Psychotropics and sexual dysfunction

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Introduction. Sexual dysfunction (SD) is common in patients taking antipsychotics, and is the most bothersome symptom and adverse drug effect compromising treatment compliance. Mechanisms involved in psychotropics–induced SD are either largely unknown or poorly understood. The aim of this review is to present an updated analysis of SD associated with the use of psychotropic drugs in psychiatric patients.
Results. Contemporary evidence from available studies demonstrates that SD rates are drug–related rather than drug–class specific, and that these rates vary widely. Mechanisms involved in psychotropics–induced SD are either largely unknown or poorly understood. Our understanding of psychotropics–induced SD is limited by the inability to differentiate whether these effects are really drug–induced or due to different inclusion criteria.
Conclusions. Rigorous research, basic and clinical, is needed to understand the exact incidence, severity and mechanisms involved in the development of SD induced by various psychotropic treatment regimens.

INTRODUCTION

Sexual dysfunction (SD) can be defined as any reduction in desire or libido, diminished arousal, a decline in the frequency of intercourse, or an undesirable delay in or inability to achieve orgasm. SD is a highly prevalent clinical entity that has been reported in different geographical communities [1]. In one study in the United States, more than 40% of women and 30% of men reported some form of SD, with low sexual desire in women (22%) and premature ejaculation in men (21%) being the most prevalent [2], whereas an analysis of SD across eight European countries revealed that up to 34% of women and 15% of men reported low sexual desire [3].

It has been well known for a long time that antipsychotic drugs contribute to the development of SD. However, until recently, limited research effort has been invested to try to understand the mechanisms that govern these interactions. Different reasons have been proposed for this lack of attention: sexual activity could be harmful to schizophrenic patients and a general lack of interest by the treating clinicians to ask about sexual topics, or a combination of both [4]. Fortunately, this trend is changing.

Recently, several studies outlined that SD is rated as one of the most distressing side effects of antipsychotics [5, 6] and a major cause of a poor quality of life [7], and that it is associated with a negative attitude toward therapy and noncompliance to treatment [8]. Furthermore, strong evidence has been presented suggesting that both typical and some atypical antipsychotics, such as risperidone, are often associated with a significant impairment of sexual function [9]. Suggested mechanisms for these unwanted effects include a disturbance of one or more of the three areas of the normal sexual–response cycle: sexual interest (libido), arousal (including vaginal lubrication in women and erection in men), and orgasm (along with further endocrine disturbances), to a higher or lesser extent depending on the pharmacological properties of each single compound [10, 11].

The aim of this review is to present an updated analysis of SD associated with the use of psychotropic drugs in psychiatric patients.

Measures of sexual dysfunction

A review of antidepressant–induced SD in randomized controlled clinical trials revealed that among 79 randomized controlled trials, 75% relied on spontaneous reports of sexual adverse effects, whereas only 8% used specific instruments [12]. It is important to encourage the use of direct assessment methods to evaluate sexual function before and during psychotropic treatments using a valid and highly reliable rating scale [13, 14, 15]. Several questionnaires are available, including the Arizona Sexual Experience Scale. This is a brief self–report scale designed to assess 5 global aspects of sexual dysfunction: drive, arousal, penile erection/vaginal lubrication, ability to achieve orgasm, and satisfaction from orgasm [16]. Also available, the Changes in Sexual Functioning Questionnaire, is comprised of 36 items for male and 35 items for female respondents, of which 21 items apply to both men and women [17]. This scale addresses 5 dimensions: pleasure, desire/frequency, desire/interest, arousal, and orgasm on the 5–point Likert scale, where a higher score reflects better functioning. Finally, the Sex Effects Scale is a brief 13–item clinician–administered or self–report scale that has been used to compare sexual adverse effects of different antidepressants. It is a gender–specific measure designed to assess changes in three domains: desire, arousal, and orgasm [14].

Psychotropics

Psychotropic drugs can be classified into two different classes, antidepressants and antipsychotics. We will discuss below the potential sexual dysfunction effects of each class.

a. Antidepressants
Major depression (MD) is the most common mental disorder. It is estimated that about 12% of men and 20% of women in the United States suffer from MD [18]. Thus, the majority of studies examining the drug–related SD during psychiatric treatment were based on the study of antidepressant drugs. It is noteworthy to mention, however, that the identification of treatment–related SD in MD can be difficult, as SD (particularly low sexual desire in women and premature ejaculation in men) is common in the general population, and because SD itself may be a symptom of MD, even in the absence of treatment [19, 20].

