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Update on Sexual Dysfunction Associated with Psychotropic Medications and Its Treatment

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Abstract
Purpose of Review The goal of this review was to evaluate recent developments in sexual dysfunction associated with psychotropic medications and its management.
Recent Findings Sexual dysfunction associated with psychotropic medications is a serious clinical problem which occurs mostly with antidepressants, especially serotonergic ones, and antipsychotics, especially those causing hyperprolactinemia. Sexual dysfunction(s) seems to be associated to a significantly lesser degree with some newer psychotropic medications, e.g., vilazodone, vortioxetine, and agomelatine among antidepressants, and aripiprazole and lurasidone among antipsychotics. There have been no significant new developments in management of sexual dysfunction(s) associated with psychotropic medications with the exception of using newer medications or switching to them. A new clinical phenomenon—post serotonin reuptake inhibitors sexual dysfunction—has emerged as a difficult management issue.
Summary Sexual dysfunction associated with psychotropic medications continues to be an important issue requiring further research to provide solid evidence for regulatory agencies and for clinicians.

Keywords Sexual dysfunction · Antidepressants · Antipsychotics · Post-SSRI sexual dysfunction

Introduction

Iatrogenic sexual dysfunction from various psychotropic medications [1] has been known almost since their introduction into clinical practice with first case reports appearing in the literature close to 50 years ago. The interest in this group of side effects increased during the 1990s with multiple reports of serotonin reuptake inhibitors (SSRIs)-associated sexual dysfunctions [2]. Over the last couple of decades, sexual dysfunction(s) (SD) became a routinely and systematically monitored group of side effects in studies evaluating the efficacy and effectiveness of psychotropic medications and in studies submitted for the Food and Drug Administration (FDA) approval. The interest in sexual dysfunction(s) associated with medications sparked also interest in the impact of severe mental disorders, such as depression psychosis and others, on sexual functioning [3]. A number of review articles and chapters addressing various clinical issues such as frequency of sexual dysfunction(s) with particular medication, effect on specific area of sexual functioning (desire, arousal, orgasm), differential diagnosis (sexual dysfunction associated with medication vs. sexual dysfunction associated with mental or physical illness), and management of iatrogenic sexual dysfunction have been published.

This brief review will thus address interesting new findings or developments over the last 5–10 years with a focus on reports of iatrogenic sexual dysfunction(s) with newly introduced medications, namely antidepressants and antipsychotics, emerging clinical issues, and regulatory and scientific issues related to the evaluation of these effects.

This article is part of the Topical Collection on *Current Controversies*

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Sexual Dysfunction Associated with Various Psychotropic Medications

Most attention in this area continues to be focused on sexual dysfunction associated with antidepressant and antipsychotic medications.

Antidepressants

Studies

As the association of sexual dysfunction with newer antidepressants, namely SSRIs has become a recognized clinical phenomenon, several clinical trial with newer antidepressants focused on the rates of SD with these medications and on the possible differences between the new antidepressant and older SSRIs in regards to sexual functioning.

