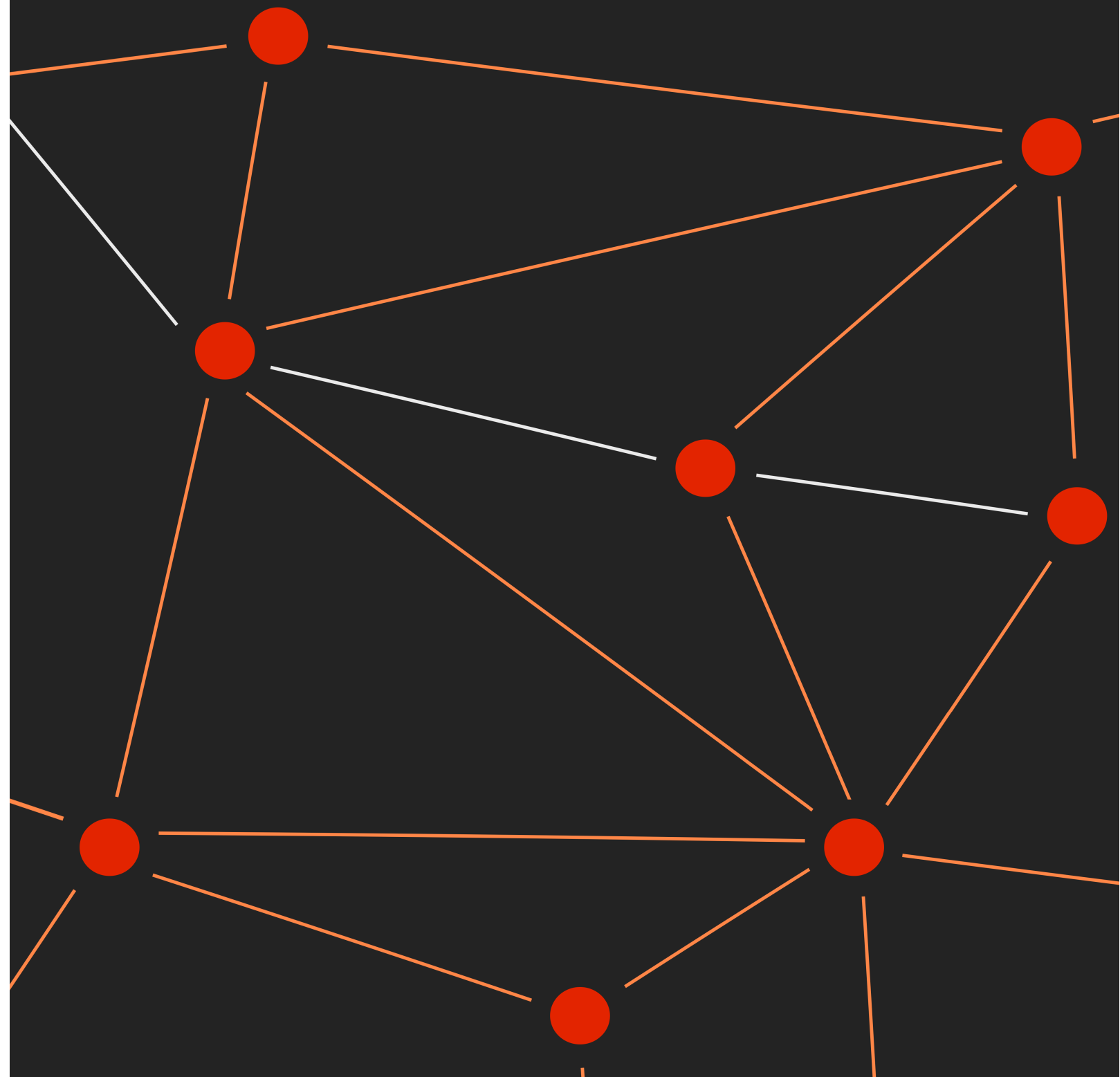


PSSD

WWW.PSSDLAB.COM

VOLUME I

2016



PSSD 2016

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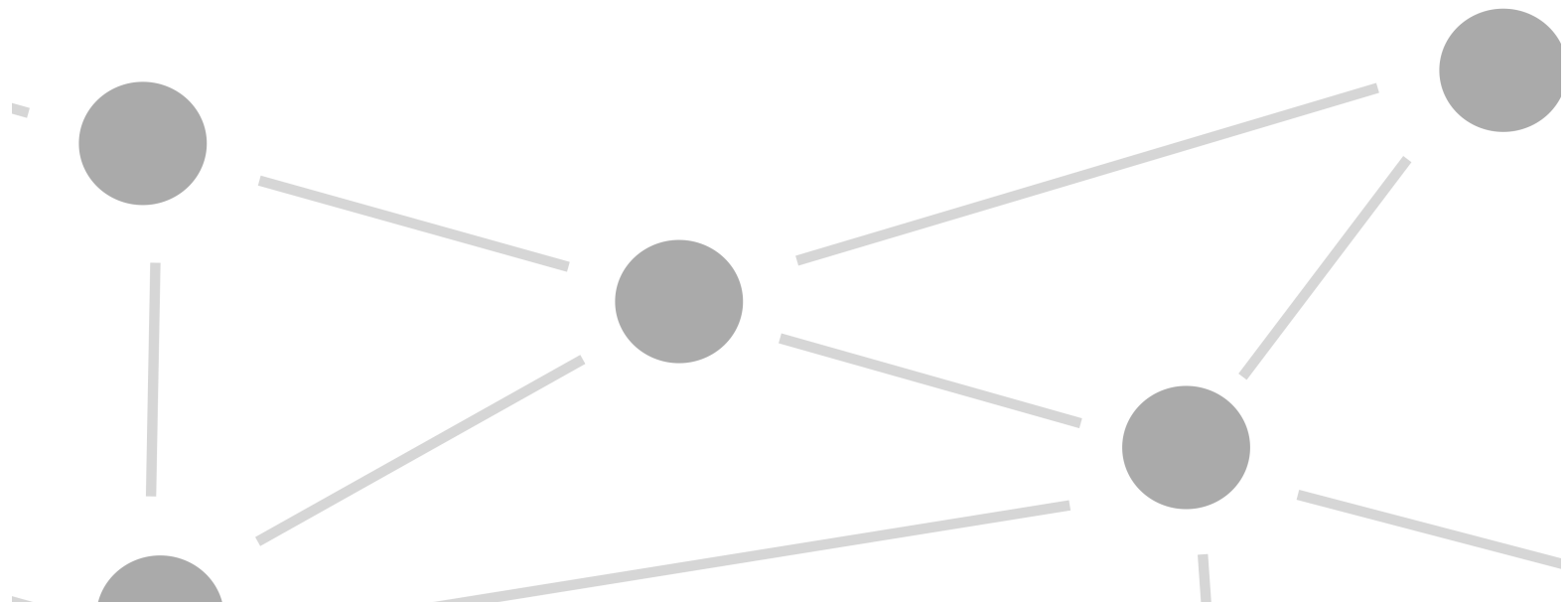
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The PSSD Journal is a yearly publication from the PSSD Lab. It summarizes the status of the PSSD community during the previous year, and serves as a platform for sharing PSSD literature with the scientific community at large.

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Inquiries on correspondence and article submission can be sent to ghostpssd@gmail.com



So You're New to PSSD? A Personal Testimony of Coping and Perseverance

P. R. Ghost ^{1,2}

¹Admin, www.pssdforum.com, ²Moderator, www.reddit.com/r/PSSD

Editorial

One of the things that became apparent to me early in my struggle with PSSD is that there are no promises of recovery. Worse, it often appears statistically likely that it won't go away: that it's permanent.

The uncertainty for the future might be the worst part of PSSD. Before PSSD, I had led a normal and active sex life, was successful in school, and was relatively happy. That doesn't mean that everything was ok, however, and I struggled with extreme anxiety over going to college in the coming months. I had always envisioned starting a family afterwards. It was just something that seemed part of my plan. PSSD changed the course of that plan overnight. I was no longer sure of how to talk to, date, or marry the right girl when I met her. The emotional toll of PSSD left me extremely unstable for over a year. This was during my freshman year of college, and seeing so many of my new friends succeed made me even more discouraged. Would I ever be normal again?

PSSD forced me to grow up. I think it forces most everyone who gets it in adolescence to. If there is some advantage that PSSD gave me, it's that it given me drive in life, and allowed me to fall in love with helping other people. PSSD forced me to think about other people: what they go through, what makes them happy, and what keeps them up at night.

PSSD has made me restless. Relentless. I search for purpose in every waking hour, and work harder than I ever did before. People in the early stages of PSSD often ask me if I've gone back to normal. My answer to them: NO! How could I? PSSD changed my view of the world so fundamentally that even if my sexually miraculously recovered tomorrow, I'd never be the same person who took Lexapro in the fall of 2014. Sexuality is no longer something that I view as functional or dysfunctional. Instead, it's an immensely intricate abyss that is fluid throughout one's life.

