The Infamous SSRIs

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Abstract:

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Abstract

Antidepressants, and in particular selective serotonin reuptake inhibitors (SSRIs), hold an important role in our current society. 13.2% of the population in the United States of America are estimated to have used antidepressants between 2015-2018, and the usage is rising. Antidepressants were developed with the goal of improving people's mental wellbeing, in particular during periods of depression. In addition to depression, antidepressants are also commonly used for treatments of anxiety, OCD, and eating disorders. Of these antidepressants, SSRIs are some of the most prescribed medications. Yet, although SSRIs now reach a broad segment of our population that struggle with mental health challenges, researchers still do not know how SSRIs work. Of greater concern, the jury is still out as to whether SSRIs have a significant impact on people's mood and wellbeing. In this article, I dive into the research testing which effects SSRIs are documented to have in the short and long-term. I also conduct a review of the side effects associated with SSRI usage, to address some of the most common concerns expressed by people considering using SSRIs. This article was first published in Subkit on August 15, 2022 (https://www.subkit.com/pernillebuelow/posts/the-infamous-ssris).

According to the Center for Disease Control (CDC), over 43 million, amounting to 13.2%, of all U.S. adults have been or are using an antidepressant between 2015-2018. The reasons for taking an antidepressant are many, including but not limited to major depressive disorder, anxiety and eating disorders. Currently, the most popular antidepressant is the Selective Serotonin Reuptake Inhibitors (SSRIs), and this is the 'drug of choice' for our Mental Health newsletter this month. You might wonder why I am writing about an antidepressant in the Mental health newsletter rather than the Neuroscience Research newsletter. To me the answer is simple: when deciding whether to start a psychopharmacological treatment (a fancy way to say 'deciding whether to take a drug or not for my mental health challenge') it is less about the biological intricacies and more about the side effects, long-term effects, and overall efficiencies. While I will give you a brief account of how SSRIs work, the focus will be on addressing the very real questions that come up when starting, or considering starting, psychopharmacological treatment with SSRIs. Further, the timing of this newsletter could not be more fitting. In the last few weeks, as I was preparing this newsletter, a research review paper came out which has created a tremendous amount of publicity and public stir. I'd highly recommend that you read one or more of the articles after finishing this newsletter. It will give you an even more comprehensive understanding of why I titled the newsletter 'the ***infamous*** SSRIs'. Here is a link to one of the many news articles. When all of this is said, we will certainly return to the neurobiology of SSRIs in future Neuroscience research newsletters. Specifically, when the time comes, we will focus on how they do so much more then 'rebalancing' the chemistry of the brain.

Are SSRIs addictive?

I started SSRI treatment in the Fall of 2019. Since 2016, my psychiatrist adamantly tried to convince me to use SSRIs to address my low-grade anxiety and rather severe insomnia. But repeatedly, I refused. I wanted to address my challenges in a non-pharmacological manner which I was certain would be better in the long-term. While I do not regret my choice, I recognize in hindsight that my psychiatrist was on the right track. My sleep transformed to the better after starting SSRIs. I had several hesitations about SSRI treatment. In addition to 'believing' in the power of non-pharmacological approaches, I was also worried about the potential addictive properties of SSRIs. Would I be able to stop if I wanted to, or had to?

The jury is still out on the addictive properties of SSRIs and antidepressants in general. An important distinction is whether withdrawal symptoms from terminating SSRI treatment reflect illness relapse (e.g. relapse into depression) or discontinuation symptoms (i.e. a physiological reaction to stopping the treatment),

with the latter representing a true 'addictive' property of SSRIs. According to recent studies, different factors determine whether and how addictive an SSRI is.

