SSRIs Part 2

Firsthand 1, SSRIs Part 2: Hi, I'm Haley, I'm 24, and this is my story with Zoloft. So growing up I was the kid who was scared of everything: insects, people in costumes, heights, you name it. But beneath all that fear were intrusive thoughts that no one else could see. For instance, my mom was allergic to bees. I was constantly worried that either of us would get stung and we would die. [00:05:00] I tried to relieve these thoughts through avoidance, skin picking, and checking with very minimal relief. I attempted to explain my fears to pediatricians and school counselors, but I was never given any real concrete answers. I began to believe this was just who I was. College is when things began to worsen. When the pandemic hit in spring of 2020, my anxiety exploded. I remember obsessively locking my windows and shutting the blinds, convinced that someone would break in or try to bring the virus inside. I was diagnosed with an adjustment disorder and was even taken off my birth control 'cause that was believed to be the issue. Eventually in the fall of 2020, I was able to get an appointment with our head college doctor. She truly listened and said, "I think this might be an anxiety disorder," and she started me on 50 milligrams of Zoloft. And for the first time I felt like I could breathe. I had very minimal side effects, only some sleepiness and some GI upset for the first two weeks.

The next fall, I began wondering if it might be OCD. I began tracking my thoughts, looking into patterns, but unfortunately, in the spring of 2022, my depression took over. My depression manifested into intrusive thoughts telling me to hurt myself, even though I really didn't want to. I knew something was really wrong, and so I went back to my head college doctor. She increased my Zoloft to a hundred milligrams, and that definitely helped. Still, none of my doctors felt qualified to diagnose OCD. My pediatrician later admitted she had suspected it for years. In 2024, one year out of college, I finally got my OCD diagnosis from my current therapist. My new primary care provider was really thrilled to hear this and wanted to find me a regimen that worked. So, typically for OCD, you give the patient a top dose of their preferred SSRI, but for me, she kept me on my 100 milligrams of Zoloft and added a dose of BuSpar, and that worked for me, and my thoughts got quieter and I was able to finally start making progress again in my OCD therapy. SSRIs have truly changed my life. I used to spend every day fighting my own mind, and now I'm able to achieve goals that I had set for years, such as applying to medical school. I'm really lucky to have had very few side effects and not have to go through many different medications. I really cannot imagine going back to a life where I was not on SSRIs. They don't just help me function. They have given me back my future.

Firsthand 2, SSRIs Part 2: My name is Sara, and I started using SSRIs during my master's degree, over 10 years ago now. So while I was studying for my master's, I started to experience really profound anxiety and a lot of obsessive thinking. Um, I became convinced that I had plagiarized all the work I'd ever done, and that I, you know, irreparably harmed every person I'd ever encountered. And I spent, you know, all day, a lot of days checking my work and seeking reassurance or reaching out to apologize to people for things I imagined I'd done. I was diagnosed with Obsessive Compulsive Disorder and originally tried to manage it with just, cognitive behavioral therapy, which helped a bit, but it reached the point where I was very unmanaged and um, was having suicidal ideation and thinking I had to drop out of school. So I began to use an SSRI. And you know, after the first few weeks when it started to take effect, I had this amazing experience of things that used to be, you know, thoughts that I would obsess over and would ruin my week because I would spend all of my time in service of those obsessions. Now as the SSRS kicked in, my brain would just sort of slide off of those thoughts and I could go on to do other things that day, and it was really wonderful. So with that under control, I was able to complete my master's degree and publish some work from that.

And, after several years of being under good control, I've been able to start studying for my PhD. So I'm very fortunate that, for me, SSRIs have not had substantial negative side effects and that they've been effective and helpful. And because of that, I've been able to, you know, really enjoy my work and do research that I think is significant and impactful for the world, while actually getting joy from that instead of just anxiety.

EW: Thank you so much for sharing your firsthand account that it really means, it means the world to us. It's so important to have that. That personal experience to, to, to learn from and to get an insight into how SSRIs work or don't work, or just the impact that they've had.

EAU: Yeah, it's, it's not something that we can convey by ourselves. So thank you for sharing with us and thank you to everybody who wrote in. I know a lot of you did. Um, and we really, really appreciate everyone's willingness to just share your story with us. It's not an easy thing to do, and it means so much. So thank

EW: does. Hi, I'm Erin Welsh

EAU: And I'm Erin Allmann Updyke

EW: And this is, This Podcast Will Kill You.

EAU: We're back as promised

EW: We are,

EAU: part two of SSRIs.

EW: how do they work? What are they, what is serotonin besides something that, uh, does stuff in medicinal leeches?

EAU: mean, you told us a lot about that, Erin, let's be honest. Um,

EW: I was just like, and it does these things. How does it do those things?

EAU: Oh, I'm not gonna get into that, erin. Watch this not be at all what you wanted to learn in this episode, but that's okay. We're gonna have fun regardless

EW: slate. I'm happy to learn anything.

EAU: If you, me too. If you missed last week's episode, uh, do check it out. Uh, Erin Wesh walked us through the history of serotonin. How did we even figure out it was a thing? Uh, wow. And how we came up with SSRIs and how pharmaceuticals have advertised them.

EW: Yeah. Yeah.

EAU: And then today we're gonna, we're gonna take it from there,

EW: Love it. Short and sweet.

EAU: But first

EW: um, we are drinking the same thing that we did last week for our quarantining, really? Placebo Rita Time. The serotonin spritz, it's apple cider and pineapple juice and soda water. And it's simple and refreshing.

EAU: Mm-hmm.

EW: Enjoy.

EAU: It's online. Check it out.

EW: Check it out. Um, I feel like I, I've been forcing you to do the website just by being like, what do we do now? So, I'll do the website.

EAU: Okay, great.

EW: Uh, you can find lots of things on our website. This podcast will kill you.com. You can find things related to our sources for each and every one of our episodes, we've got links to bookshop.org affiliate account, our good reads list, links to merch, links to Patreon, links to music by blood mobile transcripts, a contact us form, and more things.

EAU: I loved it. Erin. I also love when you go into your like semi newscaster voice. Yeah.

EW: I know. My secret dream is to be like just a voice on the, on the tv, on the documentary, and

EAU: a vo, a voice actor

EW: this is what, blah, blah, blah. Yeah. Wouldn't that be nice? I don't have the training for that.

EAU: Anyone, anyone hiring,

EW: Yeah. Please let me know. Reach out. This podcast will kill you.com on the contact us form on our website.