Croft and colleagues [4] reported that in an 8-week, randomized, double-blind placebo-controlled, parallel-group, fixed trial of vilazodone 40 mg/day in patients with major depression (MDD), sexual dysfunction adverse events were low in both groups (less than 5%). More male patients treated with vilazodone than those receiving placebo reported erectile dysfunction (4.8% vs. 0.9%) and delayed ejaculation (2.4% vs. 0%). The major methodological flaw in the evaluation of SD in this study was the use of spontaneous reporting of SD rather than standard evaluation tools. In a study comparing vilazodone, citalopram, and placebo [5] using the Changes of Sexual Functioning Questionnaire (CSFQ) [6•, 7•], some patients shifted to "normal" sexual functioning (the largest improvement was for women in the placebo and vilazodone groups), and some patients shifted from normal sexual functioning to SD (lower frequency of shifting with placebo and vilazodone, highest frequency—18% in citalopram group). The evaluation was a bit complicated as post-hoc analyses evaluated CSFQ mean score change from baseline to week 10 in male and female patient subgroups; CSFQ subscales evaluated five domains and three phases of sexual function plus satisfaction: pleasure, desire/frequency, desire/interest, arousal, and orgasm. The authors [5] concluded that, as (a) sexual function improved from baseline in both men and women in treatment responders and in patients with baseline sexual dysfunction and (b) in patients with baseline SD, all phases of sexual cycle improved in all treatment groups; it seems plausible that, "improved sexual function may be associated with improvement of depressive symptoms, which may outweigh potential direct negative serotonergic effects of antidepressants in patients with MDD" (p 223). Finally, Jacobsen and colleagues [8••] compared the effects of vortioxetine (a new antidepressant which combines direct modulation of various serotonin receptors and inhibition of serotonin transporter) and escitalopram on sexual functioning in adults with well-treated MDD experiencing treatment emergent sexual dysfunction (TESD). Patients responding to citalopram, paroxetine, or sertraline were randomized to switch to either vortioxetine (10–20 mg/day, $n = 225$) or escitalopram (10–20 mg/day, $n = 222$) for 8 weeks. The CSFQ was used to evaluate SD. Vortioxetine showed significantly greater improvements in CSFQ-14 total scores ($p = 0.013$; the difference was about 2 points on the CSFQ scale). Normal sexual functioning at the end of the treatment period (defined as CSFQ-14 score greater than 41 for women and greater than 47 for men) was achieved by 52.1% of patients treated with vortioxetine and 44.2% of patients treated with escitalopram. Similarly, a clinically relevant response on the CSFQ-14 (predefined as an increase from baseline in CSFQ-14 total score of at least 3 points at the end of week 8) was achieved by 74.7% of patients receiving vortioxetine and 66.2% of patients receiving escitalopram. Antidepressant efficacy continued in both groups after the switch. The authors concluded that switching to vortioxetine may be beneficial for patients experiencing SD during antidepressant therapy with SSRIs.

Interestingly, as depression could be a confounding variable in evaluating the effects of antidepressant on sexual functioning, two studies examined the effects of newer antidepressants on sexual functioning in healthy subjects. In a study by Clayton and colleagues [9•] comparing vilazodone, paroxetine, and placebo in healthy adult sexually active subjects (CSFQ was used to evaluate SD, 170 subjects completed the study), both doses of vilazodone (20 and 40 mg/day) had less negative impact on sexual functioning than paroxetine 20 mg/day, but the differences were not statistically significant [9•]. In the second study, Montejo and colleagues [10•] examined the effects of agomelatine 25 and 50 mg/day (an antidepressant acting as melatonin receptor agonist and 5-HT_{2C} receptor agonist; available in Europe but not in the USA), escitalopram 20 mg/day and placebo in a 9-week study - randomized, double-blind 8 week (there was a 1-week follow-up at the end) trial of 133 healthy male and female volunteers using Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ, a 5-item validated scale). The PRSexDQ) total scores were significantly lower in both agomelatine groups vs. escitalopram group at all visits ($p = 0.01$ to $p < 0.0001$) and the difference between the scores in both agomelatine groups and placebo was not statistically significant. Compared to placebo, only escitalopram significantly impaired dysfunction relative to "delayed orgasm or ejaculation" ($p < 0.01$) and "absence of orgasm or ejaculation" ($p < 0.05$ to $p < 0.01$). Specifically, 4 (16.7%) and 2 (8.3%) volunteers in the agomelatine 25 mg and 50 mg respectively, versus 14 (53.8%) in escitalopram in the escitalopram group reported delayed orgasm/ejaculation at week 8. Similarly, 3 (12.5%), and 2 (4.2%) volunteers in the agomelatine 25 and 50 mg groups and 12 (46.2%) in the escitalopram group reported absence of orgasm/ejaculation. The percentage of participants with a sexual dysfunction was higher in the escitalopram group than in agomelatine groups ($p < 0.01$ to $p < 0.05$) and placebo ($p < 0.01$). Finally, 19 (76%) and 20 (80%) volunteers reported no sexual dysfunction in the agomelatine 25 and 50 mg groups respectively, versus 13 (50%) volunteers in the escitalopram group and 27 (96.4%) in the placebo group reported no sexual dysfunction at week 8. Similar results were observed regardless of participant gender. Agomelatine demonstrated better sexual acceptability than escitalopram in healthy volunteers.