1. **The type of SSRI**: as you may know, there are a ton of different SSRIs out there and the ways they bind to and block serotonin reuptake. The more potent the SSRI is, the more likely it is to cause discontinuation symptoms and withdrawal effects in general (Jauhar et al., 2019), with the SSRI Paroxetine being one the most potent. However, it is important to note that studies find withdrawal effects in participants regardless of whether they discontinue Paroxetine treatment or a placebo pill (i.e. a 'sugar pill') (Jauhar et al., 2019). This tells us that withdrawal effects are in large part created by the habit, and reliance, on taking a pill, rather than the actual effects of the drug. This phenomenon is known as the 'Placebo Effect'. I always thought these results were fascinating and really underscored the power of our minds. If we place meaning on something, we can change our bodies accordingly. Indeed, placebo effects from treatment with a sugar pill also leads to the positive effects observed with SSRI treatments.

2. The second factor is **the length of SSRI treatment.** The longer someone has undergone SSRI treatment, the more likely they are to experience withdrawal effects (Jauhar et al., 2019). I think this is a particularly important result to reflect on, because it leads us to the fundamental question of whether SSRIs, and antidepressants in general, are supposed to be short-term or long-term treatments. We know that one aspect of what makes SSRIs effective in improving mental health is that they render the brain more plastic (i.e. more capable of changing – take a look at the 'Intro to the brain' document if you need a refresher on this cool topic!), and thus more responsive to talk-therapy and focusing on the positives of life. However, whether these effects are long-lasting by themselves is debatable, and in a few paragraphs, we will be discussing the literature looking at the long-term effects of SSRI treatment.

So, what made me turn around and say yes to the SSRI treatment? Personal circumstances led me to experience a string of panic attacks that turned me into an anxious wreck. I came to a point where I did not care about addictions and side effects. I needed relief, and preferably a long-term, consistent relief that did not simply last for a few hours (which is the case with a lot of anti-anxiety medications such as benzodiazepines or other drugs that 'numb' you).

Breaking down the actions of the SSRIs

This is where I am going to give you a quick debrief on how SSRIs work in general. I say 'in general', because SSRIs can have different ways of actions but the overall outcome is always the same across all of the SSRIs available: they increase the amount of serotonin neurotransmitter present in your brain's synaptic clefts. As you know from reading the 'Intro the Brain' document, our brain is made up of neurons that are connected via synapses. These synapses act as senders and receivers of information via neurotransmitters, one of these being serotonin. This increase in serotonin is achieved through blocking the reuptake. Normally, all neurotransmitters that are released into the synaptic clefts are recycled back into a neuron's axon so they can be reused (isn't that so cool? Even our brain understands the importance of recycling!). The SSRIs block this reuptake so that the serotonin neurotransmitter float around in the synaptic clefts for longer, presumably having effects on the dendrites for a longer period than if they had been recycled right away.