EAU: If you haven't already rated, reviewed and subscribed on your favorite podcaster. Are you listening on iHeart podcast? Are you listening on Apple Podcast? Are you listening on Spotify? Check the subscribe button and make sure that you clicked down on it. Um mm And that you left us a rating or a review. If you like us, if you don't, you don't have to do that part. You could unsubscribe. In fact,

EW: The visuals, just so you know, are very good for what Erin is currently doing. And so if you are so inclined, you can see them on YouTube. If you wanna go watch the video for these podcast

EAU: you can follow the exactly right network channel on YouTube.

EW: Yep.

EAU: The end. Shall we start now?

EW: I believe that we

EAU: Okay.

EW: Let's take a quick break and get started.

EAU: Okay, so Erin.

EW: Erin,

EAU: Um, you walked us through last week so beautifully about what we know about, like how serotonin, like where it came from, how long it's been with us, how we came to find SSRIs intentionally, which is so interesting. And some of the issues with how we have marketed them and how we think about in like the popular media sense, how we think about how they work, which I think has led to a lot of the controversies that come with SSRIs today, though there's a lot of other reasons for that, which I'll get into. So I wanna just start by just setting, setting the stage for what I am actually going to cover today. Because it's a lot of things and not a lot of things at the same time, I'm tempering expectations, so I'm doing, um. I will not just end with, we don't know how these work, okay,

EW: Okay.

EAU: though I will probably still say that a lot of times [00:05:00] as usual, but this is not an episode where I dive deep into the neurobiology of depression or anxiety because those are topics that deserve their own episodes and will have them at some point. I am not going to get super nitty gritty on the five HT one A auto receptor, blah, blah, blah. Like we're talking, there are so many serotonin receptors and I'm not going to, I'm not gonna get us. You know, up to our eyeballs in it. Okay.

EW: Okay.

EAU: But my goal is to give us all a real sense of how we actually use SSRIs today. Like how are they used in kind of clinical practice? How are they thought of, not in social media circles or political circles, or popular media circles, but how are they thought of by the medical and scientific communities that use them and that research them? What do we think that we know about how they

are treating the disorders that we use them for? Are they effective and what does that mean?

EW: What does that mean?

EAU: Okay. And then hopefully do a little bit of like myth busting and a little bit of like grounding of big picture. How do these conversations that we're having about SSRIs tell us about the way that we think about mental health conditions as a society? Oh, small feat. Ready?

EW: Yeah.

EAU: So SSRI's, selective serotonin re-uptake inhibitors are considered one of the possible first line therapies for both depressive disorders, which there are a lot of different depressive disorders. There's major depressive disorder or MDD, but there's others. There's persistent depressive disorder, there's dysthymia, like there are a lot. Okay. And also first line, one of the possible first line therapies for anxiety disorders, of which there are many generalized anxiety disorder, social anxiety disorder, P-T-S-D-O-C-D, and more.

EW: Hmm.

EAU: If anyone listening needs convincing as to the importance of these mental health disorders. The Global Burden of diseases study from 2022, which importantly includes data only up till 2019 and does not include the massive increase in mental health disorders worldwide that we saw due to COVID. But in 2019, depression and anxiety were top 10 causes of disability adjusted life, years in adolescents and adults worldwide. Self-harm behaviors, which often coincide with depression was the third leading cause of disability adjusted life, years in adolescents age 10 24. Yeah, and there's no evidence that these disorders are decreasing over time. If anything, they are on the rise. Anxiety disorders and depressive disorders are estimated to affect 300 million people each worldwide. Okay. With an estimated lifetime prevalence of depression of close to 20%, like lifetime risk. Okay. In the US in 2020, nearly one in 10 Americans experienced a depressive episode in the last year alone, and nearly 20% of adolescents and young adults experienced one. But in this study, which looked at like, I think a five year period helps seeking behavior has not been increasing, right?

EW: Right.

EAU: And in a lot of studies, less than half of people with depression reported having spoken to any healthcare professional about their depression or receiving any treatment for their depression. In Europe, according to the European Psychological Association, nearly one in five people is diagnosed with depression at some point in their lives. So that's pretty much that 20% lifetime prevalence. And they estimate 12 month prevalences of depression around 6%. And anxiety in the UK is estimated at around 4% with worldwide estimates that vary from like 1% to about 6%. And like I mentioned last week, depression and anxiety often co-occur, and when they do, it can be more refractory to treatment, especially when it comes to depression. That like overlaps with anxiety.

EW: When they co-occur, it's more challenging to treat. Just a quick question. Can you, and, and maybe you're about to do this, but define clinical definitions of anxiety, depression,

EAU: it's, it's hard because there are so many specific, you know, um, specific disorders that you can define within that. Um, so

EW: maybe what about a depressive episode?

EAU: Yeah, so a major depressive disorder is like, would count as like one depressive episode, right? And that is usually at least two weeks of at least. All of a whole bunch of different symptoms. So there's like these different checklists basically, that you go through. So there has to be [00:10:00] disruptions in sleep, which could be sleeping too little or too much. There's disruptions in your, um, interest or like what we call anhedonia. So not finding interest or pleasure and things that you used to like to do. There's energy issues, so you don't have as much energy as you used to. There's issues with concentration. Um, there's actually feeling depressed, like having a low mood or maybe crying more easily than you used to. Um, there's appetite issues, which could be eating more or eating less than you usually would. Sometimes we see psychomotor issues, so walking or moving very slowly or like more rapidly than you used to in the case of like anxiety for example. Um, and then there of course can be thoughts of suicide or suicidal ideation. I. When it comes to anxiety, kind of one of the biggest ones is generalized anxiety disorder, and there's separate criteria there, but a lot of it comes down to are you worrying about things like unnecessarily, are you not able to sleep or you know, do the things that you need to because you are up all night worrying, so you're having insomnia.

EAU: Are you And, and what's really important, and that's not an exhaustive list, but there's a bunch of different questionnaires basically, that you go through and you have to score certain scores in order to meet criteria. But the thing that's important about all of these, almost all of our mental health disorders, is that one of the criteria in order to diagnose them is they have to cause some kind of functional impairment, which means that the last question on any of these questionnaires, whether it's an anxiety questionnaire, depression questionnaire, is how much is this? How difficult is it making your life? How difficult is it making you to be able to do your work, to be able to do your home life, to be able to do the things that you need to do?

EW: Right.

EAU: And that is the kind of like final criterion. So that's like a very brief overview of how we, it's not perfect with that, how we define a lot of those things. And I've got papers you could read more. Okay.

EW: Okay.

