on for decades without much success. And then a new drug called iproniazid

EAU: Okay. Mm-hmm.

EW: Came on the scene, and if you listen to our book club episode on the Black Angels by Maria Smilios, this is one of the new anti tuberculosis drugs that the nurses at Seaview Hospital on Staten Island tested out on their patients. And when these patients, when these tuberculosis patients were getting this drug, their moods improved. Their appetite increased. There were even reports of dancing in the wards.

EAU: Whoa.

EW: Yep. Initially, these positive side effects of euphoria, psycho stimulation, increased appetite, improved sleep, weren't of much interest to the drug manufacturer, especially since iproniazid only did so-so when it came to treating tuberculosis, its sister drug, isoniazid, it did much better. The pictures of dancing patients at Seaview caught the attention of one psychiatrist, Dr. Nathan Kline, who wondered whether iproniazid held the answer to a question that had long interested him if something like schizophrenia was caused by an excess of "psychic energy", quote unquote, which was [00:35:00] kind of the idea at the time, could depression be caused by a lack of it? Could this tuberculosis drug with its euphoric effects increase psychic energy? So Kline began a trial using iproniazid to treat his patients who had severe depression at the state hospital where he worked, he detected an improvement in 70% of them,

EAU: Wow.

EW: which he reported in 1957. And so with this, iproniazid came the, became the first of our modern antidepressants on the market,

EAU: Wow.

EW: or a monoamine oxidase inhibitor.

EAU: Uh

EW: Isn't that unbelievable?

EAU: From tuberculosis. Wow. John Green had it, right?

EW: He had it right. I just, I love that it was this researcher, the psychiatrist who saw these pictures and was like, whoa,

EAU: They look not depressed. Yeah.

EW: Can we use this?

EAU: How interesting.

EW: It's, it's amazing. And the popularity of iproniazid and others similar, MO MAOIs that quickly appeared at following iproniazid in the late 1950s. They, it was, they were fairly short-lived as a, as a popular antidepressant

EAU: Mm-hmm.

EW: because while they did seem to be effective in treating depression, they came with some pretty nasty side effects like constipation, difficulty urinating, even jaundice. Death could occur if someone ate cheese or chocolate. And drug companies. Yeah. Drug companies withdrew the drug

EAU: Mm-hmm.

EW: and it would soon be replaced by another class of drugs. The tricyclic antidepressants or TCAs, which were approved in 1959. And these had first been tested as a possible treatment for schizophrenia where they were found to be not effective. No, but

EAU: Definitely not

EW: not. Um, again, it was all like depletion, you know, that that sort of the, the seesaw of what do we want? The balance? Yeah, actually. Um, but these, these TCAs did show some positive impact for people with depressive symptoms. Uh, side effects, again, left something to be desired. Dizziness, memory, impairment, drowsiness, et cetera. Um, but I just think it's amazing that we keep finding antidepressants when we're not looking, which speaks to this phenomenon that I mentioned at the very beginning. Like, sometimes we have these drugs that are effective for certain conditions, we don't know why. And stories like MAOIs and TCAs show us that we don't necessarily have to know how something works to develop effective treatments.

EAU: Uh huh.

EW: Even if we think we know, like we thought we did with SSRIs because this was like, this was a more targeted drug development and we're proven wrong about our initial hypothesis. Or if not totally right. We can still make a difference. Yeah. Okay. So we're finally at the point in the story where SSRIs come onto the scene. It's taken us a little bit to get here, but I feel like it was important to understand the big picture, like what came before. Yeah, I, it's, I just fascinating. You know, from 2 billion, 3 billion years ago, all the way to

EAU: All the way till the 1960s.

EW: Here we go. And so the advent and. Effectiveness of MAOIs and TCAs kind of lent support to the idea that depression and other mental health disorders are related in some way to serotonin, norepinephrine, and dopamine. So like there's something to the monoamine hypothesis of depression and how exactly they were involved was unclear. Uh, since they both worked in different ways, TCAs and MAOIs, but they both led to kind of the same end result.

EAU: right. You're increasing the amount of these neurotransmitters.

