

Sexual Dysfunction Related to Psychotropic Drugs: A Critical Review – Part I: Antidepressants

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Key words

- antidepressant drugs
- sexual dysfunction
- sexual side effects
- treatment-emergent sexual dysfunction

Abstract

Sexual dysfunction is a potential side effect of antidepressant drugs: this article presents a critical review of the current literature. Although many studies have been published on this subject, only some have used a validated sexual function rating scale and most lacked either a baseline or placebo control or both. In addition, many of the studies on sexual dysfunction associated with antidepressants are limited by other

methodological flaws. However, there is consistent evidence to suggest that antidepressant medication adversely affects one or more of the 3 phases of sexual response (desire, arousal and orgasm). Antidepressants with strong serotonergic properties have the highest rate of sexual side effects. Clinicians must be aware of drug-induced sexual dysfunction, since its presence can have important consequences on clinical management and compliance.

Introduction

In recent years, sexual dysfunction induced by psychopharmacological treatment has been the subject of increased interest. It is not surprising that the majority of studies on sexual dysfunction caused by psychopharmacology relate to antidepressant medication, considering that in the USA major depression is the most common mental disturbance [1]. Numerous studies have shown a relationship between antidepressant medication and sexual dysfunction [2–11]; there are also several publications on possible treatment approaches [12–14].

This review aims to examine the available evidence on sexual dysfunction caused by antidepressant medication and to identify useful strategies that might alleviate this problem.

Evidence. The full list of available journals can be viewed at <http://atoz.ebsco.com/Titles/2793>, or at the APSS web site (<http://www.apss.tn.it>). Studies published between 1982 and February 2013 were included in the review.

A literature search was conducted using the key words “antidepressant drugs”, “psychotropic drugs”, “sexual dysfunction”, “sexual side effects”, “treatment-emergent sexual dysfunction”. All resulting listed articles were reviewed. The articles analyzed in our review are summarized in **Table 1**.

Biology of Sexuality: Mechanism of Action of Antidepressants on Sexual Function

The principal neuroanatomic areas that control sexual behavior include the medial forebrain bundle, the medial preoptic-anterior region of the hypothalamus and its related limbic-hippocampal structures, and the ventral tegmentum of the midbrain [15].

Human sexual activity is modulated by a number of neurotransmitters and hormones, however, their exact mechanism of action on the 3 phases of the sexual response cycle is poorly understood. Sthal [16] suggests that the neurotransmitters involved in the 3 stages (desire, arousal and

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Methods

This study was conducted in 2013 using the paper and electronic library resources of the “Azienda Provinciale per i Servizi Sanitari (APSS)” in Trento, Italy (<http://atoz.ebsco.com/Titles/2793>, latest access: 18 February 2013). The library has access to a wide range of databases including (DYNAMED, MEDLINE Full Text, CINAHL Plus Full Text), The Cochrane Library, Micromedex healthcare series, BMJ Clinical

Table 1 In this review we have analyzed: 48 Reviews, 38 RCTs (Randomized Controlled Trials), 9 Case Control Studies, 23 Open label Studies, 19 Case Report Studies, 20 Other Articles.

	Reviews: 48	RCTs: 38	Case controls: 9	Open labels: 23	Case reports: 19	Other articles: 20
References	[145, 2, 115, 3, 4, 5, 15, 6, 58, 7, 100, 8, 59, 106, 107, 60, 61, 97, 28, 57, 12, 83, 70, 17, 63, 89, 21, 44, 13, 120, 76, 22, 23, 149, 64, 19, 20, 142, 143, 14, 105, 72, 10, 144, 121, 156, 150, 157]	[40, 87, 109, 84, 74, 155, 110, 112, 85, 122, 123, 42, 35, 129, 29, 130, 81, 43, 75, 151, 38, 66, 45, 103, 104, 98, 46, 47, 114, 93, 124, 48, 152, 113, 77, 153, 133, 154]	[108, 147, 95, 131, 86, 117, 99, 92, 134]	[88, 18, 27, 96, 91, 101, 36, 52, 37, 116, 56, 26, 102, 67, 78, 118, 90, 111, 62, 11, 82, 54, 132]	[39, 41, 79, 65, 148, 69, 141, 126, 51, 49, 80, 125, 50, 53, 68, 127, 128, 119, 94]	[140, 138, 139, 136, 30, 31, 146, 137, 16, 24, 25, 71, 9, 55, 33, 34, 135, 32, 1, 73]