EAU: Um, so full disclosure also because we use SSRIs for anxiety disorders as well as depressive disorders, but a lot of the data on them and a lot of the, like mechanistic looking into how do they work relates to how we use SSRIs and think about them for depression.

EW: Mm-hmm.

EAU: So that is most of what I'm going to talk about. But I will also mention their use in anxiety and know that a lot of the data in terms of like is it effective or not, how much of a placebo is there or not. It's also true in anxiety. The numbers might be slightly different. Um, but it, I'm mostly focusing on SSRI use in depression. They're also really important for anxiety. Okay.

EW: Yeah. Yeah, it's, it is, and I think that's just probably a historical artifact to some degree. Is that what's most of the studies have been focused on, and I'm sure that there's increasing like attention to the other Yeah.

EAU: Well, and like all of them that are kind of like approved for indications for anxiety, they had to have those studies in order to be approved for that indication. So again, the data exists, the data is there. Um, and I have a bunch of papers that people can read to do more on it, but I had to be selective, Erin, 'cause we only have so much time.

EW: Yep.

EAU: Um. So Erin, last week you walked us through how we like came up with the idea of using serotonin as a target. Right. In large part because we figured out, I'd never knew it had to do with tuberculosis, but through the effects of these older, what are now often called first generation antidepressants, the MAOIs and the TCAs, that that is how we've picked serotonin as a target. The beneficial effects of those types of antidepressants pointed to this monoamine hypothesis of depression. And like you told us last week, Erin, this is not the cause of depression. Serotonin decreases in serotonin is not the cause of depression, but it, it has led us down the road of understanding a lot more about depression than we used to.

EW: Mm-hmm.

EAU: And because all of the different antidepressants that we use. Including the kind of what are called atypical antidepressants, so they're not SSRIs or SNRIs. All of these, even the new fancy ones that people are very excited about, like ketamine and like psilocybin, all of these to some extent or another do in fact modulate some of our monoamine neurotransmitters. Serotonin, yes. Also norepinephrine and dopamine. Okay. So clearly there is something to the fact that these monoamines are involved in depression, in anxiety, and modulating these to one degree or another can help reduce the symptoms of depression and anxiety, [00:15:00] even if we don't quite understand why or how. So, to do a quick recap on what serotonin is so that we know how it's working in our bodies, i'm gonna actually take a quick step back and just talk about the idea of a neurotransmitter,

EW: Yeah.

EAU: because I wanna be able to explain like what they're doing in our brains.

EW: Yeah.

EAU: Okay. Um, and we've talked a lot about neurotransmitters on this podcast, like I've said the word a lot. Um, but let me recap what these really are. These are compounds, these are chemicals that we make in a bunch of different parts of our brain and throughout our body. Serotonin, like 90% of our serotonin, we actually produce in our gut, in neuroendocrine cells in our GI tract.

EW: What the heck? Amazing.

EAU: Know, right? Um, but so neurotransmitters broadly are these chemicals that help to translate electrical signals in our brain and our peripheral nervous system into chemical signals that then cross what is called the synapse, either between two neurons, because there's a gap at the end of a neuron before it touches another neuron. There's a gap called a synapse or between a neuron and say a muscle right. Where it's going to have an effect

EW: mm-hmm.

EAU: and. Signals are passed in our neurons and in our brain with electricity essentially. And when these signals get to the end of a neuron, in order to cross that gap, that synapse and send the message onwards, these electric signals have to be transmitted via chemicals. Chemicals are released. They cross that gap, bind to receptors on the other side and whatever neurotransmitter is released and whatever receptor it binds to, sends whatever message it is that we're trying to send. Is that generalized enough?

EW: But you gotta have somebody throwing the baseball and someone catching it.

EAU: Exactly. Erin way did you go with a baseball? Metaphors.

EW: Pew it outta the park.

EAU: (drumroll)

EW: Come on.

EAU: so, serotonin happens to be a neurotransmitter that is involved in so many parts of our brain

EW: Yeah.

EAU: and our whole body.

EW: our whole bodies.

EAU: But in our brain specifically, it helps to regulate things like mood, like sleep, like sexual activity, appetite, cognitive function. Okay. And in our peripheral nervous system, it, it does so many other things. It regulates our gut motility, our visceral sensitivity. It is part of this gut brain axis that someday we

will have to do. It's also taken up by our platelets, which is why I got so excited when you said they saw this clotty stuff. Yeah. Serotonin is involved in our clotting cascade. What? So serotonin is truly everywhere. Selective serotonin reuptake inhibitors or SSRIs are drugs that bind to a transporter protein. On the presynaptic side, that is where we are releasing serotonin from. So on our nerve cells, on our neurons. This transporter's job is usually to collect the serotonin after it's been released.

EW: The catcher,

EAU: The catcher, exactly. Wow. We're gonna keep going. The baseball analogies.

EW: don't have to

EAU: No, I like it.

EW: The goalie. Like what?

EAU: I don't. The catcher

EW: only think of sports related things right now for some reason.

EAU: and the catcher is taking all of these serotonin balls and putting them back. Maybe it's really like the ball boy, honestly.

EW: Okay.

EAU: Okay. That's a catcher slash ball boy, whatever.

EW: Yeah.

EAU: And putting them back into our neurons so that the serotonin can either be recycled, broken down by monoamine oxidase, or it can be recycled like reused again. Okay.

EW: in a pitching machine.

EAU: Exactly.

EW: Okay. We'll stop there

EAU: Please. I think that might be the end of it. So what these drugs do is they bind to these transporters and block them. So we cannot re-uptake, repackage this serotonin back into the pre-synaptic part of our neurons. What that means is there is an increase in serotonin in this synaptic space, this extracellular space.

EW: Okay.

EAU: That is how they work mechanistically.

EW: All right.

EAU: So the thought was, okay, we're increasing serotonin in the extracellular space, and that is improving depression. But like you mentioned, Erin, that happens pretty quickly after the introduction of SSRIs. But the effects that we see in terms of its improvement, these drugs, improvement on depressive and anxiety symptoms, take some time. That tells us that [00:20:00] it is not just increasing this extracellular amount of serotonin. There's actually a lot more complicated mechanisms that happen because surprise, surprise. Our brain is a complex creature.

EW: What?

EAU: I know, right? So what ends up happening is that the parts of our neuron that usually release serotonin,

EW: Mm-hmm.

EAU: the pitcher, I guess I don't, this is really getting outta control here.

EW: pitching machine, if it's because if it's multiple little serotonin

EAU: you're right. Okay. It's a pitching machine. Are serotonin pitching machine. Um, it stops doing its job because it's like, Hey, there's plenty of balls out here. Right. So we see a compensatory downregulation in the serotonin release from these. And then what we actually see later on is a post-synaptic receptors, the ones who are being flushed with all of the serotonin, because there is an increase in the synaptic serotonin. They also kind of modulate their sensitivity to that serotonin, where they're like, I'm not gonna swing at every ball. That's a really bad analogy. But the receptors aren't going to bind to every molecule of serotonin

EW: Because there's so much out

EAU: because there's more out there. Okay? And because our brain is trying to keep things, to some degree, homeostatic, it recognizes, Hey, there's been a shift in something and we don't want that to get out of control. Okay?

EW: So what happens with SSRIs is that there's a ton of serotonin just flooded into that inters, synaptic space. And then, which, go ahead.

EAU: Well, and it's not, it's not that it's like a ton. There is an increase in serotonin, but it's because the serotonin that's there already lingers for longer and can't be scooped back up. And then because of that, you would think that, oh, the pitching machine just keeps throwing out more serotonin than you have a huge increase. But we don't actually see

EW: stops

EAU: It just kind of

EW: compensates for that increase, and then the catcher or whoever's hitting or whatever is like, I'm not gonna swing at every ball

EAU: Right. Exactly. I'm not gonna

EW: So it's like, then that's interesting. Okay, so a couple of questions.

EAU: There's more.

EW: Oh, well, before we go there, how long does that compensatory reaction take? How long does it take for the, the machine to stop pumping out serotonin and the batter to stop swinging at every ball.

EAU: That's a good question. I don't know the answer to that. I don't know the timeline, per se. Yeah. Um. Did you have another before I keep going on what we, okay. Okay. So, but from that we can see that while we know this is the mechanism, like we know this is what this drug is doing and where it is binding,

EW: yeah,

EAU: but that is not alone what is helping depression. So what else is going on? And the more that we have started to look at it, what we also see is these downstream effects. Because it turns out that SSRIs and a lot of other antidepressants they end up modulating by one degree our gene expression.

Okay? Let me tell you what I mean by this, okay? Because serotonin and other monoamines are involved in so many different processes, down the line, antidepressant drugs seem to have effects on adjusting the upregulation and downregulation of other factors that are produced in our brain. So the drug is not doing this, but downstream over time. I know your face is like, this makes no sense. Okay.

EW: I'm just trying to, I'm trying to keep everything in line

EAU: I know it's not in line and there's no, uh, baseball analogy for this one. Okay.

EW: We'll see about that.

EAU: But basically. And we don't know, like this is where it gets very complicated, Erin. 'cause we, we don't know exactly what is doing this, but what we know is that in people on antidepressants or in animal studies of antidepressants, we see changes in gene expression. We see increases in things like brain derived neurotropic factor or BDNF, as well as other growth factors. Vascular endothelial growth factor, genes that are linked to neuroplasticity, activity, dependent genes, other signaling molecules and antidepressant treatment is associated with a wide array of changes in gene expression. And we think that some of these might be mediated by other serotonin receptors, not the transporter that is being affected by the drug itself, but by various other serotonin receptors. Because there are literally dozens of different [00:25:00] types of serotonin receptors in different parts of our brain and different parts of our body who do different things.

EW: Okay.

EAU: So once you've then increased the amount of serotonin down the line, what other receptors are some of these serotonins acting on that is changing other pathways in our brain?

EW: And these other pathways are serotonin related, but not the specific receptor, or they're just pathways,

EAU: are may, they may be serotonin receptor related. So like other, not the serotonin receptor that gets the most attention in SSRIs, um, and not the. Transporter protein that's being blocked by SSRIs, but by other ones. And some additional evidence that's pointing to these kinds of gene expression pathways

as being important are investigations into other types of antidepressants that are more novel like psilocybin,

EW: Uhhuh.

EAU: um, as well as ketamine, which has a lot of really great data for it, especially with treatment resistant depression. Both of these have actions on a lot of different receptors and are not mediated directly through serotonin, but they do seem to have action on other types of serotonin receptors that more directly modulate things like neuroplasticity.

EW: Mm-hmm.

EAU: And we, the more that we look at things like neuroplasticity, which is your brain's ability to kind of change and like continue to change over time, the more that we think that that is very, very involved in depression and anxiety to begin with.

EW: Okay. Uh, I just wanna put a quick plug in for an Advances in Care episode on psychedelics and psilocybin and some of these other formulations. Super fascinating. Go check it

EAU: Very interesting

EW: so, it's really, it's really interesting research. Okay. So before we keep going though, I just wanna make sure I understand.

EW: Again. So we've got, we've got the specific receptor targeted action that it's doing with this one serotonin, uh,

EAU: Transporter protein. Mm-hmm.

EW: And then that's not the only thing. There are other things that are being affected in ways that we don't quite understand that we can't quite predict, but it has to do something with serotonin, these pathways that are other serotonin type receptors. Okay. So it would be like, here's my baseball analogy. If we could, if, if we could continue, it would be like if you're changing the settings on that pitching

EAU: Mm-hmm.

EW: And that pitching machine is then being like, send out fewer balls, uh, decreased frequency wait. And then those settings though are also somehow impacting the tennis court and the soccer ball court, or the soccer field and the basketball court and the pickleball. 'Cause everyone's into pickleball

EAU: Everyone's into pickleball. Sure.

EW: of those things

EAU: All of those courts are being affected by, by blocking the Yeah. Catcher

EW: it was unexpected. It was like, whoa, this was only supposed to affect this. Okay.

EAU: Let's, let's say that that's close.

EW: Okay. Thank you for that. Throw me a bone.

EAU: I'm actually very curious to hear from like someone who really studies this, if that's a good analogy. Can someone let us know? Because that's,

EW: I'm nearly certain it's not, and I apologize.

EAU: I like the idea of it.

EW: Thank you.

EAU: I will also say like this is one potential hypothesis, right? That it's like through this gene expression, through these other, you know, pathways. There are other hypotheses as well. There is also some evidence or some hypotheses with some evidence to support them, that SSRIs don't necessarily improve our mood per se, but do induce a shift in our perceptive state. So like how we perceive positive versus negative stimuli, which then makes it easier for our brains to start interpreting things with a positive bias rather than a negative bias in our emotional processing. And, and we can actually see some of that, like positive versus negative stimuli bias change even with like short term, like really short term like, like a couple days or like one dose of SSRIs. And so then is it that change in bias over time that allows us our brain to kind, but we don't know. Okay. This is some of our ideas.

EW: Okay.

