

Original Research

Post-Selective Serotonin Reuptake Inhibitor Sexual Dysfunctions (PSSD): Clinical Experience with a Multimodal Approach

Yacov Reisman^{1,*}, Tommaso B. Jannini², Emmanuele A. Jannini³¹Department of Sexual Medicine, Flare-Health, 1183DJ Amstelveen, The Netherlands²School of Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, 00133 Rome, Italy³Chair of Endocrinology and Medical Sexology (ENDOSEX), Department of Systems Medicine, University of Rome Tor Vergata, 00133 Rome, Italy*Correspondence: reisman@flare-health.nl (Yacov Reisman)

Submitted: 28 December 2021 Revised: 24 February 2022 Accepted: 18 March 2022 Published: 1 August 2022

Abstract

Background: Post-SSRI sexual dysfunction (PSSD) is a set of heterogeneous sexual disorders, that may arise during the administration of antidepressant Selective Serotonin Reuptake Inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitor (SNRIs) and may persist after their discontinuation. PSSD is commonly associated with sexual problems with marked distress and poor quality of life. To date, however, no effective treatment is available. The study describes the clinical experience with a newly introduced systems sexology approach involving bio-psycho-social interventions. **Methods:** In this study we retrospectively analyzed (from July 2019 to July 2020) twelve PSSD male patients (mean age 31.3 ± 6.21 years old) treated according to a recently introduced approach involving system sexology and bio-psycho-social interventions. The protocol was based on a combination of lifestyle changes, nutritional supplementation, pharmacological and behavioral interventions. **Results:** 12 patients with high probability of PSSD were selected. Patients reported a significant improvement in all International Index of Erectile Function-15 (IIEF) domains and Orgasmometer scores from the baseline at 6 months of follow-up. **Conclusions:** This study described for the first time a feasible and handy treatment procedure for PSSD, framework to improve patients complains, sexual function and satisfaction, and quality of life. Future randomized, placebo-controlled clinical studies with bigger cohorts will be needed in order to better assess this efficacy and confirm our results.

Keywords: PSSD; multimodal approach; SSRI

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are one of the most used psychiatric drugs, either due to an on-label or to an off-label application [1]. However, sexual dysfunction, with a prevalence up to 80%, is a well-known side effect of SSRIs, causing many patients to drop out their therapies [2,3].

Post-SSRI sexual dysfunction (PSSD) is a set of symptoms that most frequently features genital anesthesia, anorgasmia, delayed orgasms, ejaculatory dysfunctions, and decreased libido, that may arise when SSRIs are used chronically and specifically endure when they have been discontinued [4–8]. The most frequent triad of sexual symptoms is genital anesthesia, lack of libido, and, as patients define it, a “disconnection” between the brain and the genitals [9,10].

Although the sexual dysfunction is a common side effect of SSRIs, its pathophysiology remains largely unknown. Most early evidence points out how 5-hydroxytryptamine (serotonin, 5-HT) might be implicated in regulating dopamine release in mesolimbic and hypothalamic areas, whose activation occurs during each phase of a sexual intercourse [11,12]. According to a recently introduced hypothesis, an enduring serotonin stimulation may lead to a chronic “serotonin mediated tonic inhibition” [13]. This theory is grounded in early evidence that shows how a chronic rather than an acute administration of SSRIs gives

rise to an increased and long-lasting firing rate of serotonergic neurons across all projection areas [14]. This may result in non-sexual incentives, as 5-HT neurons exert an indirect inhibitory tone on dopamine-releasing cells in the mesolimbic system, a pivotal player of sexual behavior [15].

In addition, serotonergic neurotoxicity may also further explain the pathophysiology of PSSD. Similar to 3,4-methylenedioxymethamphetamine, a persistent serotonin stimulation may cause, among predisposed patients, axonal damage in peripheral nerves, which may for instance lead to a neurogenic erectile dysfunction (ED) [4].

Some authors have also suggested how epigenetic changes may arise after a chronic serotonergic stimulation. Recent evidence shows, in fact, how a long-lasting administration of SSRIs may cause persistent downregulation of 5-hydroxytryptamine receptor 1A (5-HT1A). Since 5-HT1A is widely regarded as an auto-receptor that reduces the firing rate of the serotonergic neurons, its downregulation may persistently increase the serotonergic tone, which may concur to the overall “tonic inhibition” and eventually cause sexual impairments [16].

PSSD is challenging to diagnose as there are currently no consistent methods of investigation. In addition, PSSD presents with various degrees of severity and symptom persistence. It can indeed begin after a few doses of treatment



or only become apparent after years of exposure and it can persist for decades afterwards. PSSD may moreover occur in all ages and in both sexes, regardless of any ethnic groups [17].