orgasm) of the human sexual response cycle have different mechanisms of action. In stage 1 (desire), dopamine (DA), melanocortin, testosterone and estrogen exert a positive influence, while prolactin and serotonin (5HT) have negative effects. In stage 2, arousal correlates with erection in men and with genital swelling and lubrication in women. Several neurotransmitters facilitate sexual arousal, including nitric oxide (NO), norepinephrine (NE), melanocortin, testosterone, estrogen, acetylcholine (ACh), and dopamine (DA). As with desire, serotonin has a negative effect. Stage 3 (orgasm), which is associated with ejaculation in men, is inhibited by serotonin and facilitated by norepinephrine; dopamine and nitric oxide may have weak positive influences.

Sex hormones (e.g., estrogen, progesterone, and testosterone) substantially influence the neurotransmitter actions that modulate sexual behaviour [15]. These interactions, which occur at both a central and a peripheral level, account for intricate modulations of desire, sexual arousal, and orgasm.

A functioning hypothalamic-pituitary-gonadal axis (HPA axis) is fundamental in the modulation of sexual activity, however little else is known about the influence of the hypothalamic-pituitary-gonadal axis on female and male sexual function. Other neurotransmitters and hormones that can cause sexual dysfunction are probably involved (◉ **Table 2**).

Antidepressant-induced sexual dysfunction is mainly due to a sexual inhibitory action. Sexual problems may involve one or more phases of the sexual response cycle [18–20]. Delayed ejaculation is the most commonly reported sexual dysfunction in the literature, other frequently reported problems include delayed and/or absent orgasm, reduced and/or lack of sexual desire, and reduced and/or absent sexual arousal (erectile dysfunction and insufficient vaginal lubrication) [4, 15, 21–23].

Enhanced sexual functioning is more rarely reported, and generally tends to be associated with a clinical improvement in depression. The precise mechanism of action of antidepressant-induced sexual dysfunction remains unclear and a subject of discussion whereby no definitive conclusions have been reached [17, 21]. The pharmacodynamic actions of the various antidepressants are very different and complex; it is also very likely that multiple receptor systems are involved in the etiology of sexual dysfunction [16, 24, 25].

Overall, the evidence in the literature indicates that an inhibitory action on sexuality is expressed mainly through the activation of a particular serotonin receptor subtype: 5HT₂ receptors [17, 23, 26].

Other inhibitory mechanisms of action on sexuality include anticholinergic actions, blockade of noradrenergic receptors α -1, antihistaminergic actions, antidopaminergic actions and elevated prolactin [16, 17, 23–28]. An inhibitory action on nitric oxide synthase has also been hypothesized [16, 23, 29].

Table 2 Psychopharmacological effect of neurotransmitters on the 3 stages (desire, arousal and orgasm) of the human sexual response (from: Boyarsky [15], Keltner [17], Stahl [16]).

Stage 1: DESIRE	Stage 2: AROUSAL	Stage 3: ORGASM
dopamine (DA) (+)	dopamine (DA) (+)	serotonin (5HT) (-)
melanocortin (+)	melanocortin (+)	norepinephrine (NE) (+)
testosterone (+)	testosterone (+)	dopamine (DA) (+/-)
estrogen (+)	estrogen (+)	nitric oxide (NO) (+/-)
prolactin (-)	nitric oxide (NO) (+)	
serotonin (5HT) (-)	acetylcholine (ACh) (+)	
	norepinephrine (NE) (+)	
	serotonin (5HT) (-)	