Review Articles

Several review articles summarized the findings on antidepressant-induced sexual dysfunction. Segraves and Balon [11] noted in their article on sexual dysfunction in men that "both double-blind controlled trials and large clinical series report a high incidence of sexual dysfunction, especially ejaculatory delay, with serotonergic drugs. The incidence of sexual dysfunction in men appears to be much lower with drugs whose primary mechanism of action involves adrenergic or dopaminergic systems." They [11] pointed out that clinical data concerning sexual dysfunction in men is compatible with data obtained from research with male laboratory animals using a standardized mating test [12]. Baldwin, Manson, and Nowak [13] noted that antidepressants may be associated with both worsening and improvement of sexual functioning. They also stated that the evidence for the effectiveness of interventions to manage SD in depressed patients is limited and that none of the current approaches (e.g., adjuvant pharmacotherapy; switching to another antidepressant should be considered "ideal"). Both articles emphasized the etiology of SD, and that the underlying mechanism of SD should be taken into consideration when developing new antidepressants. Finally, Lorenz and colleagues, [14] in their review of antidepressant-induced sexual dysfunction in women, summarized some treatment strategies using the phases of sexual response cycle. They [14] suggested using augmentation with bupropion (150 mg twice daily) transdermal testosterone for desire dysfunction; various behavioral strategies, namely exercise before sexual activity for arousal dysfunction; and more intense stimulation with the use of a vibrator for orgasm dysfunction.

Management of Sexual Dysfunction Associated with Antidepressants

The traditional management strategies for SD associated with antidepressants include waiting for spontaneous remission of SD, reduction to minimal effective dose of the antidepressant;,scheduling sexual activity around the dose, switching to another antidepressant with a lower frequency of SD, and addition of "antidotes" or augmenting agents. A "preventive" measure has been the recommendation to use antidepressants with a lower frequency of SD as the initial treatment of depression or anxiety. In the past, some other nontraditional strategies were recommended without being properly studied. Lately, several nontraditional approaches (or approaches using nontraditional "antidotes") were examined.

Lorenz and Meston [15•] in their randomized, blinded study of 52 women reporting antidepressant-associated sexual dysfunction found that exercise immediately (within 30 min) prior to sexual activity (versus at least 6 hours after exercising) significantly improved sexual desire, and for women with sexual dysfunction at baseline also global sexual functioning. However, exercise did not improve the orgasm function, while regular scheduling of sexual activity did. Interestingly, neither exercise nor regular scheduling of sexual activity improved sexual satisfaction. Khamba and colleagues [16] evaluated the efficacy of acupuncture in SD associated with antidepressants in a small open-label study of 35 subjects. They noted significant improvement in all areas of sexual functioning in males and significant improvements in libido and lubrication in females. Both studies used various standard scales and measures to evaluate sexual functioning.

Several new possible "antidotes" have been studied. Although the studies examining the efficacy of phosphodiesterase-5 inhibitors in SD associated with antidepressants are over a decade old, they are worth mentioning as, interestingly, they are not used for this indication very frequently. Nurnberg and colleagues found sildenafil to be effective in antidepressant-SD in two studies [17, 18••]. One of them [18••] proved sildenafil to be actually effective in this indication in women. Women in the sildenafil group when compared to placebo group had a higher mean improvement (orgasm $p = 0.01$) in all domains of sexual functioning except for pain. This was an interesting finding, as sildenafil was not found effective in SD in women in preapproval studies and thus did not indicate for "general" sexual dysfunction in women. Segraves and colleagues [19] reported that tadalafil was effective in erectile dysfunction (measured using the International Index of Erectile Function and Global Assessment Question) in men on antidepressants.