A new consensus on enduring sexual dysfunction following treatment with antidepressants, finasteride and isotretinoin has finally set the diagnostic criteria of such disorder. PSSD, besides featuring genital anesthesia, ejaculatory and orgasm dysfunction, and decreased libido, is a condition that must be present for at least 3 months, with no current medical condition accounting for the symptoms [18]. Since PSSD has only recently been codified as a stand-alone condition, there are no well-designed clinical trials and, therefore, a clear consensus on treatment modalities has not been reached so far. For these reasons, the scope of the present article is to describe our clinical experience with patients treated according to a new multimodal approach involving the systems sexology and bio-psychosocial interventions [19]. Indeed, this project aims at developing a framework to improve patients complaints, sexual function and satisfaction, and quality of life.

2. Methods

2.1 Subjects

In the period of July 2019 and July 2020, 17 male patients from 7 European countries were referred to our clinics due to a suspicion of PSSD. Because of the COVID-19 pandemic impediment that limited travelling, for 8 of them the contact was established through digital measures.

Informed consent was given for their data to be routinely and anonymously recorded for retrospective assessment. Patients were interviewed according to a standard procedure which included questions about their demographic information (sex, age, relationship status, country of origin, occupation and daily activities), experiences of sexual dysfunction when taking any medication, specifics of all drugs used during sexual dysfunction (names, doses, durations of use, and time of use), current sexual function, questions about genital anesthesia and erectile function, reaction to sexual stimuli, current and past medical problems including potential psychiatric disorders, medication usage (names and doses of all drugs taken, including over-the-counter ones, substance use, use of alcohol and current and past smoking). To exclude co-existent depression as a confounding effect on sexual dysfunction the 21-item Beck Depression Inventory-II (BDI-II) was used [20]. Effect of the complaints on their relationship and quality of life and coping with the problems.

All patients that met the following inclusion criteria were included: age between 18 and 60 years old, no pre-SSRI treatment sexual dysfunction, treatment-emergent sexual dysfunction while taking one antidepressant of the SSRI or and serotonin and norepinephrine reuptake inhibitor (SNRI) class, the antidepressant was discontinued at least 1 month before interview, sexual dysfunction per-

sisted despite drug discontinuation, medical conditions and current medication use not associated with known sexual dysfunction, no report of addictive substances use. Only patients with high probability of PSSD according to previous published criteria have been selected [4,18].

All patients were requested to perform laboratory tests, including hemoglobin, white blood cell count, C-reactive protein, creatinine, sodium, potassium, albumin, aspartate transaminase and alanine transaminase, luteinizing hormone, follicle-stimulating hormone, total testosterone, prolactin, Sex Hormone Binding Globulin (SHBG) and Thyroid Stimulating Hormone (TSH). Free testosterone and bioavailable testosterone were also calculated according to the Vermeulen formula [21].

2.2 Outcome Measures

Patients were asked to fill in the International Index of Erectile Function-15 (IIEF-15) [22] for sexual dysfunction as well as the male Orgasmometer, a well validated psychometric tool to measure on a 0–10 visual analogue scale the intensity of the orgasm [23], at baseline and after a follow-up period of 6 months. The IIEF is composed of five subdomains: erectile function (items 1, 2, 3, 4, 5, and 15), orgasmic function (items 9, and 10), sexual desire (items 11, and 12), intercourse satisfaction (items 6, 7, and 8), and overall satisfaction (items 13, and 14). Since items 13 and 14 measure general satisfaction, a low score on them may be also intended as an indicator of sexual distress. Severity of ED was classified as severe for IIEF scores ≤ 10 , moderate for scores between 11 and 16, or mild, for scores between 17 and 25, with EF > 25 indicating no ED. All questionnaires were given in English language.

2.3 Experimental Design

The protocol of administration included bio-psychosocial interventions in the perspective of systems sexology for a period of 6 months [19].

These included: recommendations for lifestyle (i.e., all participants agreed not to use any drug of abuse or more than 2 alcohol units per day); recommendations for physical activity (i.e., supervised training consisting of 40 minutes of aerobic exercise of moderate to vigorous intensity 4–5 times a week) [24,25]; discontinuation of any form of nicotine or at least shift to non-burning cigarettes [26]; correction of possible hormonal abnormalities when needed, based on patient's laboratory findings. The patients were also instructed not to assume any serotonin or tryptophan-derivate supplements.

On the other hand, as patients often avoid the use of SSRI or other medications, we recommended the use of supplements with evidence of neurotransmitter improvement. Patients were administered with L-Arginine (3 g/d) and L-Carnitine (2 g/d) supplementation [27–32].

Sexual dysfunctions were treated with a pharmacological therapy on a shared decision-making ground. For

ED, type 5 phosphodiesterase inhibitors (PDE5i) were prescribed according to patient needs [33]. Buspirone was also off-label prescribed for hypoactive sexual desire disorder (HDD) and delayed ejaculation or anorgasmia. The dosage is the same as the one used for anxiety (15 mg to 60 mg daily) [34].