EAU: So that's what we know about SSRIs and how they work. Can, can I be done with the brain part? Whew.

EW: For now, I'll allow it. No?

EAU: Because what I want to move into next is the idea or the question of do they work? Because for some reason, this is still a question out there. The answer in short is yes, they work. And also they might not always work,

EW: Yeah. I think, again, [00:30:00] not a new,

EAU: not a new concept, but I, uh, I'm gonna get into some detail on it. Yes, there is more than a few nuance because first, there, there's so many levels of this, Erin.

EW: Mm-hmm.

EAU: So first, some people who are experiencing depression will get better on their own without any treatment or intervention. What do I mean by get better? Great question. There's two metrics that we tend to look at when we're looking at depression. There's remission, meaning that your depression scale, your depression score, it's usually the Hamilton Depression Rating Scale. Um, it drops below a threshold, usually seven. It means you don't really have any symptoms of depression. There's also response. And response means that you've got a 50% reduction in your score or in your symptoms. Okay? So there's two different metrics, re remission and response. Neither of these specifically address the fact that depression is defined by its effects on your life and function,

EW: Right. It's just the score. It's score

EAU: score related, and that is what we do. Okay?

EW: So just a quick question. So this is that final question of is this impacting your

EAU: Mm-hmm.

EW: Could still be a yes, but if the other symptoms are, if your score is reduced because the other symp, the other checklists are different, then

EAU: Then

EW: so then you could be shown to have a response,

EAU: response, but still be impacted. Absolutely. Absolutely. Especially when we look at response with remission. It really should be like, your symptoms are essentially gone. You're scoring very low, and so presumably, hopefully that's not impacting your life, but we're not necessarily looking at that part of it. We're looking at the score.

EW: Mm-hmm. Mm-hmm.

EAU: So in the short term studies that have looked at this, and all of these studies are so flawed, Erin, there's so many ways that all of these studies are flawed, but I'm just gonna give you the data that we have in studies that have looked at people on like a wait list or what they call care as usual, which I'm not even sure exactly what that entails. Basically people who are in a study about depression, but who are not getting any specific depression treatment. Short-term rates of remission over like three months or 12 weeks or so, range from about 12 to 20%. So about 12 to 20% of people who are in a study about depression not receiving treatment will get better, will have remission long term. We think that about half of people, 50% or so, will have remission of their symptoms

EW: in with, without

EAU: without treatment. Without treatment, okay.

EW: Not just SSRI, but any form of

EAU: without, without any, without any therapy. Without any treatment. This is what we think based on studies. Now, depression is also a very like waxing and waning and remitting type of disease, and so something like 70% of people who have an episode of depression might have a second episode at some point in their lives. Then if we look at placebo controlled studies, because all of these pills had to be tested against placebo pills, sugar pills, and there is so much out there about the placebo response, but in these studies, placebos tend to have a response rate, so that means a reduction in your symptoms at 12 weeks because almost all these studies are short term

EW: Mm-hmm.

EAU: of about 35 to 40% on average. So 35 to 40% of people in a clinical trial that are given a sugar pill to treat their depression might improve in their symptoms. Only about 20% might meet that remission threshold.

EW: And this is, these are short term

EAU: Short term studies

EW: so we don't know anything about sustained improvement.

EAU: correct? Correct. SSRIs across the board, and there are a lot of different SSRIs and we don't have great data to tease them all apart, but SSRIs across the board tend to have response rates of 50 to 60% and remission rates around 40 to 45%.

EW: Mm-hmm.

EAU: So what does that mean overall? What it means is that on the whole, SSRIs are consistently and significantly better than placebos alone,

EW: Yeah.

EAU: and they are statistically and significantly better than no treatment at all, or care as usual, meaning no specific treatment for your depression. When we look at other types of treatment like psychotherapies. Cognitive behavioral therapy is the best studied. Um, but other psychotherapies have been studies as well. Usually we see about a 41% response rate and a 30% remittance rate rate at eight weeks or so. [00:35:00] So better than placebo again. And relatively comparable, honestly, to SSRIs. Important.

EW: In combination with CBT?

EAU: Great question. They tend to do a little bit better. There's not quite as many studies like comparing those directly and things, uh, but they tend to do well. The other thing though, okay, there's a, there's so many

EW: I know I have so

EAU: so many other things though.

EW: Yeah.

EAU: Um, The other thing to consider is that the studies that look at these different types of therapies might sometimes be different. Um, for example, all of these studies are going to have a lot of exclusion criteria. Because these are studies that are looking at a pill versus a no pill or something like that, or a therapy versus a waiting list. The studies, especially that use waiting list controls tend to not include people who have very severe depression. Certainly they don't include people who have suicidal ideation because that would not be considered safe to like, not offer someone any treatment. Um, and and so similarly like there, there can be a lot of variation. There's also a ton of variation in like how people are doing these studies, like the settings and everything. And when we're thinking about placebo responses, which is. A combination of the effect of someone taking a pill that doesn't actually have anything in it. That's the placebo effect part. But the response that we see is also the setting of a clinical trial where participants having regular and frequent contact with a healthcare environment where someone is asking them often on a weekly basis, how are you? How is your mood? Please fill out this questionnaire about how your mood is.

EW: Check in with yourself,

EAU: Check in with yourself. Check in with me. Who's asking you these questions? You are also having an expectation that something could help. Right? And so we know that all of that. Is going to like we, I mean from the data that those things are effective for some people in improving symptoms of depression and anxiety. And still on the whole, the improvement rate of SSRIs over placebos is significant in terms of whether you're looking at effect size, whether you're looking at the like response and remission rates in terms of percentages. The other thing that we can calculate from this, and I think this is an important number because some people with depression or anxiety will improve on their own without any treatment. Some people with depression or anxiety will improve if you give them a pill or a something that says this will help you, and some people will improve because of the effects of the SSRIs.

EW: And some people won't improve

EAU: Some people won't improve at all, so we can calculate what's called a number needed to treat. To try and estimate how many people have to be given SSRIs to get one person to experience remission who would not have otherwise remitted on their own.

EW: Interesting.

EAU: And for, we can do this for therapies and we can do this for SSRI, psychotherapy and SRI, and most of the studies, big picture estimate a number needed to treat for therapy of about five. So for every five people who are in therapy or who are prescribed therapy for their depression, one person will improve, who would not have improved otherwise. And for SSRIs, it's like seven to nine. Okay? Now here's another big problem with all of those studies. They are not the real world,

EW: That's, yeah. And are are any looking long term.