Other neurotransmitters and hormones that are likely to cause sexual dysfunction: α 1 adrenergic agonist (+); α 2 adrenergic agonist (+), (central and peripheral); GABA (+/-); cortisol (+/-), (acute or chronic effect); DHEA/DHEAS (+); monoamine oxidase a (+); monoamine oxidase b (-); opioids (-), (central); progesterone (-), (central); prolactin (-), (central); prostaglandins (+), (peripheral); substance p (+), (peripheral); testosterone (+), (central and peripheral); vasopressin (+), (central) (+) = positive influence (excitatory action); (-) = negative influence (inhibitory action); (+/-) = the neurotransmitter and/or hormone may have different influences on females and males, at a central and peripheral level

Some recent evidence also suggests that genetic factors may be involved in the development of sexual dysfunction. Genetic predictors of drug-induced sexual dysfunction-dependent polymorphism of the serotonin 5HT_{2a} receptor [30–34] may exist. Specific genetic polymorphisms of the glutamate gene and variations of the enzyme CYP2D6, may also be involved, but the exact role of this enzyme in sexual dysfunction is unclear.

Antidepressants and Sexual Dysfunction



A recent meta-analysis (which included data from studies investigating sexual dysfunction relating to antidepressant treatment that used direct questions or specific questionnaires) showed that the incidence of sexual dysfunction ranged in ascending order, from 4% for moclobemide and agomelatine, 7% for amineptine, 8% for nefazodone, 10% for bupropion, 24% for mirtazapine, 26% for fluvoxamine, 37% for escitalopram, 42% for duloxetine and phenelzine, 44% for imipramine, 70% for fluoxetine, 71% for paroxetine, 79% for citalopram and 80% for venlafaxine and sertraline (◉ **Table 3**). However, it was highlighted that some findings, namely the lower sexual dysfunction found with some SSRIs such as fluvoxamine and escitalopram compared to others, may have been due to the use of scales that are less sensitive than others in assessing the incidence of sexual dysfunction [19, 20].

The side-effect profile of antidepressants varies depending on the individual drug.

Table 3 Percentage of sexual dysfunction reported in the meta-analysis by Serretti and Chiesa [20].

Class	Drug	Percentage	Class	Drug	Percentage
SSRI	citalopram	79%	SNRI	venlafaxine	80%
	escitalopram	37%		duloxetine	42%
	fluoxetine	70%	TCA	amineptine	7%
	fluvoxamine	26%		imipramine	44%
	paroxetine	71%	MAOI	phenelzine	42%
	sertraline	80%	RIMA	moclobemide	4%
others	mirtazapine	24%	others	nefazodone	8%
	bupropion	10%		agomelatine	4%

(I) Tricyclics

The early studies on the effects of antidepressant medication on sexual function mainly involved tricyclic antidepressants [35–37], of which, clomipramine in particular, but also amitriptyline and imipramine, were found to cause higher rates of sexual dysfunction (decreased libido and lubrication, inhibition of ejaculation and orgasm) [15]. In some studies on clomipramine, rates of sexual dysfunction (especially anorgasmia) were found to be between 41% and 96% [38]. In contrast, desipramine and nortriptyline appear to induce lower rates of sexual dysfunction. Clomipramine has also been successfully used in the treatment of patients with premature ejaculation [39–47]. In one study, paroxetine was found to be more effective in delaying ejaculation time [48]. Among the tricyclic antidepressants, amoxapine has been associated with painful [49] and retrograde ejaculation [50]. Spontaneous orgasms and painful ejaculation have been reported with clomipramine [23].

(II) SSRIs

All SSRIs (selective serotonin reuptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) can cause delayed ejaculation, reduced sexual desire, inhibit or make it difficult to achieve orgasm, and also difficulties in reaching and/or maintaining an erection. The first reports of sexual dysfunction induced by SSRIs related mostly to fluoxetine [51–54].