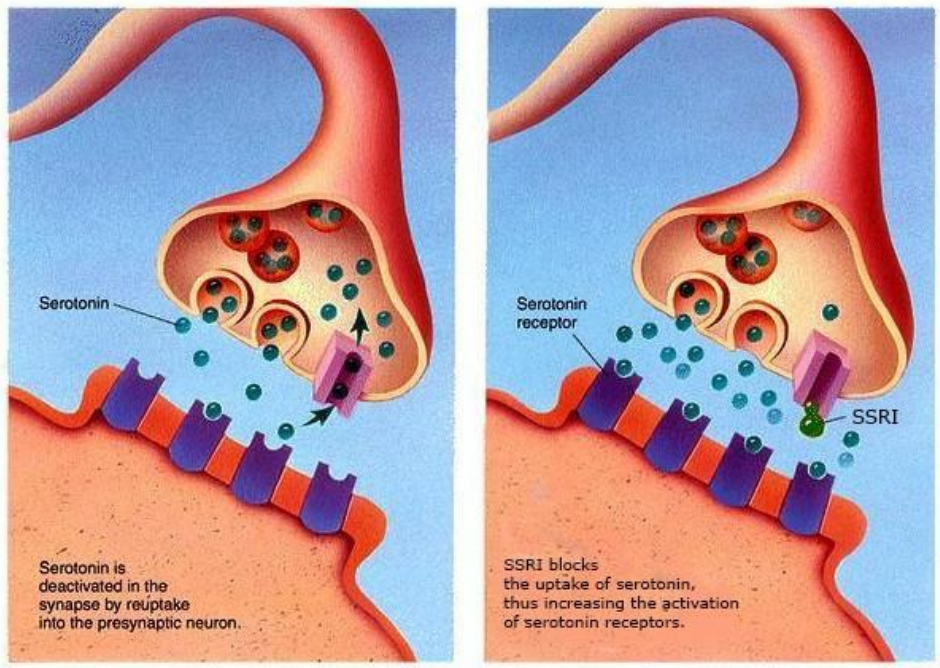

Figure 1: SSRIs increase the amount of free serotonin neurotransmitter in the synaptic cleft by blocking its reuptake (i.e. the recycling of serotonin). This figure is sourced from: https://www.ocduk.org/overcoming-ocd/medication/how-ssri-work/

However, there are multiple problems with this explanation for how SSRIs work to improve mental health. One of the major issues is that the effects of SSRIs typically do not manifest until several weeks after starting the treatment, but the increase in serotonin happens immediately. Thus, there is something that happens

during those weeks that does not have anything to do with the increase in serotonin levels. What is happening then? One theory is that elevated serotonin action on the dendrites leads to the generation of more synapses, ultimately causing structural and functional changes to how neurons communicate with one another. However, in order for the synapses to actually contribute to improved mental health, they must be made at the right places and at the right times. Hence, this theory only works if you pair SSRIs with other types of treatments, for example talk therapy. Indeed, several studies argue that SSRIs are most effective if they are paired with talk-therapy (Kamenov et al., 2017). I would argue that this is also true when pairing SSRI treatment with other forms of community-oriented activities (see last month's newsletter). An alternative idea is that the SSRIs affect the gut-brain axis, and it is the changes in the gut and microbiome that lead to the improvements in mental health (Sjöstedt et al., 2021). We will be talking about this interesting phenomenon in future letters and talks (yes, another newsletter type in video-form is coming at the beginning of next year!).

Long-term effects: cost-benefit analysis of SSRIs

Let's return to the relevant questions if you are asking yourself whether to start, or continue, an SSRI treatment. If you continue this treatment for many years, what are the long-term effects? Personally, I am still using my SSRIs and I do not have any plans on stopping. Mainly because of the transformative ways in which they have improved my insomnia. And in truth, I am scared that if I were to stop, I would go back to how it was before. Am I addicted? Maybe.

When it comes to the efficacy of SSRIs, meaning how effective they are in ameliorating symptoms, many studies show that SSRIs have clinical benefits to a person's health-related quality of life (an umbrella term for measuring health-related behaviors, e.g. smoking, drinking, medication usage) in short-term studies (2-3 months after starting treatment) (Almohammed et al., 2022). In contrast, long-term studies find only negligible effects of SSRI treatment on health-related quality of life (Almohammed et al., 2022). These results can be interpreted in a couple of different ways:

1. The positive effects of SSRIs may diminish over time due to tolerance (see Figure 2), meaning that your brain and body gets 'used' to the SSRIs in ways that change their efficacy (more on this in future letters!). In that case, we might expect the short-term improvements to reduce over time as well.
2. Alternatively, the SSRIs may hit a 'ceiling effect' after 2-3 months, meaning that the SSRIs no longer influence the brain and body in measurable ways. If

so, SSRIs may be great for triggering the start of positive changes, but they may not enable the full improvements a person is looking for. In this scenario, we would expect the positive short-term effects to be sustained in the long-term albeit without any further improvement.

Research is still hashing out which of these interpretations are correct. Here is the thing: if and how people respond to SSRI treatment really depends on a person's unique biological make up. A few months ago, I wrote an article on how research is starting to uncover the neurobiological bases of personalized treatment. I'd highly recommend reading the article if this is a topic of interest for you.

But does it harm you to keep taking SSRIs for a longer time-period, for example for several years or even decades? Below I will mention four considerations with long-term usage of SSRIs (read more about them in Thom et al., 2021), which are summarized in Figure 2. Note that most studies define long-term usage as 24 months or more.