EAU: Uh hmm. There are a long term studies, they're not great. And so I don't, I don't have like, I don't have great numbers for you on that in, in all honesty. uh no,

EW: All

EAU: we do know that, uh, relapse rates tend to be higher if somebody stops. If someone has started on an SSRI and improves, they are much more likely to relapse if that SSRI is stopped before six to 12 months of therapy.

EW: Okay.

EAU: So there is good data to suggest that you wanna continue therapy for at least six to 12 months to reduce the rate of relapse. It does not mean that someone wouldn't have another episode in the future. Um, but that can kind of help to prevent that.

EW: And just to clarify, you mean taking an SSRI, not psychotherapy.

EAU: correct. In psychotherapy, we have better data that, like a fixed term of therapy, like say 12 weeks or whatever, like timeframe it is, can have long-term benefits. Whereas with SSRIs, even if you see improvement at 12 weeks, if you then stop it, you're not gonna continue to [00:40:00] see that improvement a year from now. You would, if you continued it for a year and then tapered off, you'd be more likely to see sustained improvement. But there is a big study that was a pretty huge moment in like depression research, um, that tried to look at more real world scenarios. Um, and I'm not gonna dig like super, super deep on this study design. I do link to it and there's been a ton of papers published from it. It was called the STAR D trial. And this was pretty huge because A, it was a very large study. B, it included a much more realistic sample of people who were experiencing depression. It was like community based kind of where it wasn't just, you know, it, it included people who had comorbidities, who had

other mental health disorders, who had substance use disorders. Like just a more realistic sample than what's usually included in these pharmaceutical trials. Um, and then it walked them through this kind of stepwise therapy where we see, we give everybody one drug and then we see who responds and who doesn't. And then if they don't respond, then we randomize them. It wasn't perfectly random, but we randomize them to a bunch of different possible treatments. Either stop that and switch something new, or add things or add therapy or whatever it was. And then after level two, they go to level three, level four. There was like four levels overall. Bottom line results from this were that about one third of people reached remission with only the first line, SSRI, which was citalopram in this case.

EW: Okay.

EAU: By the end of the second stage, the cumulative remission rate was 50%, and by the end of the study, about 70% of people. So if you went through all these different possibilities, about 70% of people had remission. Again, that doesn't mean they might never relapse, but it certainly is meaningful. Now, before you even ask a question, I have to caveat this because this study is old at this point, um, and a more recent kind of re-analysis, and I will say by people who seem to not like SSRIs based on all their other published papers, but they reanalyzed this data and actually estimated a slightly lower remission rate. So they said, no, it wasn't, you know, a third of people. It was actually like 25.5% after that first level. So one SSRI trial and then they estimated only about a 40% response rate by the end rather than 70%.

EW: Interesting.

EAU: Mm-hmm. But either way, it is a much more realistic, real world trial that tells us a few things. One, it tells us that not everyone is going to respond to the first SSRI that they try, period. We know this very true. It tells us that they are still effective for a substantial portion of people. Like some might say 25 is not that much, but if you are in that 25% and your depression is remitted because of this, and usually on a much faster timeframe than what we would expect if someone has no treatment whatsoever. Right. That is meaningful. Right. What were you gonna ask Erin?

EW: Um, okay. First question that came to mind is, and I know you, you said you weren't gonna talk about the differences in SSRIs, but

EAU: Mm-hmm.

EW: broadly speaking, what are some differences between these different SSRIs?

EAU: Great question. So there, um, there's a bunch of different SSRIs that are licensed in the US and there are some that are licensed in the US that are, or some in, in Europe, in the UK that aren't used in the us. And then there's also SNRIs, which are serotonin, uh, selective serotonin re-uptake, and norepinephrine re-uptake inhibitors. So they do both, um, the differences between them. Some of them are gonna be more sedating and some of them are gonna be less sedating. Some of them make you sleepy. Some of them make you less sleepy.

EW: Do we know why?

EAU: No. Erin, no, no, no. We don't know why for any of these. Some of them, uh, are gonna, some of them can cause weight gain and some of them have much less, seem to cause much less weight gain. Um, some of them, uh, like citalopram for example, at higher doses and especially in elderly populations, um, we have seen that it can cause some effects on your heart. It can prolong your QT interval, which means it could potentially put you at higher risk for a, a heart condition in the future. We don't see that with all of the SSRIs. Um. Then in terms of, so a lot of it comes down to the side effects. So the side effect profiles can be different for different, you know, specific ones. Um, and then in terms of efficacy, there was a big study that came out that tried to compare, you know, between looking at all of these different placebo trials and the head-to-head trials that exist 'cause there are some of those. Um, are there any that kind of come out on top? And the answer is like, maybe there are a few like escitalopram, uh, which [00:45:00] is Lexapro brand name, um, often like comes out higher. Sertraline tends to be like well tolerated compared to its effect size, if that makes sense. 'cause they were comparing like side effects versus efficacy.

EW: Yes. Yeah.

EAU: But there is not like a, oh my gosh, this is the clear winner or anything like that.

EW: Well, and it's so, it's so individual, like, so person to person. Do we know anything about the individual variation and receptivity to SSRIs or efficacy and like, I remember there was, is there something about genetic testing that

EAU: I didn't get deep, I didn't get into that. But there is a lot of interest in that. Like can we, can we do any sort of genetic analysis to try and identify who might be more likely to respond to which, because one thing that we see is that like there is familial clustering sometimes. Like if you're like, oh, my sister was on sertraline and she did really well on it, then you might be more likely to also do well on sertraline. But is that again, in part because of an expectation and because of a familiarity? Or is it because of some genetic predisposition, things like that? Um, so there are,

EW: you read the wrong, the wrong testimonial like. Lexapro ruined my life, and then somebody else is like, that was the best thing that's ever happened to

EAU: And both are true,

EW: are true.

EAU: are true. There are certainly side effects to SSRIs. On the whole, their safety profiles are really quite good, especially compared to our older antidepressants like the TCAs and the MAOIs. Um, but the two biggest side effects of SSRIs are GI side effects. So nausea, vomiting, diarrhea, probably because of all the serotonin in your guts. Um, and that tends to be transient, usually improves. Sexual dysfunction though, can be a huge downside to SSRIs and this can affect any part of like your sexual cycle from like desire or libido to ability to achieve an erection or to achieve orgasm, which can be pretty debilitating, especially because depression and anxiety can also affect sexual dis sexual functioning.

EW: Mm-hmm.

EAU: Um, it does not though happen to everyone who is on an SSRI and we can't predict who it's gonna happen to and, and who it won't. It usually does not get better though, while you're on it, in contrast to the GI side effects.