EW: Exactly. And how you're doing that, eh, it's not really Sure. And how is it improving your symptoms now? We don't really know. And so it seemed like antidepressants were on a trajectory of incremental improvements. But like we talked about, those two existing classes had some serious drawbacks with their prevalent and sometimes serious or deadly side effects, which were due in part to how they weren't super specific. They were kind of ramping up all of those three, um, dopamine, norepinephrine, serotonin. It was kind of just like across the board. And so, you know, some researchers thought, well, what if, what if

we could make these more specific? What if you could target just one of these neurotransmitters? Maybe that would help with the side effects, maybe that would get to the root underlying cause of these disorders. And so by the late 1960s, interest had gathered specifically on the role that serotonin might play in depression specifically, again, its depletion with the logic following that if you could restore serotonin, you could alleviate depression.

EAU: Mm-hmm.

EW: We know that that's, that's [00:40:00] not the case.

EAU: Not exactly the truth.

EW: It's not exactly the truth, but it It was a hypo, it was a hypothesis then. It's not, yeah, it's, anyway, there's a

EAU: was a starting point.

EW: it's a starting point. Exactly. Yeah. And so pharmaceutical companies set their sights on making a compound that prevented the re-uptake of serotonin at serotonin transporters, specifically, meaning that it had reduced affinity for norepinephrine. And so put that jargon another way, and you've got a selective serotonin reuptake inhibitor.

EAU: Mm-hmm. Yeah.

EW: Eli Lilly found success in 1972 with a compound that they called fluoxetine. And 13 years later it became the first SSRI approved by the FDA under the trade name, Prozac.

EAU: Mm-hmm.

EW: And it is interesting to me that with Prozac, with Fluoxetine, we did have this plan. Here is what the drug that we wanna make and here's what we're gonna do and here's how we think it works.

EAU: Right.

EW: And it still didn't work out, but it still had some effect. And it's, it's just different than like, iproniazid, which was like, oh, tuberculosis.

EAU: Right. It's, it was much more like intentional.

EW: Yeah. It was an intentional design. Mm-hmm. Okay. So in the time between prozac's development and its approval, which is, you know, a decade and a half depression, had long time, depression had undergone quite a transformation really. So beginning in the late 1960s, clinicians started to think of it as separate from anxiety. That what had been thought of as anxiety was actually depression. So the depression was both increasing in its, uh, prevalence as well as broadening in its definition.

EAU: Okay.

EW: So the WHO in 1974 declared depression much more widespread than previously thought affecting one fifth of the global population.

EAU: Wow.

EW: Yeah. In 1974.

EAU: In 1974.

EW: Mm-hmm.

EAU: Wow. Okay.

EW: Uhhuh and part of this transformation, and also what made such estimates possible was the creation of standardized scales by which to measure and diagnose depression. These scales allowed researchers to conduct clinical trials where they could track depression symptoms over time and with or without treatment.

EAU: Mm-hmm.

EW: And these trials revealed that by and large antidepressants were effective in alleviating symptoms of depression. With some differences among formulations and of course among different individuals and their efficacy held, whether someone could identify specific reasons for their depression. Like, this thing is going on in my life, or this, you know, my dog died, my car broke down, my house was foreclosed upon. Or if they couldn't Right. So in response, like to this sort of depression happens, antidepressants work, whether or not you can define a specific incident, the, the DSM was like, we need to make some adjustments. And so the DSM-III published in 1980 removed any questions

about life circumstances, family history, triggers and so forth in its description of depression.

EAU: Ooh. Interesting.

EW: So instead it just provided a checklist of symptoms,

EAU: Okay.

EW: So because previously diagnoses depended more on whether you could pinpoint factors

EAU: life situations. That's so interesting, especially thinking about now, like when you have life stressors, a lot of times you're less likely to diagnose depression until, yeah. I mean, because, because a certain amount of depressive symptoms are to be expected with significant life events. Right. And so then it's like a grief reaction, which you then have to separate out from depression. So that's interesting. I mean, it can certainly lead to depression, but it just sort of, it complicates a picture more. And it sounds like in the past it was like, no, you need to have that in order to be depressed.

EW: Mm-hmm.

EAU: interesting.

EW: The transformation's huge,

EAU: Yeah. Yeah.

EW: huge. And so this shift though, what it did was it, it really, um, increased diagnoses across the board because now you don't have to say, oh, well, I, I don't think, I think you're just, I think you're just a little bored, or I think you're just a little bum. You know what I mean? Like, I, I, I am not saying that's exactly what was said, but it, I think, legitimized. Nonspecific cases of depression where it was like non-specific life events. Yeah. And so when Prozac hit the market in January 1988, there were many more people who sought prescriptions for this new antidepressant than there had been in past decades. Not necessarily because depression overall was on the rise, like because, and which it may, may have been just because of the world or whatever, [00:45:00] but also because our framing and perception of the condition had broadened, people now had the vocabulary to describe the things

that they felt, and then they were often, though not always taken more seriously about the impact of this on their day-to-day functioning.

