Antidepressant-induced sexual dysfunction

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Sexual dysfunction can be subdivided into disorders of sexual drive (usually loss of libido), disorders of arousal and disorders of orgasm and ejaculation, as well as other problems including dyspareunia and priapism.[1]

An extensive literature search was undertaken to explore the evidence about antidepressant-induced sexual dysfunction. This included an online search of the MEDLINE, EMBASE, PubMed and Cochrane databases, along with relevant websites and texts and reference lists from identified articles.

Summary

- Sexual dysfunction is a frequent, potentially distressing, adverse effect of antidepressants and a leading cause of medication non-adherence.
- Sexual function should be actively assessed at baseline, at regular intervals during treatment, and after treatment cessation.
- