

Impact of Antidepressant Drugs on Sexual Function and Satisfaction

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Abstract Pleasurable sexual activity is important in many human relationships and can provide a sense of physical, emotional and social well-being. Depressive symptoms and depressive illness are associated with impairments in sexual function and sexual dissatisfaction in untreated and treated patients. Most currently available antidepressant drugs are associated with development or worsening of sexual dysfunction in a substantial proportion of patients. Sexual difficulties during antidepressant treatment often resolve as depression lifts, but can persist over long periods, reducing self-esteem and affecting mood and relationships adversely. Sexual difficulties during antidepressant treatment typically have many possible causes but the incidence and nature of dysfunction varies between drugs. Many interventions can be considered when managing sexual dysfunction associated with antidepressants but no approach is ‘ideal’. Because treatment-emergent sexual difficulties are less frequent with certain drugs, presumably related to differences in pharmacological properties, and since current interventions are suboptimal, a lower incidence of sexual dysfunction is a relevant tolerability target when developing novel antidepressants.

Key Points

Sexual dysfunction is common in the general population and more common in individuals with depression.

Many antidepressants can worsen sexual function and satisfaction, and this effect is more likely with certain antidepressants. Antidepressant treatment can also improve sexual function, particularly so in patients who respond to antidepressant treatment.

Evidence for the effectiveness of interventions to manage sexual dysfunction in depressed patients is limited and none of the current approaches should be considered ‘ideal’.

1 Introduction

Depressive symptoms and depressive illness are associated with impairments in sexual function and sexual dissatisfaction in untreated and treated patients. Most currently available antidepressant drugs are associated with the development or worsening of sexual dysfunction in a substantial proportion of patients, but in other patients sexual function improves as depression lifts. This review examines the epidemiological associations of sexual problems with depressive symptoms, beneficial and detrimental changes in sexual functioning during antidepressant treatment, the assessment and management of sexual difficulties in depressed patients, and the target of reduced sexual dysfunction in the development of new antidepressant treatments.

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2 The Relationship Between Reported Sexual Difficulties and Depressive Symptoms

Sexual problems are common in women and men in all societies but more frequent among older individuals and in those with chronic medical conditions [1, 2]. The Global Survey of Sexual Attitudes and Behavior, of over 27,000 men and women aged 40–80 years, found ‘early ejaculation’ (i.e. rapid or premature ejaculation) to be the most common sexual dysfunction in men, affecting 14 % of men, with ‘erectile difficulties’ having a prevalence of 10 %, and all sexual dysfunctions in men being more common with older age [3]. The Men’s Attitudes to Life Events and Sexuality Study, of similar size but among men aged 20–75 years, found the prevalence of ‘erectile dysfunction’ to be 16 %, the proportion again being greater in older men and in individuals with depression, cardiovascular disease and hypertension [4]. The Women’s International Study of Health and Sexuality, in over 4500 women aged 20–70 years, found ‘hypoactive sexual desire disorder’ to have a prevalence range of 16–46 %, in premenopausal to surgically postmenopausal women [5]. The presence of a reported concern about an aspect of sexual function or satisfaction does not necessarily indicate the presence of a ‘disorder’ [6], for which the presence of key symptoms, subjectively perceived difficulties and persistent dissatisfaction are all important criteria [7]. For example, while the Third National Survey of Sexual Attitudes and Lifestyles (Natsal-3), in over 15,000 individuals aged between 16 and 74 years, found that 41.6 % of men and 51.2 % of women reported problems in sexual response, self-reported distress about sexual life was much less frequent (9.9 and 10.9 %, respectively). In Natsal-3, after adjustment for potential confounders, the presence of depressive symptoms was the only specific health condition associated with low sexual satisfaction [8, 9].

Depressive symptoms are so closely interrelated with sexual difficulties and dissatisfaction that an international consensus statement on sexual dysfunction in patients with chronic illness recommended screening for depression [10]. Conversely, the findings of an examination of the bidirectional association between depression and sexual dysfunction suggest that depressed patients should be screened for the presence of sexual dysfunction [11]. A longitudinal epidemiological study found the prevalence of sexual problems in depressed individuals (those with major depression, dysthymia or recurrent brief depression) to be approximately twice the prevalence in controls (50 vs. 24 %) [12]. Recurrent depressive disorder seems to be especially associated with sexual problems as the United States Study of Women’s Health Across the Nation found that only women with recurrent episodes (and not those

having experienced only a single episode) were significantly more likely to report problems in sexual arousal, physical pleasure and emotional satisfaction when compared with controls [13]. The recently reported Netherlands Mental Health Survey and Incidence Survey-2 (NEMESIS-2) found the presence of 12-month mood disorders (and also the presence of an anxiety disorder or substance use disorder) was associated with a significantly reduced likelihood of reported sexual satisfaction [14].

Given the effects of depression on mood, energy, interest, capacity for pleasure, self-confidence and self-esteem, it should be expected that it would lower sexual interest and satisfaction; this effect seems more marked in younger patients [15]. Depressive symptoms commonly coexist with anxiety symptoms, which are associated with reported sexual difficulties and dissatisfaction [14, 16, 17], and with obsessive-compulsive symptoms, also associated with loss of sexual pleasure and sexual dissatisfaction [18, 19]. Nonetheless, depression can exert an adverse effect on all phases of the sexual response, including the ability to achieve and maintain penile erection, to attain adequate vaginal lubrication, and to achieve ejaculation or orgasm [20]. Most antidepressants can exert unwanted effects on sexual function and satisfaction but the adverse effects of depression itself (and of comorbid mental or physical disorders and concomitant medication) are often overlooked when considering the management of patients with sexual dysfunction associated with antidepressant treatment.

3 Worsening of Sexual Function During Antidepressant Treatment

It has proved difficult to accurately identify the incidence of ‘treatment-emergent’ sexual dysfunction (which connotes both the worsening of pre-existing problems and the development of new sexual difficulties in previously untroubled patients) during treatment with antidepressants. Two international studies of the prevalence of sexual dysfunction in depressed patients who were prescribed either a selective serotonin reuptake inhibitor (SSRI) or serotonin-noradrenaline reuptake inhibitor (SNRI), which both accounted for the presence of self-reported sexual problems before starting the antidepressant and of the potential effects of concomitantly prescribed medication implicated in causing sexual difficulties, indicated that between 27 and 65 % of female patients and 26 and 57 % of male patients experienced either a worsening of pre-existing difficulties or the emergence of new sexual difficulties in the early weeks of treatment, with the differences in prevalence between countries probably reflecting variations in case ascertainment and local clinical practice [21, 22].

Studies of the incidence of treatment-emergent sexual dysfunction with differing antidepressants should ideally be prospective, randomised, double-blind and placebo-controlled, and conducted in defined diagnostic groups, with detailed assessments of sexual function at baseline and follow-up. Sexual dysfunction should be assessed with a reliable, valid and sensitive rating scale, rather than relying on spontaneous reports or on answers to open questions that can be interpreted variably. In studies that involve direct comparisons between drugs, they should be prescribed at doses of equivalent efficacy. Few investigations of treatment-emergent sexual dysfunction meet these criteria. Perhaps consequently, the findings of meta-analyses provide rather limited evidence to conclude that antidepressant drugs differ in the risk for worsening sexual function.

An early meta-analysis that included studies with differing designs (incorporating open-label, double-blind, cross-sectional and retrospective investigations) found that 'treatment-emergent sexual dysfunction' was no more common with the antidepressants agomelatine, amineptine, bupropion, moclobemide, mirtazapine or nefazodone than with placebo, in marked contrast to the situation with other antidepressants; all other antidepressants were significantly more likely to be associated with 'sexual dysfunction' (as a unitary category) than placebo, and nearly all were significantly more likely to be associated with dysfunction in each phase of the sexual response than placebo [23]. A meta-analysis of the efficacy and tolerability of acute treatment of major depressive episodes with 'second-generation' antidepressants found that bupropion was associated with a significantly lower rate of treatment-emergent sexual dysfunction than that with the SSRIs escitalopram, fluoxetine, paroxetine or sertraline [24], which may reflect the predominantly noradrenergic-dopaminergic mechanism of action of bupropion [25]. A more recent meta-analysis of 58 randomised controlled trials and 5 observational studies found only minor differences between most antidepressants, although with relative disadvantages for paroxetine and venlafaxine and relative advantages for bupropion [26]. A systematic review of the relative efficacy and tolerability of mirtazapine and comparator antidepressants in the acute treatment of major depressive episodes found that mirtazapine is less likely to cause adverse sexual effects than other antidepressants [27], possibly reflecting antagonist effects at α_2 -adrenergic receptors and 5-HT_{2C} receptors [28].

The findings of randomised controlled trials suggest that some novel antidepressants may have a relatively low propensity for adverse effects on sexual function. For example, randomised controlled trials with agomelatine suggest it has fewer adverse effects on sexual functioning

than other antidepressants, which is probably due to its antagonist effects at the 5-HT_{2C} receptor, rather than the agonist effects at melatonin receptors [29–31], although the absence of effects on nitrenergic relaxation of corpus cavernosum smooth muscle may also be relevant [32]. Vilazodone appears to have a low incidence of spontaneously reported adverse effects on sexual function, which may be related to partial agonist effects at the 5-HT_{1A} receptor. It does not differ from placebo in improvement of sexual function during acute treatment of major depressive episodes, and the 'number needed to harm' for sexual adverse effects has been estimated as 7 in men, and 23 in women [33–35]. Treatment with the novel and 'multimodal' antidepressant vortioxetine is associated with a low incidence of reported adverse effects on sexual function in men (3–5 %) and women (1–2 %), which may be partly related to its antagonist effects at the 5-HT₃ receptor and to indirect effects in increasing the availability of dopamine and noradrenaline [36].

4 Neuroimaging of Sexual Dysfunction with Antidepressants

Increased activation of multiple but varying brain areas is seen in the different phases of the human sexual response [37, 38]. In functional magnetic resonance imaging (fMRI) studies using the blood oxygenation level-dependent (BOLD) technique, depressed but untreated women showed evidence of decreased activation in the hypothalamus, septal area, anterior cingulate gyrus and parahippocampal gyrus when exposed to visual erotic stimuli [39], whereas untreated depressed men with sexual dysfunction showed decreased activation in the hypothalamus, thalamus, caudate nucleus, and superior and inferior temporal gyri [40]. In an fMRI study, administration of fluoxetine (and, to a lesser extent, mirtazapine) was associated with reduced activation of the anterior cingulate cortex in response to visual erotic stimulation in male depressed patients [41]. In another fMRI study, paroxetine, but not bupropion, was associated with reduced activation of the ventral striatum and ventral tegmental area in healthy male volunteers [42], and, in a resting-state fMRI study in healthy volunteers, sexual dysfunction with paroxetine was associated with functional connectivity between the pregenual anterior cingulate cortex, midbrain and insula to the sublenticular extended amygdala [43]. Although these small studies have produced intriguing findings, little is known about the neuroimaging correlates of the presence or emergence of sexual dysfunction in depressed male or female patients, or about how these correlates might change with resolution of sexual function and satisfaction.

5 Assessing Sexual Difficulties in Depressed Patients

Patients and health professionals often find it embarrassing to mention and discuss sexual symptoms, and consultation [8, 44] and recognition rates in primary medical care are low [45]. Reliance on the spontaneous reporting of sexual adverse events can lead to a substantial underestimate of the prevalence of sexual problems [46, 47]. Comprehensive evaluation of a depressed patient who reports sexual difficulties whilst undergoing antidepressant treatment can be a lengthy process. Assessment may be aided by using screening and severity questionnaires [48] but these cannot fully substitute for a sensitive but detailed assessment. The Arizona Sexual Experiences Scale, the Changes in Sexual Functioning Questionnaire, the Psychotropic-Related Sexual Dysfunction Questionnaire and the Sex Effects Scale all have adequate psychometric properties (including validity, reliability and sensitivity to change) and have been recommended for the assessment of sexual function and satisfaction before and during antidepressant treatment [48].

Risk factors for developing sexual dysfunction during antidepressant treatment include male sex, older age, lower academic achievement, absence of full-time employment, physical ill-health, multiple drug treatment, and troubled interpersonal relationships, but only some of these are amenable to intervention. Interindividual variation in pharmacokinetic parameters may be important as 'poor metaboliser' status for cytochrome P450 2D6 contributes to sexual dysfunction with paroxetine [49, 50], as does a genetic variation in P-glycoprotein which affects the transfer of paroxetine across the blood-brain barrier [51].

6 Improvement in Sexual Function During Antidepressant Treatment

Not all sexual effects of antidepressants are unwanted in all patients. For example, although behavioural approaches are effective in most patients [52], many men (including those without depression) troubled by persistent premature ejaculation can benefit from treatment with either the tricyclic antidepressant clomipramine or SSRIs on either a daily or 'as required' basis [53]. Widely available SSRIs are sometimes prescribed 'off-label' to non-depressed men with premature ejaculation, but the very-short-acting SSRI dapoxetine has proven efficacy in treating premature ejaculation, in either daily dosing or 'on demand' dosage [54], and has been approved for this indication in more than 50 countries (although not currently in the US). It has similar efficacy to paroxetine [55], although may be less

well tolerated [56]. In addition, the findings of a systematic review of randomised, placebo-controlled trials with trazodone (which has partial agonist effects at 5-HT_{1A} receptors and antagonist effects at 5-HT_{2A} and α 1-adrenergic receptors) indicate that when prescribed at a higher daily dose (150–200 mg) it can be efficacious in reducing 'psychogenic' erectile dysfunction [57], although men should be warned of the rare (approximately 1:6000–10,000) but potentially serious complication of priapism (prolonged painful erection) [58].

Although many patients experience treatment-emergent sexual dysfunction whilst taking an antidepressant [18, 19], in others the reduction of depressive symptoms through successful treatment can be accompanied by reported improvements in sexual desire and satisfaction [59, 60]. An improvement in sexual function appears more common among patients who respond to antidepressant treatment [61]. It is often argued that treatment-emergent sexual dysfunction is a cause of non-adherence with antidepressants, but the proportion of patients who stop treatment because of sexual problems is not established [62, 63], and neither is the time course of sexual dysfunction in patients who continue with antidepressant treatment [64].

7 Managing Sexual Dysfunction in Depressed Patients

Many interventions have been proposed for managing patients who report sexual dysfunction associated with antidepressant drugs but the number of randomised, placebo-controlled trials is low, there is limited randomised controlled data evaluating the effectiveness and acceptability of psychological interventions [65], and none of the current approaches can be considered 'ideal' [66].

If patients are concerned about preserving their usual sexual functioning, the choice of an antidepressant that is thought to have fewer adverse effects on sexual functioning is reasonable, when other considerations allow. However, some of these antidepressants have other side effects, limited availability, or questionable efficacy. Sexual side effects of at least some antidepressants may be dose-related, and a reduction in daily dose is therefore commonly adopted as a first-line approach to management [67], although dose reduction may contribute to a relapse of symptoms and should only be considered when patients have achieved full remission of depressive symptoms and after satisfactory completion of continuation treatment. Regular brief interruptions of treatment (sometimes denoted 'drug holidays') have been proposed as potentially useful [68], but sexual function will improve in only a proportion of patients, and only with some antidepressants. Furthermore, depressive symptoms may worsen and

discontinuation symptoms can be troublesome, making this approach potentially hazardous and consequently rather uncommon [66].

Many adjuvant interventions have been proposed for relieving sexual dysfunction associated with antidepressant drugs but few compounds have been subjected to rigorous evaluation. Randomised, placebo-controlled trials provide evidence of possible efficacy for bupropion and olanzapine [69], testosterone gel [70], and the phosphodiesterase-5 inhibitors sildenafil (both in male and female patients [71, 72]) and tadalafil [73]. Comparative studies are rare but a placebo-controlled study found no evidence of efficacy for augmentation with mirtazapine or yohimbine in female patients [74]. Augmentation of antidepressants with the antipsychotic drug aripiprazole can improve sexual interest and satisfaction in depressed women, which seems independent of the improvement in depressive symptoms [75]. Although switching from one antidepressant drug to another seems reasonable and is commonly adopted in practice [67], placebo-controlled evidence of efficacy for this approach rests on a single study of switching from sertraline to nefazodone [65]. Switching away from one drug to another may lead to discontinuation symptoms, and the replacement drug may prove less effective in controlling depressive symptoms [69]. A single study has found that regular exercise prior to sexual activity improved sexual desire and global sexual functioning in depressed women taking antidepressants [76].

8 Phosphodiesterase-5 Inhibitors in Depressed Patients

Nitric oxide is involved in the physiology of the male and female sexual response. In men, nitric oxide in the corpus cavernosum of the penis binds to guanylate cyclase receptors, which results in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation (vasodilation) in the intimal cushions of the helicine arteries, which in turn leads to vasodilation, increased blood flow into the spongy tissue of the penis, and subsequent erection. The adverse effect of the SSRI escitalopram on erectile function in rats may be due to reduced nitric oxide bioavailability mediated by increased nicotinamide adenine dinucleotide phosphate oxidase activity and reactive oxygen species production [77]. Sildenafil, tadalafil and vardenafil are potent and selective inhibitors of cGMP-specific phosphodiesterase type 5 (PDE-5), which is responsible for degradation of cGMP in the corpus cavernosum. The molecular structure of sildenafil resembles that of cGMP, and sildenafil acts as a competitive binding agent of PDE-5 in the corpus cavernosum, resulting in more cGMP and facilitation of erection

[78]. In women, the role of nitric oxide and its interplay with oestrogen is less well understood, but the PDE-5 inhibitor enhancement of nitric oxide-cGMP in non-adrenergic, non-cholinergic signaling for women seems similar to men, and nitric oxide release results in vasodilatation in clitoral and vaginal tissues [79].

The findings of a series of randomised, placebo-controlled trials demonstrate that PDE-5 inhibitors are efficacious in resolving sexual dysfunction associated with antidepressants [71–73]. Studies of men with erectile dysfunction and depressive symptoms (but not undergoing antidepressant treatment) have also shown that prescription of PDE-5 inhibitors is often accompanied by a reduction in depressive symptom severity, an enhancement of quality of life, and improvement in interpersonal relationships [80–82]. Furthermore, studies in animal models suggest nitric oxide activity is an important vulnerability factor in the Flinders rat depressive phenotype [83]; that passage of PDE-5 inhibitors across the ‘blood-brain barrier’ can occur [84]; that sildenafil has antidepressant-like effects after central muscarinic receptor blockade [85]; and that sildenafil administration can reverse reduced social interactive behaviour [84]. Treatment with PDE-5 inhibitors is often helpful in the management of patients with sexual dysfunction associated with antidepressants, but side effects such as headache, dyspepsia, and visual disturbances, as well as the need for cautious use in patients with cardiovascular disease, are all potential limitations.