1. One consideration is **side effects.** While this has not been true for me (I have used my SSRIs for three years), certain side effects can worsen, or new ones can arise with longer usage. One of the most concerning possible long-term side effects is that of weight-gain. The reason this is particularly concerning in the long-term perspective is because of the metabolic changes associated with weight gain that may lead to Type 2 diabetes. In fact, research is demonstrating that long-term usage of SSRIs predisposes people to develop Type 2 diabetes as well as a metabolic syndrome called Dyslipidemia, characterized by dysregulated cholesterol and triglyceride levels that are not caused by diet or physical activity. Because of this, it is generally recommended that people receiving SSRI treatment have their metabolic profile checked by their primary caregiver regularly.

2. Another consideration is the fact that SSRIs, as well as other antidepressants, can **interact with other medications** that you may need in the future. These interactions could impair the effectiveness of the other drugs or exacerbate certain side effects they may have. To avoid these issues, make sure to tell your doctors that you are using SSRI before starting other drugs!

3. A third concern with long-term SSRI usage is a condition called **Tachyphylaxis**: when previously positive responses to a drug, in this case SSRIs, diminish. This effect could be due to the brain developing tolerance,

and in that case, one should likely increase the dosage of the drug (only after consulting with your doctor though!), but it could also be an actual regression where the drugs are no longer effective to treat the symptoms regardless of how much you increase the dosage (see Figure 2). Interestingly, and perhaps not that surprisingly, whether a person develops Tachyphylaxis depends on their clinical history: it's often people that suffer from more complicated and severe mental health challenges that experience Tachyphylaxis, and rather than a loss of efficiency it is also possible that the onset of Tachyphylaxis simply reflects that the SSRI was not working at all to begin with and that any positive effects observed were placebo-induced.

4. If you continue or start your SSRI treatment at an older age, there is another thing to consider: **falls and fractures.** Studies have found that elderly people using SSRIs are at greater risk of falling and of fractures. Why is that? The research is still figuring it out, but it likely has to do with changes to your proprioception and possibly changes in bone density that are aggravated by SSRI usage. So far, I have not found any studies directly testing whether this is or is not true in older populations. If you find yourself falling and/or getting more fractures after starting SSRIs, this may be something to talk about with your doctor.

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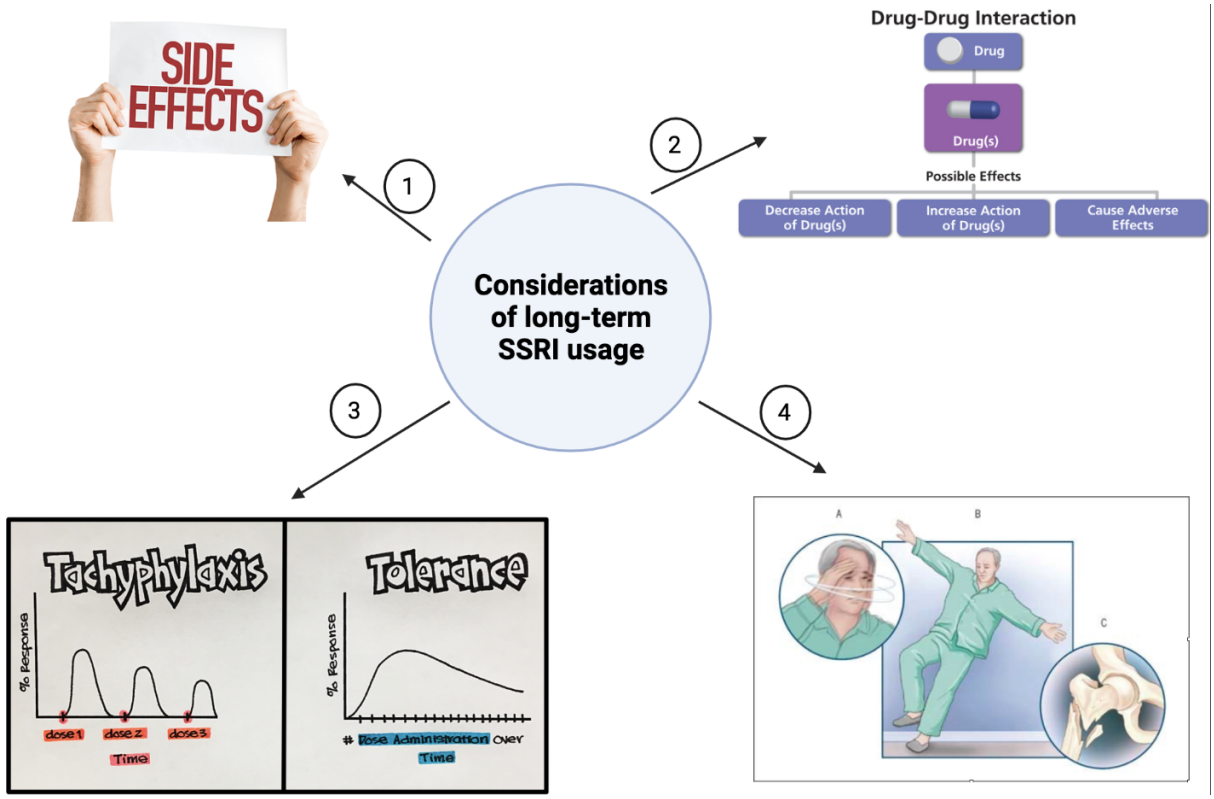