The following psychological interventions were included in the protocol. Ten patients (83.3%) were referred to mindfulness training to reduce anxiety, and tension and cognitive-behavioral therapy when sexual inadequacy and low self-esteem were apparent. Two of the twelve patients (16.3%) were referred to sex therapy & sensate focus (solo or partnered). Sex therapy and sensate focus aims to educate the partners that the sexual dysfunction is a side effect of the medication and gain pleasurable experiences [35,36].

All patients have been consulted once per 2 weeks for further instruction, counseling on specific topic and dose adaptation when needed.

2.4 Statistical Analysis

Quantitative variables were described using means and standard deviations (SD) or median and range. Normal distribution of quantitative variables was explored by means of the Kolmogorov–Smirnov test. Student's *t* test for paired samples was used to compare variables' means. Due to the non-normal distribution of the study variables and to the small number of the population, a bootstrapping analysis was performed, and results were given as 95% confidence intervals (95% CI). The bootstrap method is a resampling technique used to estimate statistics on a population by sampling a dataset with replacement. A crucial point is that bootstrap works without needing assumptions like normality [37]. Categorical variables (symptoms, complaints, and comorbidities) were summarized with numbers and percentages. Data were analyzed using SPSS software for MacOs (version 25; IBM Corporation, New York, NY, USA).

3. Results

In a period of 12 months, of the 17 patients reporting SSRI-related sexual dysfunction, only 12 male patients have been selected with high probability of PSSD. The mean age was 31.3 ± 6.21 years, with an average body mass index (BMI) of 25.3 ± 2.18 (Table 1). All patient laboratory results did not report any alteration in blood analytes. None of them had a clinical history of systemic diseases. One patient reported a recurrent urine tract infection, one reported a chronic prostatitis and another reported chronic pelvic pain. None of the patients was diagnosed with drug or alcohol abuse disorder. In Table 2 the SSRI/SNRI use and ceasing period of the patients are given.

The PSSD symptoms in order of frequency of appearance are given in Table 3. Most of the complaints started during the use of SSRI and continued after their cessation. Pleasureless orgasm, genital numbness, memory impairment and fatigue were reported to appear after withdrawal

Table 1. Sociodemographic and clinical variables.

Variables (normal range)	Patients
Age	31.3 (± 6.21)*
BMI	25.3 (± 2.18)*
Sex	12 M (100%)**
Marital status:	
Unmarried	8 (66.6%)
In a stable relationship	4 (33.4%)
Total testosterone (12–35 nmol/L)	16.2 (± 4.91)*
Free testosterone (0.173–0.777 nmol/L)	0.339 (± 0.169)*
Luteinizing hormone (1.5–8 U/L)	3.33 (± 1.09)*
Follicle-stimulating hormone (<7 U/L)	3.03 (± 1.40)*
Sex hormone binding globulin (14.6–68.9 nmol/L)	42.8 (± 11.9)*
Thyroid-stimulating hormone (0.5–3.9 mU/L)	1.98 (± 1.15)*
Prolactin (100–300 mU/L)	156 (± 46.4)*

*, mean (\pm standard deviation); **, frequency (percentage).

from SSRI in 3 (25%), 3 (25%), 2 (16.66%), and 2 patients respectively.

Routine laboratory investigations did not show any liver function or kidney function abnormality. There was no evidence for infections according to white cell blood count or c-reactive protein. Average and standard deviation (range) for the laboratory tests are described in Table 1. None of these blood values requested any pharmacological intervention.

All IIEF domains, although on average ED was classified as mild both at baseline (EF = 19.11) and at follow-up (EF = 23.69) time points, as well as Orgasmometer scores reported a significant improvement from the baseline to post-treatment. Our results indicate a decrease in the perceived overall sexual distress, as items 13 and 14 are also a surrogate marker of general sexual dissatisfaction, as well as an improvement in the orgasmic function at the Orgasmometer (Table 4).

All patients were adherent to healthy lifestyle program offered. No drop-out event was registered within the 6 months of the study protocol. They all used the supplements proposed. It should be mentioned that during the first 2 to 3 months of treatment, patients needed to be motivated to continue the treatment as limited improvement were noticed. Four patients (33.3%) were using PDE5i (tadalafil 5 mg once a day, vardenafil 20 mg or sildenafil 50 mg orodispersible pills, sildenafil 75 mg orodispersible film for 3 to 5 months). Five patients (41.6%) with orgasmic complains were using Buspirone at 5 mg dose 3 times a day for six months.

4. Discussion

This real-life retrospective study describes a small series of patients diagnosed with PSSD according to the recently published selection criteria and treated with a new multimodal approach, consisting of system sexuality and bio-psycho-social interventions (Fig. 1) [18].

Table 2. SSRI/SNRI use and ceasing period of the patients.