The reported rates of sexual dysfunction in men and women taking SSRIs, measured using the Rush sexual inventory, were 60% and 57%, respectively [55]. However, different rates have been reported in other research. For example, Montejo et al. [56] identified the following rates of SSRI-induced sexual dysfunction: citalopram 72.7% (48/66 patients), paroxetine 70.7% (147/208 patients), sertraline 62.9% (100/159 patients), fluvoxamine 62.3% (48/77 patients), fluoxetine 57.7% (161/279 patients). In contrast, Gregorian et al. [57] indicate lower rates of sexual dysfunction, between 30 and 60%, while Clayton et al. [58] report an even lower prevalence of between 36% and 43% between the different SSRIs: the same authors maintain that any differences in the sexual side effect profile of SSRIs, are not clinically significant. In support of this, comparative studies of SSRIs have generally not identified any statistical difference in their sexual side effect profile [10,21,58–62]: this finding also seems to be confirmed by the most recent reviews and meta-analyses [14,19,20,22,63,64]. Despite such strong evidence, a retrospective study in 2005 (conducted on only 47 patients) [65] seems to suggest an improvement (even more evident after dose reduction) of sexual dysfunction after a switch from some SSRIs (fluoxetine, paroxetine, citalopram, sertraline) and an SNRI (venlafaxine) to escitalopram. The double-blind study of Reimherr et al. [66] demonstrated (in men only) a higher percentage of sexual dysfunction in patients treated with the SSRI sertraline

compared to the group treated with the tricyclic antidepressant amitriptyline.

Among the SSRIs, a study on sertraline and paroxetine showed that there was a difference in sexual side effects between men and women: among men, a marked worsening of sexual functioning was reported, whereas in women, there was an improvement in sexual performance, due to an increase in desire and arousal [67]. Isolated cases of increased sexual desire [68], spontaneous orgasms and orgasms during exercise [23,69] have been reported with fluoxetine. Priapism has also been reported with citalopram, while increased desire and anorgasmia have been reported with sertraline [23].

Among the SSRIs, it appears that paroxetine, followed by citalopram and sertraline, are most likely to induce delayed ejaculation. In general, all SSRIs have been proposed as potentially useful in the treatment of premature ejaculation, due to this side effect [44,70–73]. Dapoxetine, a new SSRI whose exclusive indication is the treatment of premature ejaculation, has recently been marketed in some European countries [73].

(III) NARI (selective noradrenaline reuptake inhibitor)

Reboxetine: There is a low rate of reported sexual dysfunction for this antidepressant group [14,74–77]. However, there is insufficient published data in the literature to draw any definitive conclusions.

(IV) Antidepressants with dual action (on both serotonin and norepinephrine)

Among the antidepressants with dual action (on both serotonin and norepinephrine) we distinguish between:

(a) SNRIs (serotonin and noradrenaline selective reuptake inhibitors)

Venlafaxine: this drug inhibits orgasm and ejaculation in 12% of male subjects, therefore less frequently compared to conventional SSRIs, but more frequently compared to nefazodone, trazodone, mirtazapine or bupropion [15]. Kennedy et al. [78] came to similar conclusions, reporting that venlafaxine induced lower rates of sexual dysfunction compared to the SSRIs, but higher rates compared to moclobemide, thus placing it in an intermediate position between these 2 classes of antidepressants: the conclusions of this study must be interpreted with care because some of the statistically significant differences in sexual dysfunction occurred in women but not in men.

Montejo et al. [56] however, reported a high prevalence of side effects: 67.3% (37/55 patients), a prevalence that increases to 80% in a recent meta-analysis [19]. In contrast, this prevalence drops to 30% in research by Clayton et al. [58]. There are reports of increased libido, orgasm and spontaneous erections [79,80].

Venlafaxine has not been shown to be effective in the treatment of premature ejaculation [81].

Duloxetine: this drug appears to be superior to placebo in delaying ejaculation [82]: similar conclusions were reached by the review by Hirschfeld et al. [83], although the differences (measured using ASEX) between placebo and duloxetine were not significant. A comparison study [84] with escitalopram showed an incidence of sexual dysfunction after 8 weeks of treatment, of 33% for patients treated with duloxetine and 48.7% for those treated with escitalopram; however, after 12 weeks of treatment, no significant differences were found between the two patient groups. Delgado et al. found lower rates of sexual dysfunction for duloxetine compared with paroxetine [85]. Also, in the study by Nelson et al. [86], sexual dysfunction caused by duloxetine (46.4%) was significantly lower than that in the group of patients treated with paroxetine (61.4%).