Interestingly, some of the new antidotes include nutraceuticals or herbal products, such as saffron [20, 21], maca root [22], Rosa damascena oil [23], and s-adenosyl-l-methionine (SAMe) [24]. The clinical utility of these products remains questionable, though. The two studies on saffron in fluoxetine-associated SD [20, 21] were small (30 men in one study and 34 women in another study), the differences between saffron and placebo were small and significant only in some area of sexual functioning, i.e., erectile function in men [20] and arousal, lubrication, pain, and total Female Sexual Functioning Index in women [21]. Similarly, the study with maca root [22] had only ten subjects who completed the study; patients were on various medications and the differences were small; the study was comparing two doses of maca root and had no placebo group. The double-blind, placebo-controlled study of Rosa damascena oil [23] included 50 completers on various SSRIs and duloxetine. The results are not completely clear, as the authors state that subjects on Rosa damascena oil improved more, but no statistically significant differences between groups were observed. Finally, the examination of SAMe [24] was a byproduct of a study on efficacy of SAMe in SSRI treatment nonresponders in MDD. Results were not significant in women, and significant only for ability to become aroused and ability to achieve erection in a small group of men (14 on SAMe and 10 on placebo).

Concluding Remarks

Antidepressant-induced SD has been recognized as an important clinical issue which needs to be properly studied and addressed in clinical practice. It has been known that some of the antidepressants, such as bupropion, mirtazapine, and nefazodone (available in generic formulation in the USA), have lower frequency of this side effect(s). It seems that some newer antidepressants, vilazodone and vortioxetine, have lower frequency of SD, too. Some research studies addressed an important methodological issue in assessing SD associated with antidepressants—the confounding variable of depression—by studying it in healthy (i.e., non-depressed) subjects.

The treatment of SD associated with antidepressants remains a complex and difficult problem. There has not been a lot of development in this area. A systematic examination of some nontraditional approaches to SD associated with antidepressants such as exercise and acupuncture [15•, 16] seems to be the only significant development in this area. The studies on nutriceutical or herbal augmentation/antidote strategies do not seem provide enough evidence for a new development regarding the augmentation/antidote strategies. The conclusion of the Cochrane review from 2013 [25] probably summarizes the current situation most appropriately: "The evidence currently available is rather limited. For men with antidepressant-induced erectile dysfunction, the addition of sildenafil or tadalafil appears to be an effective strategy. For women with antidepressant-induced sexual dysfunction, the addition of bupropion at higher doses appears to be the most promising approach studied so far."

Antipsychotics

Antipsychotic-associated SD has been a well-known, yet less noted and studied side effect of this group of medications. The older agents, also known as first generation antipsychotics, such as haloperidol or thioridazine, are known to cause various sexual dysfunctions. The most frequently presented explanation of the mechanism of SD associated with antipsychotics is the hyperprolactinemia due to blockade of the D_2 receptors in the tuberoinfundibular pathway. The older antipsychotic and risperidone cause hyperprolactinemia (HPRL) quite frequently (in up to 100% of patients to some degree). The hyperprolactinemia is probably not the entire story behind the antipsychotics-associated SD, as it for instance does not explain the high frequency of ejaculation delay associated with thioridazine. Antipsychotics do not affect just the D_2 receptors, but also various other ones, such as muscarinic, alpha-adrenergic, and serotonergic. Nevertheless, hyperprolactinemia has been the focal point in studying SD associated with antipsychotics.

Studies

Rubio-Abadal and colleagues [26] examined the relationship between (HPRL) and SD in 101 patients with a spectrum of psychotic diagnoses on a stable dose of antipsychotic medications. The CSFQ was used to evaluate SD. The majority of patients (71.3%) showed HPRL. SD was significantly higher in HPRL patients than in non-HPRL patients (79.2% vs. 51.7%) and no sex differences were found in HPRL and in SD.