Patient No.	SSRI/SNRI used	Daily dose (mg)	Duration (months)	Duration since discontinuation (months)
1	Fluoxetine	40	14	9
2	Sertraline	100	12	16
3	Escitalopram	20	9	26
4	Fluoxetine	20	6	16
5	Escitalopram	20	12	12
6	Venlafaxine	75	16	8
7	Escitalopram	10	4	6
8	Amitriptyline	50	3	14
9	Escitalopram	10	4	21
10	Paroxetine	20	36	3
11	Paroxetine	20	36	4
12	Escitalopram	20	12	6
Mean (\pm SD)		33.5 (\pm 28.1)	13.66 (\pm 11.3)	11.8 (\pm 7.10)
Median		20.0	12.0	10.5
Range		90 (10–100)	33 (3–36)	23 (3–26)

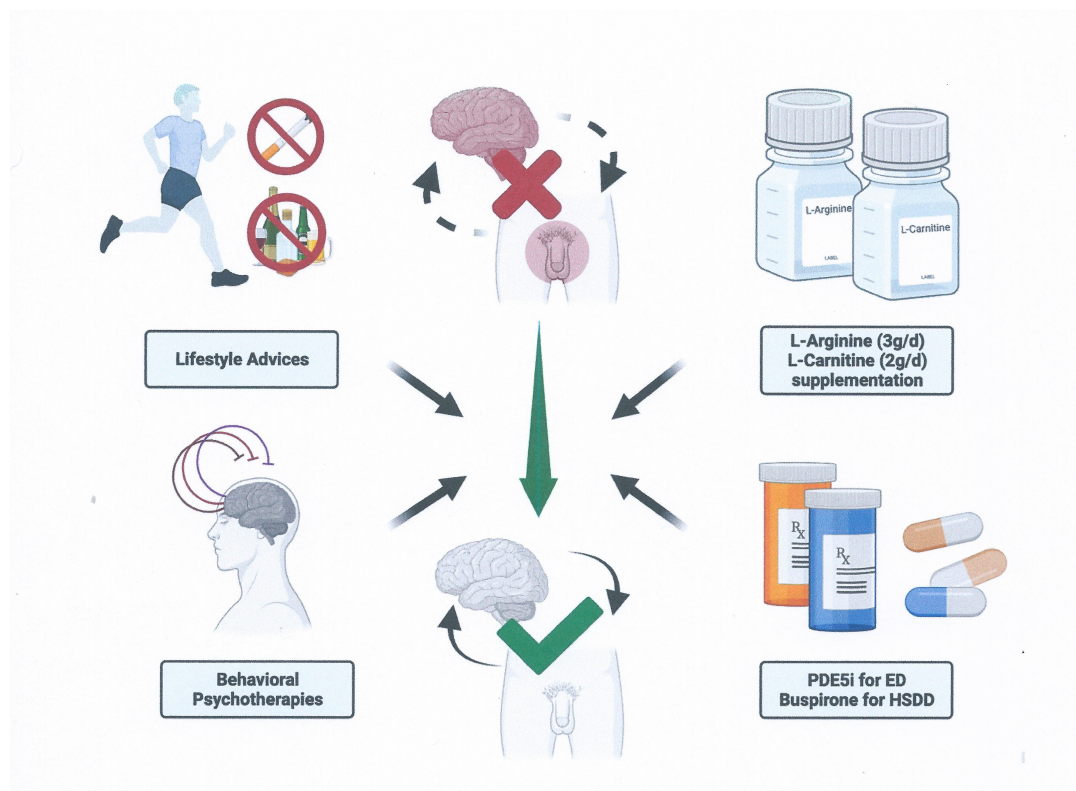


Fig. 1. PSSD is frequently described by the patients as a “disconnection” between the brain and the genitals, featuring lack of libido, anorgasmia, ejaculatory-orgasm delay and genital anesthesia. The present multimodal approach consists of systems sexology and bio-psycho-social interventions aiming at restoring such brain-genital connection and achieving a better sexual health.

Consistent with evidence from the literature, we did not find any peripheral hormonal abnormalities which requested treatment [17,38]. The sexual clinical history of the couples involved in our study did not show primary female sexual dysfunction (FSD). However, the possibility of a reactive FSD due to the male PSSD is currently a matter of further examination [39].

Our multimodal treatment, based on life style interventions, L-carnitine/L-arginine integrators, PDE5i and bupirone administration, and behavioral psychotherapies significantly improved every IIEF domain as well as Orgasmometer scores in a cohort of 12 PSSD patients.

In this regard, recent evidence is showing how physical exercise positively impacts on erectile function as well as on a self-concept [24,25]. In addition, a review arti-

Table 3. Frequency of symptoms appearance according to patient's complaints.