My first piece of advice to those on the first steps of their PSSD journey is to keep hope. Hope that PSSD will resolve, but even more hope that they can grow to be happy again. Millions of people are miserable even without PSSD (that's why antidepressants are even around in the first place), and I know plenty of people with PSSD who lead happy and fulfilling lives. If you make happiness contingent of the status of your PSSD, you might never find it again. That doesn't mean that it comes easy, or that the path is

always clear. It simply means that regardless of what happened yesterday, nothing done today can ever change the past. This is most important on the days when you feel that nothing is left.

My next piece of advice is to stop reading the sob stories. There are many of them. Marriages ruined. Lives destroyed. Careers ended. STOP. Stop. It is addicting when you first get PSSD. It was for me at least. Even earlier today I got caught up reading a few of them, but I am now careful to catch myself before they can send me spiraling into an abyss of worry and defeat. If I've learned anything from PSSD, it's that nothing in life is truly certain besides birth and death. Everything in-between is a mystery. Don't fill yourself with absolutes and stories written from unknown people from around the world. They are not you. They do not define you or your experience with PSSD.

Finally, don't let PSSD stop you from living your life. I say that for the days when it's easier, but especially for the days when it's hard. Run blindly into the unknown, and do not fear it. If you do fail, you will do so knowing that you've tried. If you are unsure if you should ask the cute girl at the party for her number: do it. Do it fearlessly. Do it unapologetically. You are you no matter what has happened from an SSRI. Try everything. Love everyone. Hope everyday.

The Mechanisms of Post-SSRI Sexual Dysfunction (PSSD)

P. R. Ghost^{1,2}

¹Admin, www.pssdforum.com, ²Moderator, www.reddit.com/r/PSSD

Abstract

SSRI antidepressants are among the most widely prescribed prescription medications in the United States. They are most commonly prescribed for Major Depressive Disorder (MDD), Panic Disorder, and Anxiety. SSRIs are widely deemed to be the safest and most effective chemical treatments for these prevalent disorders. While SSRIs have a much lower side effect profile than most traditional antidepressants, they still have many side effects that drive patients to end treatment prematurely. In a vast majority of cases, these side effects recede within days or weeks of the end of treatment. For a few very unlucky people, they persist for months or years after the last pill. This has been largely undocumented in medical literature. Recently there have been a few studies that back up what the people with these lasting side effects already know: Things that go wrong while on SSRIs don't always go away.

Introduction

In the Raphe Nuclei (RN), the 5HT_{1A} receptor acts as a presynaptic somatodendritic autoreceptor. At the ends of its projections in the hippocampus, frontal cortex, and hypothalamus, it functions as a presynaptic autoreceptor and a postsynaptic heteroreceptor (Sotelo et al., 1990; Burnet et al., 1995; Riad et al., 2000). When more Serotonin (5-HT) is found in the synapses in the RN, binding of autoreceptors inhibits the release of 5-HT in the projections of RN neurons (Koek et al., 1998; Gobbi et al., 2001). In this manner, 5-HT_{1A} autoreceptors work as an effective regulator of 5-HT levels in the brain (Bang et al., 2012). Decreased 5-HT transmission has long been associated with MDD (Van Praag et al. 1970) and it is thought that the RN is where SSRI antidepressants exhibit their therapeutic effects. It then comes as little surprise that the 5-HT_{1A} has been heavily implicated in effective clinical treatment of depression and anxiety. SSRIs are believed to block 5-HT reuptake by binding to SERT (5-HTT) and reducing its reuptake abilities (Murphy et al., 2004). If this was the only result, increased somatodendritic and terminal autoreceptor binding would inhibit release of 5-HT into the synapse: Resulting in no increased 5-HT levels. Through a process that is still unknown, serotonin transmission is eventually enhanced by "desensitization" of both the somatodendritic and terminal autoreceptors (Chaput et al., 1985), allowing synaptic 5-HT to accumulate in the synapse. This accounts for the characteristic 4-8 week delay between treatment origins and therapeutic relief (Gartside et al., 1995; Blier, 2010; Richardson-Jones et al., 2010). 5-HT and 5-HT_{1A} agonist binding on the presynaptic autoreceptor inhibits 5-HT activity by hyperpolarizing the neuronal membrane (Penington and Fox, 1994). Presynaptic 5-HT_{1A} receptors are preferentially desensitized by chronic SSRI treatment while postsynaptic receptors are not

(Pineyro and Blier, 1999). This preferential presynaptic desensitization is also seen after chronic administration of 5-HT_{1A} agonists (Blier and de Montigny, 1994). 5-HT_{1B/1D} autoreceptor agonists have shown less inhibitory action in cells treated chronically with low dose Fluvoxamine (Blier and de Montigny, 1983).

