SEXUAL MEDICINE REVIEWS REVIEWS

Post-SSRI Sexual Dysfunction: Preclinical to Clinical. Is It Fact or Fiction?

Enis Rauf Coskuner, MD, FECSM,[1] Mehmet Gokhan Culha, MD,[2] Burak Ozkan, MD,[1] and Elcin Orhan Kaleagasi[3]

ABSTRACT

Introduction: Selective serotonin reuptake inhibitors (SSRIs) are a widely used class of drug for various psychiatric disorders during the lifespan, including pregnancy, lactation, childhood, and adolescence. Deterioration in sexual functioning is a major and serious adverse effect of SSRIs. There is emerging evidence that SSRIs can have long-lasting effects on sexuality.

Aim: To summarize the long-lasting effects of SSRIs on sexuality, starting with animal models and continuing with the clinical experience of different investigators.

Method: A literature review of relevant publications in PubMed.

Main Outcome Measures: To assess the long-lasting effects of SSRIs on sexuality.

Results: Although the persistent effects of SSRIs on sexuality have been little studied in humans, animal studies suggest that SSRIs might cause permanent sexual dysfunction after ending SSRI exposure at a young age but not in adulthood in rats. There are no prospective randomized controlled trials in humans and the present evidence is derived from case reports, incidental research findings, and experiences of some internet communities.

Conclusion: There is some preclinical evidence from animal studies for enduring SSRI-induced sexual dysfunction, but the available clinical information could prevent a clear decision about the existence of post-SSRI sexual dysfunction, its pathophysiology, and its management. We need more research to fill in the gaps in our knowledge. **Coskuner ER, Culha MG, Ozkan B, Kaleagasi EO. Post-SSRI Sexual Dysfunction: Preclinical to Clinical. Is It Fact or Fiction? Sex Med Rev 2017;X:XXX–XXX.**

Key Words: Post-SSRI Syndrome; Serotonin; Sexual Dysfunction; Selective Serotonin Reuptake Inhibitors

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) have become one of the most commonly prescribed classes of drugs to treat depression, anxiety, and obsessive-compulsive disorder.[1] They also are prescribed off-label for the management of conditions such as perimenopausal and postmenopausal hot flashes, chronic fatigue syndrome, chronic pain syndromes, premature ejaculation, and paraphilias.[2]

SSRIs can be recommended for the treatment of depression during pregnancy and lactation, which is a significant health problem that affects up to 20% of women.[3] However, these medications cross the placenta, enter the fetal circulation, and are present in breast milk.[4] SSRIs are prescribed and subsequently administered to children no older than 6 years.[5] The reasons for the use of SSRIs in children are the increased rate of depression in this age group and pediatricians' awareness of depression. In consequence, there is a significant and increasing likelihood that children and adolescents will be exposed to SSRIs prenatally through the placenta and then directly during the course of treatment for childhood and adolescent psychiatric disorders.[5]

The serotonergic system is one of the first neurotransmitter systems to appear in the developing central nervous system (CNS), and serotonin has been proposed to play a trophic role.[6] Serotonergic neurotransmission has a crucial function in sexual behavior.[7] SSRIs are well known for inducing sexual side effects, thereby affecting the quality of life of patients.[8] The incidence of treatment-emergent sexual dysfunction can be 50% to 70%, mainly when the mechanism of action is related to the high profile of the serotonin reuptake blockade.[9] In male and female mammals, SSRIs can affect all phases of sexual activity, including deteriorating and decreasing desire, arousal, and orgasm.[9–11]

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[1]Department of Urology, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkey;

[2]Department of Urology, Health Sciences University, Okmeydani Training and Research Hospital, Istanbul, Turkey;

[3]Department of Psychology, Acibadem Bakirkoy Hospital, Istanbul, Turkey

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The prevalence of SSRI-induced sexual side effects is underestimated in the product literature, whereas the research available poorly captures the possibility of treatment-related sexual side effects that can persist in some patients after stopping these medications.[12] Searching databases yielded published investigations in animal and clinical research studies showing directly that the problem of sexual side effects persists after the discontinuation of SSRIs.

AIM

The aim of this review was to summarize the long-lasting effects of SSRIs on sexuality, starting with animal models and continuing with the clinical experience of different investigators.