Symptom	Percentage and (number)
Loss of libido	91 (11)
Reduced sexual activities	75 (9)
Pleasureless orgasm	75 (9)
Loss of morning erections	75 (9)
Genital numbness	67 (8)
Erectile dysfunction	50 (6)
Disconnection between genitals and brain	50 (6)
Emotional blunting	41 (5)
Reduced orgasmic intensity	41 (5)
Difficulty to achieve orgasm	33 (4)
Memory impairment	17 (2)
Fatigue	17 (2)
Reduced power of ejaculation	8 (1)

cle indicates an improvement in the concentration of serum testosterone by physical activity, which is key for each phase of a sexual intercourse [40]. Similarly, by means of the vaginal photoplethysmography, genital arousal was found to be increased without any effect on self-reported arousal perceptions among women who do daily exercises [41].

L-arginine administration could have played a pivotal role in patients with PSSD. Nitric oxide (NO) is indeed the main factor involved in endothelial-dependent relaxation of human corpora cavernosa and oral L-arginine is an efficient donor of NO. It is therefore possible that boosting the nitrergic pathways may have rebalanced the iatrogenic dysfunctional serotonergic tonic inhibition. In this regard, a consistent body of literature stresses how L-arginine have shown a certain efficacy in the treatment of ED, especially in combination with PDE5i [42].

On the other hand, L-carnitine is a necessary nutrient for the generation of energy in vital organs, including the liver, kidneys and brain. L-carnitine supplementation (2 g/day) may indeed potentially reduce chronic fatigue [43]. In addition, findings indicate that the favorable cardiovascular effects of L-Carnitine may also reflect on male sexual function [31,32]. Most of early evidence also highlights how carnitines might contribute to treat ED, being synergistic with PDE5i. Such molecules may be in fact responsible for reducing free radical production, by depleting fatty acid peroxidation. Moreover, they also act on mitochondrial membranes, restoring their phospholipid composition. Consistently, carnitine acts also on cellular energetics, increasing the cytoplasmatic availability of acetyl-coenzyme A, eventually resulting in an improvement of the antioxidant activity [44]. Although evidence on this topic is not large, the role of nutraceuticals and dietary supplements in treating sexual dysfunction, both in women and in men, seems indeed promising [45–47]. To this end, a recent case report shows how the administration of supplements con-

taining L-citrulline was effective in treating PSSD in a 23-year-old man [48].

Buspirone is a 5HT1A partial antagonist and it has been developed as an anxiolytic compound to treat generalized anxiety disorder. However, a consistent body of literature provides evidence for its use to treat sexual dysfunctions, such as hypoactive sexual desire disorder [49,50]. Indeed, an established protocol requires patients to take buspirone once a day [34]. The dosage is the same as the one used for anxiety (15 mg to 60 mg daily). The mechanism for buspirone treat sexual dysfunctions might be the stimulation of somatodendritic and presynaptic 5HT1A receptors which in turn may counteract the serotonergic inhibition tone, leading to an improvement of sexual function [34].

Patients were referred to mindfulness training to reduce anxiety and tension and therefore to obtain a better sexual life [35]. A mindful model of sexual health has been extensively regarded as a foundation to investigate on one's own mind-body connection, in order to promote physical, mental and sexual well-being [51]. In this regard, our aim was to navigate patients' feelings of disconnection between brain and genitals, increasing awareness to explore their own mind and body and therefore restoring such lost connection (see Fig. 1).

The scope of the cognitive-behavioral therapy (CBT) was instead to help patients to treat negative thoughts and cognitions, such as sexual inadequacy and low self-esteem [34]. Partners were meant to be involved in this approach as well, since they were collaterally affected by PSSD. CBT has also been used to help patients reach a better understanding of their condition and cope with their situation [52].

Sex therapy and sensate focus (solo or partnered) aimed to educate partners that sexual dysfunctions are a side effect of the medication and not a lack of interest. In addition, sex therapy provides emotional and psychological support for patients and partners and teaches them to focus on pleasurable sexual experience and not on performance.

As PSSD is frequently described as a “disconnection” between the brain and the genitals, our multimodal approach consisting of systems sexology and bio-psychosocial interventions aimed at restoring such brain-genital connection and achieving a better sexual health. The combination of lifestyle advice, essential nutrient supplementations, PDE5i and buspirone administration, and behavioral interventions may, in fact, act synergically to improve every domain of sexual life (Fig. 1).

The present study adds important insights to the clinical presentation and management of patients with PSSD. In addition, it provides a handy and feasible treatment procedure for such a condition. Nonetheless, this work suffers from a number of important limitations. Firstly, as this work was conducted in a retrospective fashion and based on self-administered outcome measures, and patients may not be able to report symptoms or details accurately, a recall

Table 4. Bootstrap* for Paired Samples *t*-test. IIEF-domains and Orgasmometer score at baseline and after 6 months follow-up.