This model explains the widespread negative sexual and emotional changes that many people with PSSD report. Increased synaptic levels of Serotonin at RN projections would lead to more post-synaptic 5-HT receptor binding. Activation of post-synaptic 5-HT receptors inhibits the release of dopamine (DA) (Montgomery et al., 1991). Synaptic DA levels have been shown to have their activity and firing rate reduced after the administration of Escitalopram (a common SSRI antidepressant) for as little as two days (Dremencov et al., 2009). This suggests that there are several 5-HT receptors and autoreceptors that play a role in PSSD. With each SSRI likely affecting specific receptors differently. Dr. Dremencov observed that administration of a 5-HT_{2C} antagonist completely reversed this DA inhibition in the VTA (Fig. 1). It is well known that Dopamine plays a critical role in pleasure and reward: Especially in the sexual response. A decrease in DA activity and firing rate could explain many of the symptoms associated with PSSD. Further, DA D₂ binding has been shown to inhibit the secretion of Prolactin by the pituitary gland (Ben-Jonathan et al., 2001). Increased Prolactin levels are shown to negatively impact male sexual drive and ability, and play a role in the refractory period (Haake et al., 2003) (This can be seen as Hyperprolactinemia in some patients on D₂ antagonists for the treatment of Schizophrenia). Because of these downstream implications of desensitization of the 5-HT_{1A} Autoreceptor, it is very common to see sexual dysfunction in SSRI patients.

However, this dysfunction is relieved in nearly all cases after the cessation of medication. Why then, do we see thousands of antidotal reports of sexual dysfunction after treatment has ceased? Even in the absence of residual mental illness? Male mice who had mothers on SSRIs showed a permanent decrease in sexual drive (Gouvêa et al., 2008) Recently there have been new studies that are reiterating what people suffering from PSSD already know (Sheetrit et al., 2015) (Farnsworth et al., 2009) (Stinson, 2009) (Waldinger et al., 2015) (Leiblum et al., 2008) (Bolton et al., 2006) (Csoka et al., 2006), sexual side effects can remain after treatment.

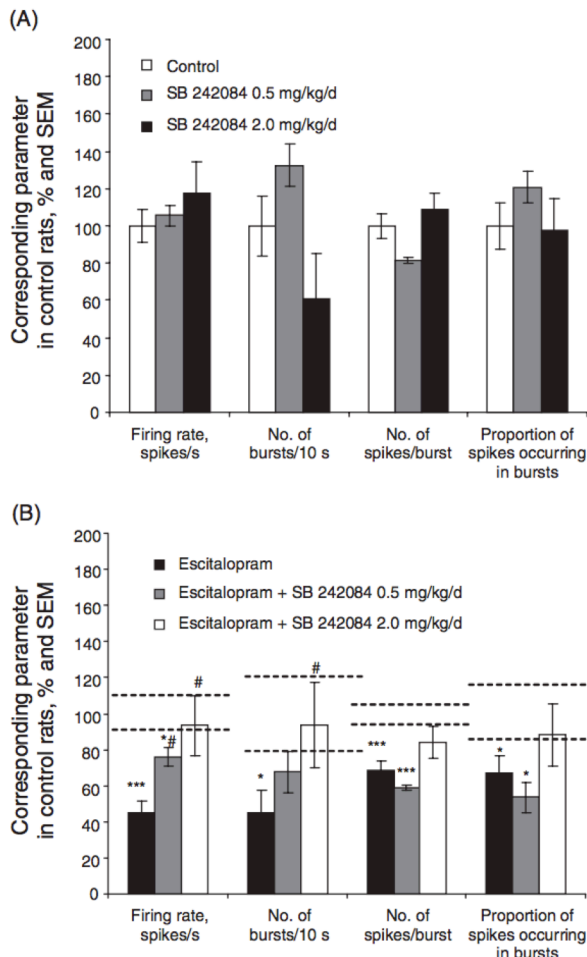


Fig. 1: 5-HT_{2C} antagonist SB-242084 completely reverses SSRI-induced DA inhibition in the rodent VTA (From Dremencov et al., 2009).

Discussion

Due to the stigma of sexual dysfunction, and doubt from physicians that persistent sexual dysfunction from SSRIs is possible, many PSSD sufferers remain silent (Stinson, 2013). Even more patients may have dysfunction that is mild or that they attribute to other factors such as aging. The emotional, social, and sexual implications of PSSD are widespread, and often lead to patients feeling alienated from their peers and loved ones (Stinson, 2013). There are several anecdotal

reports of spontaneous recovery but they are quite rare in the PSSD world. Many with PSSD therefore fear that their dysfunction is permanent. The terror of this realization adds to preexisting depressive, obsessive, or anxious behavior. Further research should focus on the methods of 5-HT autoreceptor downregulation in the DRN, and the downstream neural and hormonal effects of DRN disinhibition.

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