Antidepressant treatment is associated with significant rates of SD [21] and there are also significant variations among the effects produced by different drugs in this class [22] (for detailed information, please refer to reference [9], Figure 1), reflecting specific differences in the pharmacological profiles of individual antidepressants. A recent meta–analysis that analyzed data from selected studies investigating treatment–emergent SD, by means of structured interviews and standardized SD questionnaires, revealed that drugs with a predominantly serotonergic action, including selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, had the highest likelihood of inducing treatment–related SD (ranging from 26% for fluvoxamine to 80% for sertraline and venlafaxine) [21].

However, several points need to be addressed. First, it is not totally clear whether the lower rates of SD associated with fluvoxamine and escitalopram are in fact attributable to the specific characteristics of these drugs or whether they simply reflect differences in the methods of inquiry. Second, it is again unclear how duloxetine, imipramine, and phenelzine, compared to a placebo, could be significantly related to SD rates, whereas no significant difference was observed between the effects of a placebo and those of moclobemide, agomelatine, amineptine, nefazodone, bupropion, or mirtazapine [21]. Finally, it is uncertain how antidepressants that have an overall association with SD affect all three phases of the sexual cycle. Overall, it is reasonable to suggest that men are more likely to experience higher rates of dysfunction in the desire and orgasm phases than women, whereas women are more likely to experience higher arousal dysfunction than men [21].

Mechanisms underlying the well–documented drug–mediated SD are largely unknown. A widely appreciated hypothesis is that SSRIs and venlafaxine reduce dopaminergic transmission via serotonin receptors in the mesolimbic area, which is primarily associated with sexual desire and orgasm, and thus SD associated with these drugs is expected. [23]. This hypothesis is further supported by the suggestion that serotonergic agents such as mirtazapine and nefazodone, with antagonist rather than agonist action on 5HTR2 receptors, do not induce SD [24]. Other mechanisms proposed, which include reduction of nitric oxidase synthase and the anticholinergic effects related to paroxetine – could also be involved in antidepressant–related SD [23].

b. Antipsychotics
SD rates are significantly higher in subjects with schizophrenia than in healthy controls and patients with other psychiatric disorders [25, 26]. There is

strong and consistent evidence to suggest that both conventional and new–generation antipsychotic drugs significantly impair sexual function [27]. Historically, drugs causing hyperprolactinemia have been accused of causing SD. However, current evidence shows that the prevalence of antipsychotic–induced SD, in fact, may not be related to the drug's potential to increase prolactin levels [28].

Risperidone and olanzapine have the highest likelihood of causing SD [27]. Several large observational and placebo–controlled studies suggest that risperidone affects sexual function in approximately 60 to 70 percent of patients, particularly erectile and ejaculatory dysfunction in men, menstrual irregularities, amenorrhea, and decreased vaginal lubrication in women, and reduced libido and impaired orgasm in individuals of both sexes [25, 29]. More than 50% of the patients treated with olanzapine experience SD. Clozapine, another antipsychotic, has been considered as having one of the lowest associations with SD with respect to conventional antipsychotics, but produces higher rates of erectile and ejaculatory problems than other atypical antipsychotic medications. Furthermore, quetiapine seems to be associated with SD rates of about 50–60% [25], but the severity of such dysfunction may be lower than in patients treated with risperidone or olanzapine [27]. The drugs quetiapine, aripiprazole and the novel antipsychotic, ziprasidone, have little published evidence to make any conclusions about their effects on sexual function.

There are several possible mechanisms by which antipsychotic drugs could induce SD. The most well–known hypothesis is that several antipsychotics lead to hyperprolactinemia through D2 receptor antagonism, resulting in decreased libido as well as impaired arousal and orgasm [30, 31]. Another proposed mechanism involves the anticholinergic and alpha–adrenergic action of several antipsychotic drugs, which could affect sexual function by inhibiting motivation and reward, increasing sedation, and reducing peripheral vasodilatation [30, 31]. Other factors, including histamine receptor antagonism and hormonal changes, could also be involved. In–depth research is definitely needed to understand the pathophysiological mechanisms responsible for antipsychotic drug–related SD.

Several new antidepressant drugs have been shown to have sexual enhancing properties. For example, VML–670, a novel 5–HT1A agonist with weak 5–HT1D agonist properties, was shown to cause improvement in sexual function compared to the placebo in remitted patients with depression, experiencing treatment emergent sexual dysfunction with SSRIs. The difference, however, was not significant [32].