IIEF domains	Mean at baseline (\pm SD)	Mean at 6 months follow-up (\pm SD)	Mean difference	Standard error	95% Confidence interval (lower)	95% Confidence interval (upper)
Sexual desire	3.78 (\pm 1.39)	5.53 (\pm 1.32)	-1.75	0.358	-2.583	-1.083
Erectile function	19.11 (\pm 4.76)	23.69 (\pm 3.12)	-4.58	1.487	-7.509	-1.500
Orgasmic function	4.67 (\pm 1.73)	5.83 (\pm 1.42)	-1.16	0.453	-2.167	-0.500
Intercourse satisfaction	5.22 (\pm 1.64)	7.88 (\pm 2.92)	-2.66	0.525	-3.583	-1.833
Overall satisfaction	3.56 (\pm 1.01)	6.22 (\pm 0.66)	-2.66	0.174	-2.833	-2.417
Orgasmometer	3.22 (\pm 1.42)	4.39 (\pm 1.19)	-1.17	0.41	-1.813	-0.087

*, bootstrap results are based on 3000 bootstrap samples.

bias may surely impact on the study results. Secondly, the study population is small and not randomized.

Lastly, the present study does not have a controlled population of healthy patients. This raises the question whether symptoms remitted spontaneously or as a result of our multimodal approach. Hence, we cannot exclude for our findings to be due to a placebo effect. Indeed, caution must be taken when generalizing these results, as this limitation does not leave enough room for causal inferences. For these reasons, further randomized clinical trials with standardized protocols and larger populations will be desirable in order to draw more consistent conclusions.

However, that our treatment must have been effective is suggested by the adherence of the patients. Psychotherapies for sexual dysfunction given without nutritional supplements or medication have been associated with high dropout rates and reports of undue patient burden, at least in women [53].

5. Conclusions

The study described for the first time a multimodal, systems bio-psychological approach for the treatment of PSSD. The protocol of intervention based on a combination of lifestyle changes and nutritional supplementations and pharmacological and psychological interventions reported significant improvement of patients complains. Further research will be needed to better define this treacherous condition and develop a standardized treatment.

Availability of Data

The datasets generated during and/or analysed during the current study are not publicly available due to privacy reasons but are available from the corresponding author on reasonable request.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by YR, EAJ and TBJ. The first draft of the manuscript was written by YR. YR, EAJ and TBJ commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study is complying with the specific requirements of the institution for ethics of retrospective studies and performed in accordance with the Declaration of Helsinki. There is no relevant approval number as it is an institutional policy. Informed consent was given by the participants for their data to be routinely and anonymously recorded for retrospective assessment.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. EAJ has been speaker and/or paid consultant for Bayer, Ibsa, Lundbeck, Menarini, Otsuka, Pfizer, Shionogi, and Viatrix. YR has been speaker and/or consultant for Lundbeck, Pfizer, Coloplast, Ohhmed and Besins. YR is serving as one of the Editorial Board members and Guest Editors of this journal. We declare that YR had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Akira Tsujimura.

References

- [1] Jannini TB, Di Lorenzo G, Bianciardi E, Niolu C, Toscano M, Ciocca G, *et al.* Off-label uses of selective serotonin reuptake inhibitors (SSRIs). *Current Neuropharmacology*. 2021. (Preprint)
- [2] Atmaca, M. Selective Serotonin Reuptake Inhibitor-Induced Sexual Dysfunction: Current Management Perspectives. *Neuropsychiatric Disease and Treatment*. 2020; 16: 1043–1050.
- [3] Clayton AH, Croft HA, Handiwala L. Antidepressants and sexual dysfunction: mechanisms and clinical implications. *Postgraduate Medicine*. 2014; 126: 91–99.
- [4] Ben-Sheetrit J, Aizenberg D, Csoka AB, Weizman A, Hermesh H. Post-SSRI Sexual Dysfunction: Clinical Characterization and Preliminary Assessment of Contributory Factors and Dose-Response Relationship. *Journal of Clinical Psychopharmacology*. 2015; 35: 273–278.
- [5] Bolton JM, Sareen J, Reiss JP. Genital anaesthesia persisting six years after sertraline discontinuation. *Journal of Sex and Marital Therapy*. 2006; 32: 327–330.