9 Reduced Sexual Dysfunction as a Target in Pharmacotherapy and Drug Development

Increased knowledge of the influence of genetic polymorphisms on treatment tolerability might encourage the use of laboratory approaches to identify subgroups of patients at particular risk of developing sexual side effects of antidepressant treatment. For example, a genome-wide association study associated with the United States STAR*D programme (for managing resistant depression) found that ten single nucleotide polymorphisms (SNPs) may mediate the effects of bupropion on sexual function [86]. In addition, a genome-wide association study conducted in Japan suggested that 11 SNPs are associated with sexual dysfunction with the SSRIs fluvoxamine and paroxetine and the SNRI milnacipran [87]. Smaller studies have suggested that sexual dysfunction associated with SSRIs may be influenced by both the GG [88] and AA [89] genotype of the 5-HT_{2A} receptor 1438 G/A polymorphism. By contrast, treatment-emergent sexual dysfunction is not associated with the 5HTTLPR polymorphism, a region in the gene that encodes for the serotonin transporter (for escitalopram or nortriptyline) [90], or with the 2A-1438 G/A SNP [91].

Management options in the future might be extended by developing novel antidepressants with reduced risks of causing sexual problems. These might include further compounds with effects at the 5-HT_{1A} receptor, with anti-inflammatory effects, or with noradrenaline reuptake inhibitor properties, or even based on findings from investigations of complementary approaches, such as the use of *S*-adenosyl-L-methionine (SAME) [92], Maca root ('Peruvian Ginseng') [93], saffron [94, 95] and *Rosa damascena* oil [96]. The mechanisms underlying sexual dysfunction during treatment with lithium in patients with bipolar disorder are not established but a recent placebo-controlled trial found that aspirin was efficacious in reducing sexual dysfunction [97], suggesting that compounds with anti-inflammatory effects might be beneficial [98]. Evidence relating to the effects of drugs acting on the 5-HT_{1A} receptor is mixed. The partial agonist buspirone can reduce sexual dysfunction associated with SSRIs [99, 100], and the partial agonist gepirone can improve sexual functioning in depressed men, independent of antidepressant or anxiolytic effects [101]. However, an experimental 5-HT_{1A} full agonist (VML-670) was not efficacious in reversing sexual dysfunction associated with fluoxetine or paroxetine [102], whereas preclinical studies suggest that selective 5-HT_{1A} antagonists can both prevent and reverse fluoxetine-induced sexual dysfunction in rats [103]. Although the selective noradrenaline reuptake inhibitor reboxetine has limited antidepressant efficacy [104], it probably has fewer adverse effects on sexual function than SSRIs [59, 105, 106]. Development of compounds with noradrenaline reuptake inhibitory properties as part of their mechanism of action has resulted in mixed findings. A proof-of-concept, placebo-controlled study with the novel 'triple reuptake inhibitor' amitifadine indicated a low propensity for worsening sexual function in depressed patients [107], whereas the novel noradrenaline reuptake inhibitor LY22166884 was associated with significantly more sexual adverse events than placebo in a randomised controlled trial [108]. In the future, neuroimaging techniques may prove fruitful in identifying potential new antidepressants with reduced sexual adverse effects.

10 Conclusions

Pleasurable sexual activity is important in many human relationships and can provide a sense of physical, emotional and social well-being. Depressive symptoms and depressive illness are associated with impairments in sexual function and sexual dissatisfaction in untreated and treated patients, and the presence of sexual dysfunction confers an additional burden in depressed patients. At present, optimised management of patients with sexual

difficulties who are undergoing antidepressant treatment relies on making the best use of currently available treatments. This comprises making careful but sensitive enquiries to establish whether sexual difficulties are present; choosing antidepressants with a lower likelihood of worsening sexual dysfunction, when other considerations allow; reducing antidepressant dosage judiciously, when this is feasible; and becoming familiar with the potential benefits and drawbacks of phosphodiesterase-5 inhibitors and other adjuvant treatments.

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Compliance with Ethical Standards

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