Milnacipran: we did not find any clinical trials specifically designed to determine the sexual side effects of this antidepressant.

(b) NASS (noradrenergic and serotonergic antidepressant specific)

Mirtazapine: the majority of research indicates a low prevalence of sexual dysfunction [57,87–90]. Labbate [89] reports that although mirtazapine is noted for its tendency to cause less sexual dysfunction than SSRIs, this observation has only been made in non-randomized studies and has not been specifically tested in randomized clinical trials with placebo. In the study by Montejo et al. [56], the reported percentage of sexual dysfunction is 24.4% (12/49 patients). In the study by Gelenberg et al. [91], there is some weak evidence to suggest that a switch from an SSRI to mirtazapine may improve sexual functioning. However this data must be interpreted with caution, given the small sample size (19 patients) used in this open study. Similar considerations apply to the study by Versiani et al. [92], which found that the sexual side effect profile of mirtazapine was more tolerable than that of fluoxetine. The double-blind study by Wade et al. [93] also indicates less sexual side effects with mirtazapine compared to paroxetine. In an open label pilot study of depressed patients, an increase in sexual functioning was reported, especially in women [88]. The addition of mirtazapine was found to resolve SSRI-induced sexual dysfunction in four patients [94].

(V) NDRI antidepressants (norepinephrine-dopamine reuptake inhibitor), which have both dopaminergic and noradrenergic inhibitory activity

Bupropion: clinical efficacy studies estimate that sexual dysfunction secondary to treatment occurs in less than 3% of cases [15], while Modell et al. [95] indicate a percentage of 14%. There is some evidence to indicate that bupropion has a positive effect on sexual functioning [96,97], by increasing sexual desire [98,99], which leads to an improvement in psychosexual function [100]. The addition of bupropion during treatment with SSRIs seems to improve sexual side effects [101–105].

Dhillon et al. [106,107] have reported a more tolerable sexual side effect profile for bupropion compared to the SSRIs sertraline, fluoxetine, and escitalopram and compared to the SNRI venlafaxine: similar conclusions were reached by other researchers who compared bupropion with paroxetine [29,108], escita-

lopram [109], fluoxetine [110,111], sertraline [112,113] and venlafaxine [114].

(VI) Antidepressants with reversible inhibition of monoamine oxidase activity (RIMA)

Moclobemide: this drug is associated with a low prevalence of sexual dysfunction [21,78,115,116]. Philipp et al. [117] have argued that it has sexual enhancing effects, increasing sexual desire in 18% of patients. In a small open study (conducted on only 5 patients), a switch from fluoxetine to moclobemide led to a resolution of sexual dysfunction [118].

(VII) Antidepressants with irreversible monoamine oxidase inhibitory activity (MAOI)

Phenelzine, isocarboxazid and tranylcypromine: Sexual dysfunction associated with MAOIs includes reduced sexual desire, erection difficulties, and a reported incidence of between 20% and 40% of delayed orgasm and inhibited ejaculation [2,15,35]. A case of priapism has been reported following treatment with phenelzine [119]. There have been some reports of ejaculatory dysfunction with phenelzine (delayed ejaculation and failure to ejaculate). Similarly, anorgasmia in females has also been shown to be a common problem with phenelzine; it has also been shown to occur with isocarboxazid and tranylcypromine [120]. In recent years, a transdermal formulation of selegiline (a new monoamine oxidase inhibitor) has been approved in the USA as an antidepressant. Culpepper et al. report that the incidence of patient-rated sexual dysfunction is low and is comparable between selegiline and placebo treatment groups [121].

(VIII) Other antidepressants

(a) Mixed serotonergic activity (Nefazodone and Trazodone)

Nefazodone: the prevalence of sexual side effects is low (8%) according to the study by Montejo et al. [56]. In a double-blind comparative study, nefazodone was associated with significantly less sexual dysfunction compared to sertraline [122]. Similar conclusions appear to have been reached by Ferguson et al. [123]. One study found that nefazodone did not delay orgasm or ejaculation, unlike paroxetine and sertraline [124]. A case of spontaneous ejaculation and priapism has been reported [125].

Trazodone: seems to increase sexual desire and prolong time to orgasm [126,127], there has also been some documented cases of priapism [128], a medical emergency. In general, both nefazodone and trazodone are associated with a very low incidence of sexual dysfunction [15].

(b) Melatonergic agonist activity (MT1 and MT2) and to a lesser extent, serotonin 5-HT_{2C} receptor antagonist (agomelatine)

Agomelatine: this drug appears to be associated with very low rates of sexual side effects [129]. In a placebo-controlled study by Kennedy et al. [130], agomelatine was shown to have a lower tendency to cause sexual dysfunction in patients with major depressive disorder compared with venlafaxine, although this difference did not reach statistical significance. In the study by Montejo et al. [131], volunteers who received agomelatine showed a lower rate of sexual dysfunction compared to those taking paroxetine.

(c) Adenosylmethionine, gepirone, St John's Wort (*Hypericum perforatum*), tianeptine, vilazodone

An open label study has suggested that switching to *tianeptine* (a selective serotonin uptake enhancer, with structural similarities to the tricyclic antidepressants) can help to alleviate sexual dysfunction caused by other antidepressants (clomipramine, paroxetine, sertraline and fluoxetine) [132]. In the randomized, double-blind trial of Dording et al. [133], men treated with adjunctive *adenosylmethionine* had significantly lower erectile dysfunction at endpoint than those treated with adjunctive placebo. We did not find any clinical trials specifically designed to measure sexual side effects induced by adenosylmethionine or *St John's Wort* (*Hypericum perforatum*).

Gepirone: this new 5HT1A partial agonist, seems to improve sexual functioning in depressed men [134]. The new antidepressant *vilazodone* (with both selective serotonin reuptake inhibitor and 5HT1A partial agonist properties) seems to have a low incidence of adverse effects on sexual functioning [135].

Discussion

▼
The existing research on sexual dysfunction caused by antidepressive medication is often limited due to epidemiological aspects and methodological flaws of the research.

With regard to antidepressant therapy (especially the SSRIs), the prevalence of sexual dysfunction reported in the literature ranges from as low as 10% to as high as 80% [4,23]. There are many reasons for the discrepancy in reported prevalence rates, most however are related to methodological research flaws [4,21], some of which include the following:

1. The failure by researchers to adopt a standard definition for sexual dysfunction has been a particular problem, with the result that epidemiological data varies greatly between studies. Also, the definitions used for sexual dysfunction are often unclear or imprecise (e.g., "abnormal ejaculation", "changes in libido").

The classification of sexual dysfunction as proposed by ICD-10 and DSM-IV-TR (both of which receive greatest international consensus) is rarely used. Similar considerations apply for other proposed classifications [136,137]. It should be noted that even DSM-IV-TR definitions have been subject to criticism [138,139] and that revised definitions for sexual dysfunction have been suggested for the DSM-V diagnostic criteria [140].

DSM 5 is not due to be published until May 2013, however, the "proposed revision" of "DSM 5 Development" (available online at: <http://www.dsm5.org/Pages/Default.aspx>, accessed on 10 February 2010) proposes the following new diagnostic categories:

- ▶ Sexual interest/arousal disorder in women, which includes previous diagnoses of hypoactive sexual desire disorder (DSM IV code 302.71) and female sexual arousal disorder (DSM IV code 302.72).
- ▶ Sexual interest/arousal disorder in men.
- ▶ Genito-pelvic pain/penetration disorder, which includes previous diagnoses of vaginismus (not due to a general medical condition) and dyspareunia (not due to a general medical condition).

2. Some researchers have used the term "libido," which unfortunately does not determine which specific phase of the human sexual response is affected by the sexual dysfunction. In fact, the

term "libido" is very generic and does not discriminate between the various phases of the sexual response cycle [21]. In this review the authors have tried to avoid the use of the term "libido," retaining it only in cases where it was used in the original publication.