EAU: Right.

EW: By 1990, this is just two years, within two years of its release in the us, Prozac became the most widely prescribed drug in North America.

EAU: Wow.

EW: Just a few years later, the second most sold drug in the world.

EAU: Wow.

EW: This was unexpected. I don't think Eli Lilly anticipated this. Prozac was not the first antidepressant, or even the first SSRI. There were other previous SSRIs, but they

EAU: huh

EW: never approved for the US market, and they seemed to have, um, more side effects, but Prozac had fewer side effects, and so it was considered a safer drug compared to like TCAs, which meant that physicians were more likely or felt better about prescribing it not only to their patients who had like severe depression, but also those with milder symptoms. The continued popularity of Prozac and later SSRIs showed that clearly these medications were working, but how were they working?

EAU: Mm-hmm.

EW: even before their release researchers knew that these SSRIs were not acting under the hypothesis of low or imbalance serotonin equals depression.

EAU: Mm-hmm.

EW: That idea had been rejected decades before.

EAU: It's just so fascinating that that doesn't, like that is so often left out of the story.

EW: get translated. It's like people are like, oh, serotonin is not the only thing related to depression. Re you know, scream the headlines. And it's like all the researchers are like, what year is this? We've known this. I was taught this

EAU: Who said that? Who said that it was, sorry?

EW: Said that? It was, yeah, it's a straw man argument because if that was the hypothesis, then it, they would've expected to see, you would expect to see improvement in symptoms in someone very soon after someone starts taking SSRIs. Not after weeks, which is the timeline that we usually

EAU: Mm-hmm.

EW: But given that these drugs are effective. Serotonin likely plays some role in depression and other mental health disorders, maybe in like a regulatory capacity. But even though researchers had long acknowledged that the biological underpinnings of depression are more complicated than just serotonin.

EAU: serotonin.

EW: Yeah,

EAU: some serotonin.

EW: little serotonin on top. This message didn't reach the general public until, I feel like relatively recently you've got, again, like popular media articles or TikTok saying things like, "you've been lied to, antidepressants, don't do what we think." And it's like, yeah. Or "the final nail in the depression-serotonin coffin."

EAU: Is that a real headline, Erin?

EW: I don't remember. It

EAU: Okay.

EW: I think it actually, I, I think it was, um, because researchers again were like, "final nail, that thing's been dead for decades. It's been buried. What are you talking about?" Uh, but a few promoted or even were behind this misrepresentation of the science of SSRIs. Uh, you know, this is where, like it,

the, the, again, this, the serotonin hypothesis as the straw man argument against these medications. And this, I mean, to go, I, I don't wanna go too much into like the motivations or the reasons for this misrepresentation, because I do think that there is like a antip psychiatry movement that you don't need drugs. You just need to pull yourself up by the

EAU: By the bootstraps.

EW: And work hard. Just get outta bed, clean your house. Just do it. Just push

EAU: do it. Just do it. I mean, that's the same thing as before anyone recognized that depression was a thing. Right? It's It's the same, that's the same end result.

EW: It's the same end result. The thing is this, this misrepresentation saying that scientists think that SSRIs work on depression in this way and they're wrong. That has the capacity to do real damage.

EAU: To, especially to people who are on SSRIs who have benefited from SSRIs, who are now in charge of regulating our SSRIs.

EW: It, it has and or could encourage people to stop treatment under these false pretenses. And it also just overall deepens mistrust in science and medicine. The truth is that the general public has been lied to, or at least not been told the whole truth about our understanding of SSRIs and depression. Ads, like pharmaceutical ads, which should be outlawed in my opinion, um, for antidepressants, have long claimed that the drugs work by correcting a chemical imbalance and these ads [00:50:00] reduce these complicated disorders to a simple issue of brain chemistry.

EAU: Hmm.