Figure 2: A summary of the four considerations when taking SSRIs for long-term treatments. 1) Side effects such as weight gain and metabolic challenges. 2) Medication interaction. 3) Tachyphylaxis and tolerance: the diminishing effect of the SSRI after previously positive responses. 4) Falls and fractures in older populations.

If you search 'side effects of SSRIs' or 'are SSRIs bad for you' in google, you will find a TON of results. Please keep in mind that this research is still developing and many of the scientific reports have yet to be replicated. One "fun" example is that of dementia. Some studies find that SSRIs make people more likely to develop dementia later in life (Wang et al., 2018). That does not sound great obviously. However, in that same google search, you will find other scientific reports that demonstrate how SSRIs protect people against developing dementia (Bartels et al., 2020). When you search on these topics always double check research findings. I understand it can be overwhelming to figure out on your own, and your doctor/psychiatrist may not be on top of the (newest) data either. This presents a challenge that may lead you to seek out personalized treatment consultants of which there are plenty. Please feel free to send me any questions regarding treatments in the mental health field, and I will do my best to give you an objective consideration of the validity of the current research.

It may not seem like it, but the major message I want you to take away from the above paragraph is that studies are generally demonstrating few adverse health effects of long-term usage of SSRIs. However, considering that SSRIs generally do not have significantly positive effects on your mental health after 3-4 months, it may be worth asking if the drugs are actually doing anything for you? And if so, does this positive effect have more to do with you believing that they are working (i.e. placebo), than the actual pharmacological effects from the drug? Personally, I plan on continuing my SSRI treatment, but I also recognize that I may be taking a pill for the comfort of thinking that it helps me. I am privileged to have a private health care insurance that covers most of my SSRI drug bills, but that is not true for everyone. In fact, demographic studies show discrepancies in who receives SSRI treatment in the US as well as other countries. The majority of the patients are white adult females, usually living in a higher socioeconomic setting (Torres et al., 2022). People of color and/or people that live in lower socioeconomic areas are much less likely to receive SSRI treatments. This could be because they choose not to take it, or, perhaps more likely, because the doctors are biased and do not provide the proper care to these populations (Williams and Rucker, 2000; Nong et al., 2020), a sad yet well-established fact in the medical and research field. Addressing financial support for mental health treatments **and** ensuring fair, unbiased treatment of all people will be an ongoing topic and challenge of my Mental health newsletters.

SSRIs during pregnancy and breast-feeding – does it impact your child's brain development?