3. Despite a vast amount of literature on the subject, only a small amount of research has intentionally set out to investigate sexual dysfunction caused by antidepressants: in most studies, the prevalence of sexual dysfunction caused by antidepressants was neither considered as a primary or a secondary goal of research. In addition, much of the available data was collected using non-standardized or non-uniform methods (controlled clinical trials, post marketing surveys, case reports, etc.) [21]. The identification of sexual dysfunction often relies on the spontaneous disclosure by patients rather than through the use of direct questioning and/or the use of specific rating scales and questionnaires [26,141].

Other methodological limitations need to be carefully considered when interpreting research findings: this applies equally to comparative studies (i.e., studies comparing 2 or more active agents) and non-comparative studies, conducted in mixed populations of patients taking antidepressants for depression or anxiety disorders [21]. Regarding non-comparative studies, in 2002 Montgomery et al. [21], concluded that it is impossible to make reliable comparisons between these studies. They include patients with depression of varying severity, as well as patients with and without anxiety disorders. No two studies have used the same method of assessing sexual dysfunction, which varied from spontaneous descriptions of specific problems, to the use of non-validated questionnaires. In fact, it is still the case that few recent studies have used specific validated rating scales for assessing sexual dysfunction.

4. The various psychometric rating scales (e.g., **ASEX**: Arizona Sexual Experience Scale; **CSFQ**: Changes in Sexual Functioning Questionnaire; **DSFI**: Derogatis Sexual Function Inventory; **PRSexDQ**: Psychotropic-Related Sexual Dysfunction Questionnaire; **RSI**: Rush Sexual Inventory; **Sex FX**: Sex Effect Scale; **UKU**: Udvalg for Kliniske undersøgelser; etc.) have different sensitivity levels: a recent analysis of the sensitivity of these scales revealed that rates of sexual dysfunction appeared to vary across studies depending on the rating scale used. Some rating scales (e.g., CSFQ) seem to have a greater sensitivity than others. It also appears that the assessment of patients using direct questions rather than specific questionnaires, reduces the ability to correctly diagnose drug-induced sexual dysfunction. Similar considerations appear also to apply to the research on sexual dysfunction induced by anti-psychotic medication [19,20,142,143].

It should be highlighted that relatively few double blind studies have been conducted using any of the above specific rating scales. Although, many studies have been published, only a few used a validated scale for assessing sexual dysfunction and the majority lacked a baseline or placebo control group.

5. In those studies that did not use a specific scale for measuring sexual functioning, the criteria for defining sexual dysfunction or the criteria for attributing it to a specific phase (rather than to another) of the sexual response cycle is often unclear.

6. The sexual history of patients has not always been systematically explored in the various research projects. Furthermore, a recent published literature review, conducted on 79 clinical trials showed that studies published since 2000 reported a higher percentage (48.6%) of drug-induced sexual dysfunction com-

pared to studies published before the year 2000 (in which the percentage drops to 18%) [12].

7. An additional problem is the difficulty in distinguishing and identifying drug-induced sexual effects from the consequences of suffering from a psychiatric disorder, which may in itself have a direct heavy impact on relationships and sexual function [144]: it is important to assess both whether and to what extent, sexual dysfunction represents the expression of an underlying psychiatric disorder. Unfortunately, many studies do not provide data on sexual function prior to the commencement of pharmacological treatment. To understand the relationship between sexual dysfunction and medication, it is necessary to obtain information on baseline sexual functioning (in particular, before the onset of any psychiatric disorder) as well as level of sexual functioning before and after the initiation of any drug treatment. Also, the fact that sexual dysfunction is a common problem in the general population, should not be overlooked [145].

8. Cultural and social factors, such as people's expectations about their level of sexual functioning and their willingness to discuss the subject with a health professional, can vary greatly across different cultures [2]. Many terms used to define sexual dysfunction are subjective and depend on what one considers "normal." Cultural factors, therefore, influence reports on the incidence of sexual dysfunction, which may also vary over time in the same population [21].