EW: Oh, interesting.

EAU: Yeah. Um, and there are some reports of sexual dysfunction persisting after discontinuation, but as of right now, it's not like a well-studied or well-recognized phenomenon like in the medical literature, but I know there's a lot of interest in studying it more deeply

EW: Mm-hmm.

EAU: in people who are depressed, like in a depressive episode, but perhaps actually have undiagnosed bipolar disorder. SSRIs can potentially precipitate a manic episode, and so they're not usually used in bipolar depression, and there are caveats to every rule when it comes to that. But probably the most headline generating warning or side effect as it relates to SSRIs is its relationship with suicide and suicidal ideation.

EW: Yeah.

EAU: Um, an increase in suicidal ideation is often, it's a black box warning. Now on all SSRIs, the data suggests that this might, this association might exist like exposure to SSRIs and an increase in suicidal thoughts or attempts at suicide might exist for pediatric and adolescent populations.

EW: Right. Yeah.

EAU: The evidence in adult populations actually looks at, looks like there is actually a decreased risk of suicide, especially in the older populations, like in our older adult populations over 65. But in adults over age 25, 25 is the cutoff. Um, there is not an increased risk of suicide that we see with SSRIs. There may be in those under 25.

EW: Hmm.

EAU: And that still doesn't mean that we don't ever prescribe them because in some cases they still can really help with all of the other symptoms of anxiety and depression. So, but it is like, it's an important, that is why it's a black box warning and it's an important thing that people are really looking into. There are a lot of other potential harms that have been scrutinized very deeply in their literature in these like large scale observational studies to try and figure out long term are there other detrimental effects to SSRIs? And all of the rest of them don't hold up to scrutiny. They don't hold up to the statistical analyses. There's like, is there effects on autism rates or A DHD rates in people who are pregnant who are on SSRIs? So far, those don't hold up to the statistical analysis. It doesn't mean there's not some suggestion, but there's, there's not like a clear consensus at this point.

EW: What about, um, dementia was another one that I saw.

EAU: I Nothing that holds up to [00:50:00] Yeah, the, at least all the meta-analyses that I read.

EW: Right. What about, um, serotonin syndrome? Are you going

EAU: Great question. So serotonin syndrome is an important, um, potential effect of overdosing essentially on SSRIs. And importantly because self-harm and suicide, which overdose is one mechanism that people might try to attempt a suicide. Um, SSRIs are actually much safer in overdose compared to TCAs or MAOIs or like benzodiazepines that we use for anxiety, for example. We don't use them very often, but we do sometimes. Um, but serotonin syndrome can absolutely be a thing, and that is something where you basically just have way too much serotonin. And then, uh, there's a mnemonic that I'm sure I learned in med school, but I didn't write it down, so I can't tell you the exact symptoms of it, but it's like, it can be quite dangerous. It's an emergency room situation.

EW: Yeah.

EAU: It is still safer again, than overdoses of other older antidepressants. Um, and it is a treatable condition, but one concern is not necessarily like overdose, but when a person is on multiple serotonergic medications, because Erin,

EW: would they be?

EAU: a lot of our medicines actually have some serotonin effects. Um, Zofran. So Odansetron, or I think that's how you pronounce it, which is a medicine we use for nausea. Trazodone, which is like an antidepressant that no one uses for depression, but we use it for insomnia. There. There are so many gabapentin, so many medications that we use for a whole bunch of different things. Tricyclics, we use a lot actually for migraine. Um, and sometimes for neuropathic pain or for IBS.

EW: Hmm.

EAU: And so if you're taking multiple different medications, which we very often see in our elderly populations, you do have to think about how many of these might have effects at some point on serotonin or on serotonin receptors. 'Cause some of them, like Zofran acts on serotonin receptors.

EW: Right, right. Okay.

EAU: So yeah, it is something that we have to kind of keep in mind. But on the whole, they are really pretty safe medications on, on the whole, especially compared to what we had previously.

EW: Yeah.

EAU: For me though. Do you have any other questions, Erin, about like the, the nitty gritty? 'Cause that's my end of nitty gritty, and I wanna tell you what I feel like.

EW: I mean, let me think about the nitty gritty. I think the thing that, like in reading all these papers and reading the research, is that because the effects of SSRIs are so broad. Because the way that we measure those effects are so broad and so imperfect and so varied.

EAU: Mm-hmm.

EW: And because the number of conditions that SSRIs are used for can also be very, you know, varied. People can draw whatever conclusions they want almost out of this. And, and that is, I think, what, what makes, there's so much noise around SSRIs and I think what gets lost in that noise is the signal that for many people, SSRIs are very effective. For many people, maybe they want to weigh the pros and cons of SSRIs, but it's, it's like there are these sweeping statements that research groups, I think there are one in particular I'm thinking of wants to

EAU: Mm-hmm.

EW: that are harmful. SSRIs are not more effective than placebo,

EAU: And that's not

EW: uh, not true. Right? Yeah.

EAU: The end of the day, not

EW: I mean, it can be true if you cherry pick your studies and you, you know, throw out the ones that don't suit your end, uh, agenda, but,

EAU: I also think what, for me, there's a few different things I feel like are really left out. A lot of, a lot of these conversations that are happening about SSRIs and really like it's left out of the conversations that we're having about how we treat major depressive disorder, how we treat generalized anxiety disorder, any of these affective or mental health disorders, a lot of which we treat with SSRIs or other medicines, right?

EW: mm-hmm.

EAU: We do not understand the biology of these conditions. We do not know what these mechanisms are. We do not have biomarkers or tests that we can run to diagnose these conditions. We don't even have a like measurement that is not subjective, right? Because these are disorders that we diagnose based on timeframes, based on questionnaires of symptoms and based on their effect on our daily lives and our ability to function. So of course, we cannot expect to fully understand how a drug is working if we don't understand the disease that we're treating. And at the exact same time, we cannot ignore, refuse to treat or withhold effective treatment from millions of people just because we don't understand the mechanism. So I really want to [00:55:00] provide everyone a compare contrast. And some people might get mad and say, that's apples and oranges, to which I say those are both fruit. Okay? So allow me

EW: Actually orange is a vegetable. No, I'm just kidding.

EAU: It scared me for a second. 85 to 95% of cases of hypertension or high blood pressure are what is called essential hypertension, which is our fancy way in medicine of saying we have no idea what causes it. And yet we have dozens of different drugs that work on very disparate mechanisms from diuretics to calcium channel blockers to angiotensin receptor blockers, none of which, not a single one is targeting the primary cause of hypertension because we do not know what the cause of hypertension is.