The last thing I want to converse about in this newsletter is the question of using SSRIs during pregnancy and while breast-feeding. I get a lot of questions on this, and I think it is a very important topic. Unfortunately, there is so much information out there that it can quickly get confusing as to what the 'true' answers are. Below I summarize the results that have adequate scientific evidence and I try to address any 'myths' that are not supported by science. For a quick overview, take a look at Figure 3.

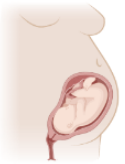
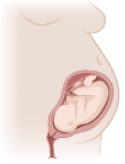
	Mouse receiving SSRIs during pregnancy	Human receiving SSRIs during pregnancy	Human that is depressed during pregnancy
			
Scientifically supported effects on child	• Greater likelihood of neurodevelopmental disorders, such as Autism Spectrum Disorders (ASDs) • Greater likelihood of depression, anxiety, and altered stress responses	• More likely to have preterm deliveries and lower birth weight • Higher likelihood of placental vasculature complications and heart defects • Altered epigenome	• More likely to have preterm deliveries and lower birth weight • Higher likelihood of placental vasculature complications and heart defects • Altered epigenome
Not scientifically supported effects on child		• It is not scientiifcally supported that there is a greater likelihood of neurodevelopmental disorders, such as ASDs • It is not scientiifcally supported that there is a greater likelihood of depression, anxiety, and altered stress responses	

Figure 3: A summary of the scientifically supported effects of SSRIs and depression during pregnancy in mice and humans. Note the differences between SSRI treatment during pregnancy in mice vs humans, and the identical effects of SSRIs to depression during pregnancy in humans.

- In animal models, SSRI during pregnancy leads to behavioral changes that correlate with neurodevelopmental disorders (Maloney et al., 2018), as well as increased likelihood of depression, anxiety and altered stress responses in adulthood (Ansorge et al., 2004; Zullino et al., 2018). Several of these studies have demonstrated that these risks are further exacerbated if the dam (i.e. the mouse mother) has predispositions for ASD, which speaks to the synergistic effects between SSRI exposure and genetic inheritance.

- In contrast to animal studies, studies in humans are **not** consistently finding that SSRI usage during pregnancy leads to increased risk of ASD, depression, PTSD, or anxiety. Instead, the factor that influences a child's likelihood of any of these mental health challenges is if the primary caregiver(s) suffered from depression while the child was growing up (Moreau et al., 2022). We will be talking more about this phenomenon in upcoming newsletters.

- What has been reported when SSRIs are consumed during pregnancy is a greater likelihood of preterm deliveries, lower birth weight and, more seriously, correlates with placental vasculature complications and heart defects (Toh et al, 2011; Huang et al, 2014; Ghimire et al., 2021). A major complication in human research studies is the confounding variable of the depression itself. Could it simply be the depression that causes these issues? Indeed, studies consistently report similar outcomes (e.g. preterm delivery and heart defects) when the child is born by someone who was depressed but did not receive SSRI treatment during the pregnancy (Jimenez-Solem et al., 2012).

- If you read the most recent Neuroscience Research newsletter, you learned about epigenetics. The epigenome is also altered if the infant was exposed to SSRIs during the pregnancy (Gemmel et al., 2018). But this was, again, also the case when the person who carried the pregnancy experienced an untreated depression (Viuff et al., 2018). It will be important for future studies to compare what types of epigenetic changes are caused by SSRIs and depression, respectively, during pregnancy. It's possible that these epigenetic changes affect brain development potentially leading to an increased vulnerability for developing depression, anxiety, and other mental health challenges, but that these epigenetic effects only affect behavior under specific environmental circumstances, e.g. an abusive household.

Here is the thing: whether a child develops depression, anxiety or other mental health challenges later in life depends on a lot of factors, and two of the most influential are

1. How the primary caregiver interacts with the child throughout its childhood
2. The environment they grow up in (e.g. safe vs unsafe or wealthy vs impoverished).