- [6] Csoka AB, Bahrack A, Mehtonen OP. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors. *Journal of Sexual Medicine*. 2008; 5: 227–233.
- [7] Healy D. Antidepressants and sexual dysfunction: a history. *Journal of the Royal Society of Medicine*. 2020; 113: 133–135.
- [8] Healy D, Le Noury J, Mangin D. Mangin, Enduring sexual dysfunction after treatment with antidepressants, 5 α -reductase inhibitors and isotretinoin: 300 cases. *International Journal of Risk and Safety in Medicine*. 2018; 29: 125–134.
- [9] Reisman Y. Post-SSRI sexual dysfunction. *British Medical Journal*. 2020; 368: m754.
- [10] Giatti S, Diviccaro S, Panzica G, Melcangi RC. Post-finasteride syndrome and post-SSRI sexual dysfunction: two sides of the same coin? *Endocrine*. 2018; 61: 180–193.
- [11] Keltner NL, McAfee KM, Taylor CL. Mechanisms and treatments of SSRI-induced sexual dysfunction. *Perspectives in Psychiatric Care*. 2002; 38: 111–116.
- [12] Wise NJ, Frangos E, Komisaruk BR. Brain Activity Unique to Orgasm in Women: an fMRI Analysis. *Journal of Sexual Medicine*. 2017; 14: 1380–1391.
- [13] Bijlsma EY, Chan JSW, Olivier B, Veening JG, Millan MJ, Waldinger MD, *et al.* Sexual side effects of serotonergic antidepressants: mediated by inhibition of serotonin on central dopamine release? *Pharmacology, Biochemistry, and Behavior*. 2014; 121: 88–101.
- [14] Blier P, de Montigny C, Chaput Y. Modifications of the Serotonin System by Antidepressant Treatments: implications for the therapeutic response in major depression. *Journal of Clinical Psychopharmacology*. 1987; 7: 24S–35S.
- [15] Pfaus JG. Pathways of sexual desire. *Journal of Sexual Medicine*. 2009; 6: 1506–1533.
- [16] Csoka AB, Szyf M. Epigenetic side-effects of common pharmaceuticals: a potential new field in medicine and pharmacology. *Medical Hypotheses*. 2009; 73: 770–780.
- [17] Bala A, Nguyen HMT, Hellstrom WJG. Post-SSRI Sexual Dysfunction: a Literature Review. *Sexual Medicine Reviews*. 2018; 6: 29–34.
- [18] Healy D, Bahrack A, Bak M, Barbato A, Calabrò RS, Chubak BM, *et al.* Diagnostic criteria for enduring sexual dysfunction after treatment with antidepressants, finasteride and isotretinoin. *International Journal of Risk and Safety in Medicine*. 2022; 33: 65–76.
- [19] Jannini EA. SM = SM: the Interface of Systems Medicine and Sexual Medicine for Facing Non-Communicable Diseases in a Gender-Dependent Manner. *Sexual Medicine Reviews*. 2017; 5: 349–364.
- [20] Wang YP, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Revista Brasileira De Psiquiatria*. 2013; 35: 416–431.
- [21] Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *Journal of Clinical Endocrinology and Metabolism*. 1999; 84: 3666–3672.
- [22] Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997; 49: 822–830.
- [23] Limoncin E, Lotti F, Rossi M, Maseroli E, Gravina GL, Ciocca G, *et al.* The impact of premature ejaculation on the subjective perception of orgasmic intensity: validation and standardisation of the ‘Orgasmometer’. *Andrologia*. 2016; 4: 921–926.
- [24] Gerbild H, Larsen CM, Graugaard C, Areskoug Josefsson K. Physical Activity to Improve Erectile Function: a Systematic Review of Intervention Studies. *Sexual Medicine*. 2018; 6: 75–89.
- [25] Giannine LM. An investigation of the relationship between physical fitness, self-concept, and sexual functioning. *Journal of Education and Health Promotion*. 2018; 7: 57.
- [26] Corona G, Sansone A, Pallotti F, Ferlin A, Pivonello R, Isidori AM, *et al.* People smoke for nicotine, but lose sexual and reproductive health for tar: a narrative review on the effect of cigarette smoking on male sexuality and reproduction. *Journal of Endocrinological Investigation*. 2020; 43: 1391–1408.
- [27] Calabrò RS, Polimeni G, Bramanti P. Current and future therapies of erectile dysfunction in neurological disorders. *Recent Patents on CNS Drug Discovery*. 2011; 6: 48–64.
- [28] Cormio L, De Sisti M, Lorusso F, Selvaggio O, Mirabella L, Sanguedolce F, *et al.* Oral L-citrulline supplementation improves erection hardness in men with mild erectile dysfunction. *Urology*. 2011; 77: 119–122.
- [29] Courtois F, Carrier S, Charvier K, Guertin PA, Jorrel NM. The control of male sexual responses. *Current Pharmaceutical Design*. 2013; 19: 4341–4356.
- [30] Gad MZ. Anti-aging effects of L-arginine. *Journal of Advanced Research*. 2010; 1: 169–177.
- [31] Gianfrilli D, Lauretta R, Di Dato C, Graziadio C, Pozza C, De Larichaudy J, *et al.* Propionyl-L-carnitine, L-arginine and niacin in sexual medicine: a nutraceutical approach to erectile dysfunction. *Andrologia*. 2012; 44: 600–604.
- [32] Sato S, Namisaki T, Furukawa M, Saikawa S, Kawaratani H, Kaji K, *et al.* Effect of L-carnitine on health-related quality of life in patients with liver cirrhosis. *Biomedical Reports*. 2020; 13: 65.
- [33] Jannini EA, DeRogatis LR, Chung E, Brock GB. How to Evaluate the Efficacy of the Phosphodiesterase Type 5 Inhibitors. *Journal of Sexual Medicine*. 2012; 9: 26–33.
- [34] Norden MJ. Buspirone treatment of sexual dysfunction associated with selective serotonin re-uptake inhibitors. *Depression*. 1994; 2: 109–112.
- [35] Bossio JA, Basson R, Driscoll M, Correia S, Brotto LA. Mindfulness-Based Group Therapy for Men with Situational Erectile Dysfunction: a Mixed-Methods Feasibility Analysis and Pilot Study. *Journal of Sexual Medicine*. 2018; 15: 1478–1490.
- [36] Nobre PJ, Pinto-Gouveia J. Dysfunctional sexual beliefs as vulnerability factors to sexual dysfunction. *Journal of Sex Research*. 2006; 43: 68–75.
- [37] Johnston MG, Faulkner C. A bootstrap approach is a superior statistical method for the comparison of non-normal data with differing variances. *New Phytologist*. 2021; 230: 23–26.
- [38] Reisman Y. Sexual Consequences of Post-SSRI Syndrome. *Sexual Medicine Reviews*. 2017; 5: 429–433.
- [39] Limoncin E, Tomassetti M, Gravina GL, Ciocca G, Carosa E, Di Sante S, *et al.* Premature ejaculation results in female sexual distress: standardization and validation of a new diagnostic tool for sexual distress. *Journal of Urology*. 2013; 189: 1830–1835.
- [40] Allen MS, Walter EE. Health-Related Lifestyle Factors and Sexual Dysfunction: a Meta-Analysis of Population-Based Research. *Journal of Sexual Medicine*. 2018; 15: 458–475.
- [41] Stanton AM, Handy AB, Meston CM. The Effects of Exercise on Sexual Function in Women. *Sexual Medicine Reviews*. 2018; 6: 548–557.
- [42] Xu Z, Liu C, Liu S, Zhou Z. Comparison of efficacy and safety of daily oral L-arginine and PDE5Is alone or combination in treating erectile dysfunction: a systematic review and meta-analysis of randomised controlled trials. *Andrologia*. 2021; 53: e14007.
- [43] Bjørklund G, Dadar M, Pen JJ, Chirumbolo S, Aaseth J. Chronic fatigue syndrome (CFS): Suggestions for a nutritional treatment in the therapeutic approach. *Biomedicine and Pharmacotherapy*. 2019; 109: 1000–1007.
- [44] Cavallini G, Modenini F, Vitali G, Koverech A. Acetyl-L-carnitine plus propionyl-L-carnitine improve efficacy of silde-