EW: It's a catchy thing. You got, you know, 30 seconds for an ad. Of course you're gonna say the the simplest thing possible. And what drug company wants to be like, we don't know how this works. course, they're gonna say something like it's a chemical imbalance. I think that that under represents, or falsely represents the complexity of the issue and how much we know or don't know about this. And I think this trickles down into physicians who will use the same language when explaining the medications to their patients. Again, not wanting to sit there in an office. You have five minutes to talk to your patient and you don't wanna say, we don't know how this works, number one. Number two, um, let me tell you about how serotonin receptors work in your brain and in your gut. Right.

EAU: know I'm laughing. I'm.

EW: Chemistry. It's an imbalance.

EAU: Laughing so much Erin because I, um, it's my favorite thing when I get to explain mechanisms to my patients, like in the office where I get to be like, okay, this is too detailed, but just gimme one second. and then, and then at the end be like, yes. So we don't know how it works, but,

EW: Right.

EAU: But no, most people don't

EW: it works. Yeah.

EAU: Most people also don't, don't do that. And like, yeah, okay, we learned the mechanism in med school and then you obviously forget it because there is way too much to know. And what you really need to know is, do I have something that can help my patient or not?

EW: Right,

EAU: You know? So,

EW: And I think that like, you know, I, I was thinking, I just, I've spent so much time thinking about SSRIs, like in a very focused, directed way where I'm like, okay, this, these ads, for example, or this, this message, I'll say, whether it's in an ad or in your doctor's office or wherever, about depression and other men, mental health disorders being a result of an imbalance in your brain chemistry. That message has been really important for reducing stigma and for underscoring the idea that these disorders are real and that they can be treated with medical solutions. But by framing it in this un nuanced way, by not acknowledging that there are still unknowns, it ignores the need for more research, both on SSRIs as well as depression and other mental health disorders. It disregards the experiences of many people for whom these medications don't work, and it minimizes the importance of non-pharmaceutical interventions such as therapy, and it does a disservice to everyone who uses, prescribes or researches these medications or alternative treatments for depression and other mental health disorders.

EAU: Yeah,

EW: there is no question that in the decades since Prozac's release, SSRIs have completely changed the landscape of depression. They have provided relief to so many people. They've been a lifesaving to so many people. They have helped to reduce stigma surrounding depression and other mental health disorders. They have forced us to reconsider how we think of mental illness. They are not perfect, but I don't know anyone who claims they are besides maybe the pharmaceutical companies.

EAU: don't know any drug. That is perfect,

EW: is perfect. Yeah, I am. I'm excited though, for next week, Erin, when you get to tell me about more about how much we don't know and how much we do know about these medications and how we can make them maybe not perfect, but better.

EAU: Hmm, that's a good one. I probably won't answer that question, but I will provide quite a lot of data to support what we do and don't know. Um, and then a little bit of my opinions about how we talk about all of this

EW: Ooh, love it. Okay.

EAU: More next week. Don't forget to subscribe so that you don't miss an episode.

EW: Never miss an ep. Uh, and in the meantime, how about some reading?

EAU: How about some reading? I'd love to do more reading. Erin,

EW: Uh, I have a bunch of sources, but I'm gonna shout out three in particular. There's, uh, by Whitaker as Meia in 1999, the discovery of Serotonin and its role in neuroscience from Hillhouse in Porter 2015. A brief history of the development of antidepressant drugs from monoamines to glutamate, and then kind of just the broad scope, big picture of depression and the advent of SSRIs and how that changed the landscape. There was, uh, a couple great chapters in a book called Mind Fixers: Psychiatry's Troubled Search for the Biology of Mental Illness by Anne Harrington. And um, I've got more. I'll post them on our website. This podcast will kill you.com.

EAU: Thank you again so much to the providers of our firsthand account. We appreciate you so, so, so much. And thank you to everybody who wrote in to share your story about SSRIs. We really appreciate it.

EW: [00:55:00] Yeah. Thank you. Thank you. Thank you also to blood mobile now on Instagram. For the music that you provide for this episode in all of our episodes.

EAU: Thank you to Leanna and Tom and Brent, and Pete, and Mike, and Jess and everybody at Exactly right. For all your help making these episodes happen.

EW: yes. Thank you. And thank you to you listeners, uh, and watchers and anyone who partakes in the podcast in some way. We really appreciate it.

EAU: Yeah, we do. Thank you. Thank you. Thank you as always, too, to our patrons for your support over on Patreon. We really, really appreciate it. It means a lot,

EW: we do. Well, uh, until next time, wash your hands.

EAU: you filthy animals.