Considering the role of HPRL in SD, studies of newer antipsychotics focused on those antipsychotics that do not cause HPRL (or cause it to a lesser degree) and thus may be associated with lower frequency of SD. One such a drug is aripiprazole, which is a partial antagonist of a subgroup of D_2 receptors and a partial agonist of another subgroup of D_2 receptors, in addition to acting on D_3 receptors. In a small open-label pilot study of 19 Japanese schizophrenia patients stable on various antipsychotics, Fujioi and colleagues [27] assessed the usefulness of adjunctive aripiprazole in addressing SD in these patients. At week 4, prolactin levels were significantly lower than at baseline and SD, measured by Nagoya Sexual Function Questionnaire, significantly improved. Interestingly, erectile dysfunction was significantly reduced at week 24, and in women, galactorrhea and menstrual irregularity were significantly reduced at week 24. Potkin and colleagues [28••] compared the impact of two long acting antipsychotics—aripiprazole 400 mg once monthly (AOM) with paliperidone palmitate (PP) (D_2 antagonist) with respect to SD and HPRL. The study included 100 AOM completers and 83 PP completers and lasted for 28 weeks; sexual functioning was assessed using the Arizona Sexual Experience Scale (ASEX) [29•]. Baseline rates of SD were not statistically different, while the rates of SD at week 29 were significantly different—37.9 % for AOM and 63.1% for PP—and more AOM patients switched to no SD at all (21.4% AOM patients vs. 11.9% PP patients). Prolactin levels decreased in AOM group and increased in PP group.

The effects of lurasidone (a novel antipsychotics with high affinity to D_2 receptors but also high affinity to several serotonin receptors) on SD was evaluated in a trial by Clayton and colleagues [30•]. This was a double-blind, placebo-controlled flexible dosing (lurasidone 20-60 mg/day) study of patients with major depressive disorder with subthreshold hypomanic symptoms (109 patients on lurasidone, 100 on placebo). Sexual functioning was evaluated by CSFQ. Interestingly, at a week 6, treatment with lurasidone was associated with significant endpoint improvement in CSFQ total scores versus placebo (+ 5.1 vs. + 3.1, $p < 0.001$). Fewer lurasidone patients shifted from normal to abnormal sexual functioning. No treatment emergent side effects related to sexual functioning were reported with lurasidone.

Treatment Issues

Two small studies [31•, 32] examined treatment options for antipsychotic associated SD. Yoon and colleagues [31•] studied 52 patients suffering from schizophrenia and treated with various antipsychotics. Sexual functioning was evaluated using ASEX. Patients with severe HPRL (serum prolactin > 50 ng/mL) were randomized to an aripiprazole-addition group (adding aripiprazole to previous antipsychotic) or a switching group (switching to aripiprazole). Patients in both groups had reduced prolactin levels and menstrual disturbances, and improved sexual functioning at week 8. However, mean ASEX showed no significant change over time and the population sample was small. The number of patients with HPRL and menstrual disturbance was significantly lower in the switching group at week 8. In a small, double-blind, placebo-controlled study [32], add-on mirtazapine to first generation antipsychotic regimen in schizophrenia or schizoaffective disorder significantly improved orgasmic function ($p = 0.03$), with no changes in any other sexual function in either mirtazapine or placebo group.

Concluding Remarks

A couple of newer antipsychotic drugs (aripiprazole, lurasidone) seem to have low to none associated SD, which could be used in treatment planning (choosing a medication with low frequency of SD) or in treatment of SD (aripiprazole). The only new possible antidote for SD with antipsychotics seems to be the possible addition of mirtazapine.

Regulatory Issues

Two interesting articles [33, 34] discussed regulatory and scientific issues in studies evaluating SD in antidepressant drug trials. According to the summary of the FDA Regulatory Science Forum "there seemed to be general agreement among academic experts that the currently available quantitative measures of sexual function (if used and analyzed correctly), in particular the CSFQ-14 and ASEX, are adequate" [33]. The second article [34] discussed issues such as potential drug labeling claims, scales to measure sexual function (again, CSFQ [6•, 7] and ASEX [29•]), clinical trial design issues (e.g., study population, stratified randomization, statistical analysis plan). The authors [34, p 1063] concluded that "From both regulatory and a scientific perspective there was general consensus…that sexual dysfunction associated with antidepressants is an important entity that should be adequately assessed during clinical trials with the use of available instruments and described in product labels. It is important to appreciate the need for a positive control to establish assay sensitivity for any trial evaluating the impact of antidepressant medications on sexual function. We hope this article will encourage meaningful research into treatment-emergent sexual dysfunction with antidepressants to generate the evidence the psychiatric community now lacks in addressing this very important issue."