Research supports that SSRIs ultimately help a caregiver become better capable of showing positive and loving behavior towards their child, and this is the most critical aspect of their child's mental health in the short and long-term (Moreau et al., 2022; Blier et al., 2006). While I want to emphasize that taking SSRIs during pregnancy outweighs the risk of being depressed during pregnancy, I do want to acknowledge that SSRIs do affect the infant brain and may change their genetic composition through epigenetic changes (Gemmel et al., 2018). However, the jury is still out on to what extend these changes determine the development and life quality of the child.

The current scientific knowledge tells us that there are more negative effects of being depressed during pregnancy than taking SSRIs during that period. Sadly, more often than not, depression aggravates during pregnancy, further emphasizing the importance of seeking mental health treatments as early on in the pregnancy as possible (Blier et al., 2006). Our mission as researchers in the mental health field is, of course, to find ways to ameliorate and improve mental health before a conception has even taken place.

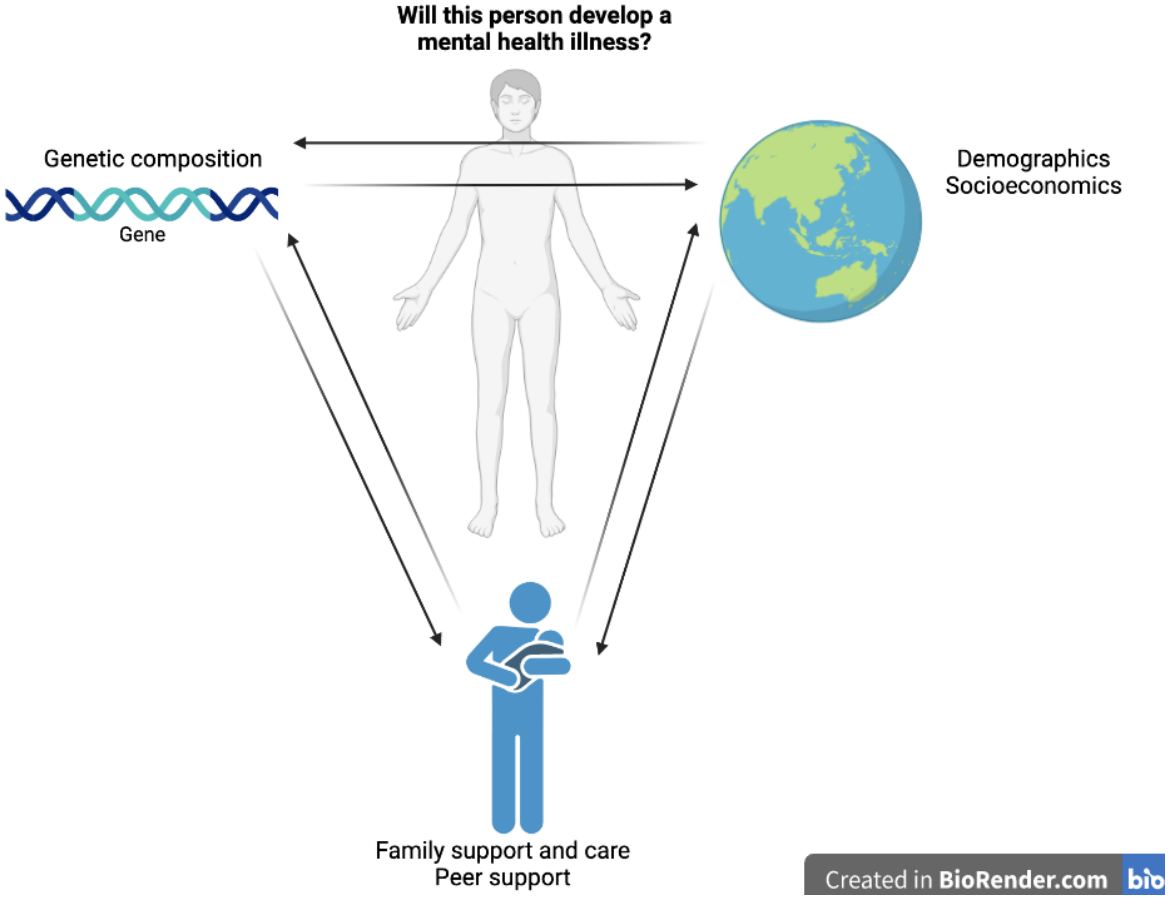


Figure 4: Whether a person develops a mental health illness depends on the interaction between their genetic composition, their family support, and the environment they grow up in. Even in the face of genetic changes caused by SSRI exposure during pregnancy, their upbringing and environment appear to be even greater determinants in determining their long-term mental health.