- nafil in treatment of erectile dysfunction after bilateral nerve-sparing radical retropubic prostatectomy. *Urology*. 2005; 66: 1080–1085.
- [45] Borrelli F, Colalto C, Delfino DV, Iriti M, Izzo AA. Herbal Dietary Supplements for Erectile Dysfunction: a Systematic Review and Meta-Analysis. *Drugs*. 2018; 78: 643–673.
- [46] Caruso S, Cianci S, Cariola M, Fava V, Rapisarda AMC, Cianci A. Effects of nutraceuticals on quality of life and sexual function of perimenopausal women. *Journal of Endocrinological Investigation*. 2017; 40: 27–32.
- [47] Jalali-Chimeh F, Gholamrezaei A, Vafa M, Nasiri M, Abiri B, Darooneh T, *et al.* Effect of Vitamin D Therapy on Sexual Function in Women with Sexual Dysfunction and Vitamin D Deficiency: a Randomized, Double-Blind, Placebo Controlled Clinical Trial. *Journal of Urology*. 2019; 201: 987–993.
- [48] Calabrò RS, De Luca R, Manuli A, Portaro S, Naro A, Quattrini F. Towards Improving Post-SSRI Sexual Dysfunction by Using Nutraceuticals: Lessons from a Case Study. *Journal of Sex and Marital Therapy*. 2019; 45: 562–565.
- [49] Abdel-Hamid IA, Elsaied MA, Mostafa T. The drug treatment of delayed ejaculation. *Translational Andrology and Urology*. 2016; 5: 576–591.
- [50] Goldstein I, Kim NN, Clayton AH, DeRogatis LR, Giraldi A, Parish SJ, *et al.* Hypoactive Sexual Desire Disorder: International Society for the Study of Women's Sexual Health (ISSWSH) Expert Consensus Panel Review. *Mayo Clinic Proceedings*. 2017; 92: 114–128.
- [51] Blycker GR, Potenza MN. A mindful model of sexual health: a review and implications of the model for the treatment of individuals with compulsive sexual behavior disorder. *Journal of Behavioral Addictions*. 2018; 7: 917–929.
- [52] Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. *Drug, Healthcare and Patient Safety*. 2010; 2: 141–150.
- [53] Pyke RE, Clayton AH. Psychological Treatment Trials for Hypoactive Sexual Desire Disorder: a Sexual Medicine Critique and Perspective. *Journal of Sexual Medicine*. 2015; 12: 2451–2458.