Agomelatine, another novel antidepressant with direct agonist effects on the melatonin MT1 and MT2 receptors, and with 5–HT2C antagonist properties, was shown to have significantly lower SD effects compared to paroxetine (5% for agomelatine, 62% for paroxetine, 0% for placebo) [33].

c. Other psychotropic medications
Mood stabilizers
Little is known about the sexual effects of mood stabilizers. Initially, no significant SD was observed with the use of lithium (a well–known mood stabilizer) [34]. However, a more recent study demonstrated an impairment in sexual function, particularly erectile dysfunction [35]. Other studies in patients with epilepsy or bipolar disorder reported significant rates of SD related to the use of anticonvulsant drugs, including valproate and carbamazepine [36]. On the other hand, lamotrigine has been reported to be associated with an improvement in sexual function [37]. There exists no convincing explanation for why some mood stabilizers cause SD, while others, like lamotrigine, can actually enhance sexual function.

Anxiolytics
The co–administration of benzodiazepines and lithium resulted in significantly higher rates of SD (49%) than with either lithium alone (14%) or lithium in combination with other drugs (17%) [34]. In another study, alprazolam led to significant rates of decreased libido and increased erectile and orgasm dysfunction in a group of patients treated with panic disorders [38]. However, a study of 100 male patients suffering from posttraumatic stress disorder did not find any evidence of SD associated with alprazolam, lorazepam, or diazepam use, whereas approximately 43% of the patients treated with clonazepam reported SD, particularly erectile dysfunction [39]. The combination of limited studies, together with conflicting evidences, make it difficult to draw any substantial conclusions about the effects of anxiolytics on sexual function.

Treatment strategies of Antidepressant–induced SD

As antidepressants are the most studied group of psychotropics regarding their SD effects, several authors advocated treatment strategies for management of the SD complaint [40]. Other groups of psychotropics could follow the same guidelines. Current treatment strategies for antidepressant–induced SD are listed below:
a. Change of antidepressant to one with known lower SD effects. One randomized trial found that for pa-

tients with sertraline–induced sexual dysfunction, switching to nefazodone was an effective strategy [41]. However, the usefulness of such practice is now reduced by limited nefazodone availability [40].

b. Phosphodiesterase–5 (PDE5i) inhibitors. They carry the strongest evidence to treat antidepressant–induced SD. The use of sildenafil for this indication is well documented in the literature [42, 43, 44]. A retrospective analysis demonstrated that sildenafil was effective in men with erectile dysfunction receiving antidepressants [43]. These men were a subset (n = 98) of 3414 men randomized in 10 phase II or III trials. In these studies, it was not clearly shown that the erectile dysfunction was due to the antidepressants themselves (it may have been due to another cause). Subsequently, a small, placebo–controlled study of 21 men recovered from mood or anxiety disorder, and with SSRI– or SNRI–associated erectile dysfunction, similarly found benefit of sildenafil use [44]. Tadalafil has shown similar efficacy in men with erectile dysfunction receiving antidepressants. In a prospective, double–blind, 12–week study of tadalafil 20 mg or placebo taken on demand (n = 50), the net median score change from baseline to endpoint compared with placebo was 26 for the 15–item International Index of Erectile Function. It included meaningful improvements in erectile function, intercourse satisfaction, overall satisfaction, orgasmic function, and sexual desire domains [45]. Regarding side–effects and safety measures, no clinically significant changes attributable to tadalafil use were found [45]. In another recent double–blind, 12–week study, tadalafil 20 mg treatment significantly improved sexual function in 50 men who were taking SSRIs for depression, with mild to moderate, well–tolerable adverse events [46].

c. Bupropion. This drug has been trialed as an additional treatment to reverse dysfunction induced by other agents. The three RCTs published thus far report mixed results [47, 48]. In one study, 48 women and seven men responding to SSRI treatment of major depression, but who developed SSRI–induced SD, were randomized to either bupropion sustained release, 150 mg twice daily, or placebo with ongoing SSRI use over 4 weeks. Results tended to favor bupropion; however, only an improvement in feelings of desire and frequency of sexual activity reached statistical significance [47]. Two other similarly sized, placebo–controlled randomized trials, using a dose of 150 mg once daily found no benefit of treatment with bupropion sustained release [48, 49]. Further research, including more study subjects and different doses of bupropion, is needed to clear the conflicting data [50].

d. Other approaches, including drug holidays and psychological interventions, have all been tried with mixed unconfirmed results [50].

CONCLUSIONS

SD is a very common side effect associated with the use of various psychotropic medications, worldwide. Contemporary evidence from available studies demonstrates that SD rates are drug–related rather than drug–class specific, and that these rates do vary widely. Mechanisms involved in psychotropics–induced SD are largely unknown or poorly understood. Our understanding of psychotropics–induced SD is limited by the inability to differentiate whether these effects are really drug–induced or due to different inclusion criteria. However, clinicians should continue to ask their patients on psychotropic therapy about any SD complaints using validated questionnaires. Rigorous research, basic and clinical, is needed to understand the exact incidence, severity and mechanisms involved in the development of SD induced by various psychotropic treatment regimens.

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