9. Recent evidence has shown that doctors tend to underestimate the prevalence of sexual dysfunction in depressed patients [146, 147].

Despite these research methodological flaws, there is consistent evidence to suggest that all antidepressants can cause some sexual dysfunction.

Treatment of Antidepressant-Induced Sexual Dysfunction

A number of treatment approaches have been suggested for the management of sexual dysfunction caused by antidepressants. It is worth highlighting that adding or switching to other medication may be associated with some disadvantages, for example, unwanted side effects (sometimes significant) and the inconvenience of having to take additional therapy, which in turn may even lead to reduced or impaired compliance. The treatment strategies, outlined below, should be carefully evaluated on a case by case basis and due consideration should be given to non-pharmacological interventions. It should also be noted that, the evidence to support these strategies is limited, given that few studies used a double-blind study method [14, 60, 148–150]. In addition, studies have sometimes arrived at contrasting conclusions, as in the case of the study by Michelson et al. [151], which demonstrated that neither bupropion nor amantadine were effective in the treatment of sexual dysfunction induced by fluoxetine. Similar conclusions were found by Wheatley [152], who reported no significant differences between *Ginkgo biloba* and placebo.

Some recommended approaches for the management of sexual dysfunction induced by antidepressants include the following:

1. Wait for a spontaneous reduction of side effects over time.
2. Reduce dose of drug.
3. Arrange a temporary drug reduction or a suspension of drug for 2 days in the week (so-called "therapeutic vacation" or

"drug holiday"). This strategy does not apply to fluoxetine, due to its longer half-life.

4. Switch to a different antidepressant drug with fewer sexual side effects, such as bupropion, mirtazapine, or nefazodone.
5. Add a symptomatic therapy [28, 151, 155–157], including other antidepressants (bupropion, nefazodone or mirtazapine), partial serotonergic agonists and also partial alpha-noradrenergic antagonist (buspirone), serotonin antagonist (cyproheptadine), alpha-adrenergic antagonist (yohimbine), dopaminergic agonists (amantadine, lisuride, bromocriptine), psychostimulant dopamine agonists, (methylphenidate and dextroamphetamine), cholinergic enhancers (neostigmine, bethanechol), phosphodiesterase inhibitors (sildenafil, tadalafil, vardenafil) or herbal medicines ("*Ginkgo biloba*" [152]; "maca root:" Peruvian Ginseng [153]; saffron: "*Crocus sativus*" [154]). However, among these, the only treatment shown to be of benefit in randomized controlled trials, has been the addition of other antidepressants with a more tolerable sexual side effect profile (such as bupropion or nefazodone) and the addition of phosphodiesterase inhibitors for erectile dysfunction [149].

Sexual Dysfunction Induced by Antidepressants: Conclusions

Although there is extensive evidence that antidepressants cause sexual dysfunction in both men and women, it is difficult to estimate the exact prevalence. The great variation in methodological approaches makes it extremely difficult to systematically review the literature on the prevalence and incidence of antidepressant-associated dysfunction: it is not surprising that reported rates of sexual dysfunction induced by antidepressants fluctuates widely.

Existing literature confirms that sexual dysfunction is a possible adverse event associated with the use of any antidepressant. However, some studies suggest that antidepressants such as agomelatine, bupropion, mirtazapine, moclobemide and nefazodone are not associated with increased sexual side effects when compared to placebo, even if the data supporting this is only replicated consistently for bupropion [10, 19, 20, 143].

The findings of this review confirm that sexual dysfunction induced by antidepressants is a common problem, with notable associations among patients being treated for depression with SSRIs or SNRIs.

The impact of antidepressant-induced sexual dysfunction negatively affects quality of life [11, 62]; has potential implications for patient adherence to medication and the success of antidepressant treatment.

Routine enquiry about sexual dysfunction during clinical interviews at follow-up is essential for drug compliance and disease prognosis.

Various strategies have been proposed to manage sexual dysfunction associated with the use of antidepressants.

Conflict of Interest

The authors declare no conflicts of interest.

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