METHODS

The literature on sexuality after SSRI exposure was reviewed through a PubMed search for articles published from January 1980 through August 2017 using the following combination of keywords: *post-SSRI sexual dysfunction* and *SSRIs*. All articles were screened based on titles and abstracts. The final selection was made after reading the full texts of these articles. Reference lists from selected articles were searched manually for additional relevant references.

Persistent Sexual Dysfunction After Early Exposure to SSRIs in Preclinical Research

All pharmacologic treatments for human diseases carry the risk of different adverse effects that might become evident only after long-term follow-up. These long-term effects are particularly important when medications that affect the CNS are administered to pregnant women, children, and adolescents. Because of substantial and protracted developmental changes in the molecular and structural features of the human brain, early exposure to some medical treatments can result in persistent abnormalities in adult behavior. However, detecting such long-term effects can be problematic in human studies. One strategy for addressing this challenge is to conduct experimental drug administration studies in animals.[13]

Although few studies have examined persistent SSRI-induced effects on sexuality in humans, animal studies suggest that SSRIs might cause subsequent and permanent sexual dysfunction if SSRI exposure is terminated at a young age.[14] Unfortunately, the methodologic qualities of these studies are generally poor, but they can make significant contributions to health care.

Brain growth in rodents begins prenatally and continues to postnatal day 28, whereas brain growth in humans begins prenatally and continues beyond 18 to 36 months postnatally.[15] Synaptogenesis and glial proliferation begin during the late prenatal period and continue through postnatal day 40 in rats and through 4 to 6 years of age in humans.[16] In rats and humans, neurotransmitter receptor development continues into adolescence, but the competency of the blood-brain barrier is not mature until well after birth.[17] Thus, the developing CNS during the prenatal and postnatal periods in rats provides an informative resource that is similar to the human brain for examining the teratogenic effects of exogenous drug exposure.[18]

In neonatal rodents, regular administration of SSRIs during the early period of life results in a pattern of maladaptive behaviors that persist into adulthood.[19] These behavioral changes in rats include modified locomotor activity, decreased male sexual activity and competence, a dysregulated hypothalamic-pituitary-adrenal axis, increased rapid eye movement sleep time and decreased latency to enter the rapid eye movement sleep phase, increased ethanol consumption, and increased immobility in the forced swim test.[13,20,21]

Recent preclinical research has shown that developmental exposure to SSRIs can have a long-term impact on sexual behavior in male offspring. Regular neonatal exposure to a potent and highly selective SSRI results in profound decreases in the serotonin synthetic enzyme (tryptophan hydroxylase) in the dorsal raphe and in serotonin transporter expression in the cortex that persist into adulthood.[22]

The normal masculinization process in the brain requires a transient decrease in serotonin levels during the 2nd postnatal week.[23] Throughout this period, the regulation of androgen receptor and gonadotropin-releasing hormone expression is important for the control of male reproductive and sexual activity. The early-life inhibition of serotonin transporters alters this regulatory process of androgen receptor expression in the medial preoptic area of male offspring, likely causing decreased sexual behavior.[24]

In addition, developmental exposure to SSRIs can have a long-term impact on hippocampal plasticity in adult offspring because the hippocampus plays a major role in cognition and emotion. Thus, it is likely that these alterations are related to significant behavioral changes.[25]

The constellation of behavioral disturbances after neonatal SSRI exposure in rats has been proposed as a model of endogenous depression in adult rats.[26] The pattern of abnormalities found in adult rats resembles elements comprising the syndrome of human endogenous depression, including changes such as a decrease in sexual, aggressive, and pleasure-seeking activities; an increase in motor activity and rapid eye movement sleep disturbances; and a reversal of these behavioral changes by adult antidepressant treatment.[27]

Autism spectrum disorders (ASDs) are severe neurodevelopmental disorders with early childhood onset and characterized by qualitative alterations in social reciprocity, communication, and breadth of interests manifested by repetitive behaviors or restricted interests. The effects of early-life SSRI exposure on serotonergic neurons parallel the characteristics of ASDs in adult rats.[28] Exposed rats show below-normal social interaction that can be expressed as disrupted male sexual