EW: Right.

EAU: it goes further arian. Not everyone who receives the same benefit from one anti-hypertensive is going to receive it the same way. In fact, only 25 to 30% of people with hypertension are going to have their blood pressure controlled with a single agent. Most people are gonna require at least two, if not three. The same can be said for antidepressants. No, we don't understand how they work because we don't understand depression. But we do know that a substantial proportion of people who try one will derive benefit from it. And those that don't might benefit from a different version of one or a different type of antidepressant. And this is not just because of a placebo effect,

EW: Yes, it's, I mean, I feel like I, I saw it described somewhere, which I really like, and that using the hypertension analogy is that hypertension is not caused by a lack of antihypertensive.

EAU: right?

EW: Depression is not caused by a lack of serotonin. But we have drugs, antihypertensive, antidepressants, uh, SSRIs that have an impact for some people. And so. The, it's not like a one-to-one, here's the problem, here's the solution, but it is here is a problem and here is an imperfect solution that some, that can work for some people.

EAU: A hundred percent Erin. A hundred percent. And I will also say too, that like there is a lot of discussion of like, oh, mild versus moderate versus severe depression. And like most of the guidelines from the European societies, from the American societies actually recommend psychotherapies, like cognitive behavioral therapies for mild to moderate depression over SSRIs. But realistically, a lot of people either do not want that or are not ready for that, or cannot do it because their insurance won't cover it

EW: I was going to say,

EAU: because they don't have the time,

EW: Right. As sort of like a, oh, you need, in order to be prescribed SSRIs, you need to undergo six months of, of, of therapy first.

EAU: Yeah.

EW: How are you gonna take time to do that? How? And for some people, maybe that's realistic. For other people it absolutely is not

EAU: Exactly, and I think a lot of this, like a lot of this discussion comes down to the stigma that we have when it comes to mental health disorders. I think another part of the problem, which is in part due to the stigma, is that when it comes to something like hypertension, we have really great data on if we control blood pressure, by whatever means we can prevent death from cardiovascular disease long-term, that's a pretty big deal. This is probably worth it, right? We don't have as good of data on the long-term effects of treatment versus non-treatment and things like that when it comes to depression and anxiety, because who's gonna fund those studies? Who's gonna put up the money for that? Right? So that I think is another part of this problem is that there is a lot more data that needs to be gathered and a lot more understanding that we need of these medicines and alternatives because treatment resistant depression is very real and affects a huge proportion of people. Um, so yeah, there's still a lot, but. But SSRIs are safe and they're effective for a lot of people.

EW: I mean, it's like we, we just come to the same conclusion in every episode. More research is needed.

EAU: Oh, funding.

EW: more nuanced view is crucial.

EAU: Mm-hmm.

EW: And, uh, transparency.

EAU: Wouldn't that be great, Erin?

EW: Yeah, I think it's, um, it, it's, it's been very interesting to, to like explore

EAU: I

EW: SSRIs.

EAU: To get like so over my head deep in this literature and still feel like I don't have a great handle on it, honestly,

EW: Right. And I think that that in itself is the lesson. Yeah. It's like who, who has a really, who can raise their hand and say, I know how they work for each person. Whether that person has derived benefit or has, you know, sub described that they have had benefits or is [01:00:00] treatment resistant. You know,

EAU: Yeah. Or has had only side effects, right. Or yes, benefit, but also side effects that were bad enough that it's not worth it. Right. And that, and that we absolutely see all the time. And I mean, looking forward, like I would not be surprised if there is a time when SSRIs are almost entirely replaced, like the same way that MAOIs or TCAs are not really used very commonly. But that needs to come because we have found better, more effective alternatives because we've invested in mental health research and in expanding access to services, in normalizing therapy, in taking time off work to do these other things. And because we've come to a better understanding of the causes of depression and we have safer, more effective medicines, not because we lie and say that SSRIs are addictive, they are not. There is no data for that, that they're dangerous, like heroin. They are not right. Like they, this needs to happen for good reason, not just taking something away That has been lifesaving for a lot of people, even though it is imperfect.

EW: Yeah, it's um, it's a real bizarre cont it's a real, it's, it's a ugly new manifestation of the stigma that has long been with

EAU: Exactly. A hundred percent. It's an ugly manifestation of that, that stigma. I, I really don't like it.

EW: No, no.

EAU: So if you wanna read more and get as deep as I did, I cannot, this was such a big episode for me, Erin, that I actually tried to, um, organize all my sources. Usually they're just like a, I throw them all into a. Spreadsheet. This was like, I have a whole section for papers on the mechanism of action. Um, I've got a whole section for papers about the guidelines, who's making these guidelines. I've got a huge section on the efficacy and effectiveness studies. I've got a separate section on looking at the placebo responses versus efficacy studies, another section on papers specific to children and adolescents, because it is a very different conversation when we're talking about these medicines in children and adolescents and we have less data. And like I said, there's more potential for risk and that doesn't mean they're not used. I have a few papers on long-term data, not great, but I have some, I have more than I realized actually. And then other papers on untreated depression. I'm just scrolling through all of

EW: I love this. I mean, you have just made life so much easier for someone writing a term

EAU: I know seriously, could someone like take all these and write a paper? Um, I also have separate section. I should move this up to the top about what we know of depression and anxiety, like what we think about their neurobiology, some papers on the epidemiology, and then a few that I call myth busting. And then those you mentioned, Erin, the like very controversial straw man argument about serotonin and whether or not it's involved. I included that paper and all of the responses to it.

EW: Oh my God, there are so many responses.

EAU: you can read about it on our website. This podcast will kill you.com.

EW: Thank you again so much to the providers of our firsthand accounts for these episodes and all of our episodes, really, um, it, it really means so much to hear these perspectives and your experiences, so thank you. Thank you.

EAU: Yeah. Thank you so much. Thank you also to Blood Mobile who provides the music for this episode and all of our episodes now on Instagram.

EW: Now on Instagram, uh, thank you to everyone at Exactly, Right Who helps us make this podcast. Tom, Liana, Brent, Pete, Jess, you know, everyone. There's so, so many, so many people. So thank you. Thank you.

EAU: Thank you. And thank you to you listeners. Hopefully you liked this two part deep dive. Did you tell us genuinely? Uh, also, how about that baseball analogy?

EW: Yeah. Sorry about that. Oh, I thank you also to our wonderful, generous patrons. We appreciate your support. It means the world to

EAU: It really does. Thank you,

EW: Well, until next time, wash your hands.

EAU: you filthy animals.