Emerging Clinical Issues

Two interrelated entities—post-SSRI sexual dysfunction (PSSD) and Persistent Genital Arousal Disorder (PGAD) following exposure to SSRIs—emerged as new challenging clinical issues.

Reisman [35] noted that there are some indications that antidepressant-emergent SDs do not always resolve after medication discontinuation and can persist indefinitely in some individuals. Some symptoms of SD may develop during the treatment and continue after treatment discontinuation; however, other sexual symptoms may develop. Reisman [35] also noted that this symptomatology could always be confounded with anxiety and depression, but the fact that new symptoms develop may help in diagnosis. Bala and colleagues [36••] in their review of PSSD described a number of common PSSD symptoms: genital anesthesia (decrease in sensation and numbness in genital area), pleasure-less or weak orgasm, decreased sex drive, erectile dysfunction, premature ejaculation, and in women also vaginal lubrication problems and nipple sensitivity. The most characteristic triad consists of genital anesthesia, loss of libido, and erectile dysfunction [35]. These symptoms can start within days or weeks after starting SSRIs and can persist after SSRI discontinuation. The exact prevalence of PSSD is not known. The condition could be debilitating, especially since there is no efficacious treatment. Suggested strategies include serotonergic antagonists and dopaminergic agonists. Reportedly 20 15-min sessions of low-power laser irradiation was helpful in penile anesthesia in early onset PSSD associated with paroxetine [37], as the patient reported partial return of penile touch and temperature sensation and 20 to 40% improvement of glans penis sensitivity. However, anejaculation and erectile difficulties remained unchanged. Another report [38] described a case of a young male with loss of libido, erectile dysfunction, and anejaculation which developed on citalopram 20 mg/day and persisted for a year after citalopram discontinuation. Mirtazapine, trazodone, and bupropion did not alleviate his symptoms. He was then prescribed Edovis (a dietary supplement containing L-citrulline, *tribulus terrestris*, *peruvian maca*, *turnera diffusa*, *muira puama*, and folic acid) one sachet daily containing 3 g of L-citrulline. His sexual functioning was almost completely restored after 3 months of Edovis administration.

Interestingly, PSSD has been also studied in animals. The results of a systematic review [39] of animal studies measuring sexual behavior after end of treatment with SSRIs or serotonin norepinephrine reuptake inhibitors showed substantial and lasting effect on sexual behavior in rats after exposure to an SSRI early in life on important outcomes such as mounting, intromission, and ejaculatory behaviors.

PGAD is a rare entity originally described by Leiblum and colleagues [e.g., 40] consisting of a host of symptoms such as persisting physiological arousal which is perceived as intrusive, distressing, does not resolve with orgasm and is not related to subjective experience of sexual desire or excitement. de Magalhaes and Kumar [41] described a case of a 57-year-old female who developed PGAD-like symptoms after cessation of citalopram. She also experienced relapse of her depression. She improved on 30 mg of duloxetine and 1 mg of lorazepam/day. Whether this case of PGAD was a part of PSSD is not clear.

Conclusion

Sexual dysfunction(s) associated with psychotropic medications are well-established side effects. Sexual dysfunction(s) occur most frequently with certain antidepressants (mostly serotonergic ones, such as SSRIs) and antipsychotics (especially those causing hyperprolactinemia). During the last decade or so, several new antidepressants (i.e., vilazodone, vortioxetine, and agomelatine) and antipsychotics (aripiprazole, lurasidone) have demonstrated lower or no sexual dysfunction in clinical trials. There have been no substantial developments in the management of SD associated with psychotropic medications except for switching to aripiprazole in cases of SD associated with antipsychotics causing hyperprolactinemia, and possible usefulness of exercise and acupuncture in SD associated with antidepressants.

A new phenomenon—post-SSRI sexual dysfunction—has emerged as a possibly highly distressing and difficult to manage clinical entity. Some [36] have suggested starting with or switching to antidepressants with low or no sexual dysfunction (bupropion, nefazodone) or using cognitive-behavioral therapy in the management of PSSD. Nevertheless, this entity and its treatment require further study.

Compliance with ethical standards

Conflict of Interest The author declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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