Final thoughts, what to consider, & everything else

The major take away is **that studies show few adverse health-effects from long-term usage of SSRIs**. The relevant question is rather, **are the SSRIs actually doing anything for you?** I think my SSRIs are doing something for me. Whether

that effect is a placebo or not, is not something I am willing to test out at this point. However, I am comforted by the fact that my continued usage **does not correlate with adverse health in the long run**. And should I one day choose to carry out a pregnancy, I would continue my SSRI treatment. Because I know that the benefits outweigh the potential costs.

Based on what I have written here, these are the things you can do if you start SSRIs:

1. Never use SSRIs as a stand-alone treatment. Make sure to pair it with talk therapy and/or community-engaging activities. See the most recent Mental health newsletter for more thoughts on this.
2. Make sure to evaluate your mental health regularly with a professional to ensure that the SSRIs are still working for you. There is a ton of SSRIs out there that all have distinct effects on your body. Finding the ones that work for you may take time and professional help.
3. Make sure to let your primary care doctor know that you started SSRI treatment and set up regular visits to have your cholesterol and triglyceride levels checked.
4. If you are older, make sure to have your bone density and balance checked regularly.
5. If you (plan to) become pregnant, consult your therapist, doctor, and psychiatrist about whether continuing the SSRI treatment confers more benefits than risk for you and your child.

Here are some of the things I have **not** mentioned in this newsletter due to lack of space and choice of focus:

1. Serotonin receptors are made up of five different subunits, that means, five different proteins, that come together and form the 'receptor complex' which can catch serotonin neurotransmitters. But these subunits are not the same and they each have different capabilities. Something I find very cool is that each serotonin receptor can be made up of a different constellation of subunits, which really influences how fast and for how long the receptor opens and closes. This can have huge implications for how likely serotonin neurotransmitters are at causing a neuron to activate, i.e. fire an action potential. Research in this area is very rich and it may be that people that are more vulnerable to developing mental health challenges have unique

differences in the constellation of their serotonin receptors. More about this in future letters, but for now, keep in mind that we really do not understand how SSRIs may impact people differently depending on their receptor constellation. Could it be that people who do not benefit from SSRIs have a distinct type of receptor subunit constellation?

2. In this newsletter I have focused on the direst effects of SSRIs on adults and on the indirect effects on fetuses/infants. However, I did not discuss what we know about SSRI treatment on adolescents. This is an important topic and should really be a stand-alone newsletter because it is full of complexities given the continued brain development and puberty that adolescents experiences. If you are interested in learning more about this specific topic, let me know and I will create a newsletter on SSRI treatment in adolescence!

3. I alluded to it several times but never addressed it directly: around 30% of people taking antidepressant for major depressive disorder in the US do not benefit from the treatment (Zhdanava et al., 2021). When traditional treatments such as psychotherapy and psychopharmacology do not work, we call it 'treatment-resistant depression'. We will address what researchers are doing to help this population of people in future newsletters.
4. Lastly, a challenging reality is that people that receive SSRIs and other antidepressants are more likely to relapse compared to patients receiving talk-therapy or simply a placebo pill (Kirsch, 2019). Why is that? And what do we do to help those people? Is there a way we could find out who is more likely to relapse? All of this is ongoing research that we will continue to address as it develops.

Next month's Mental health newsletter will take a different turn: we will talk about how self-awareness is a major predictor of mental health. We will discuss the research behind this seemingly obvious fact, as well as the applied research demonstrating evidence-based ways to increase self-awareness and ultimately mental health.

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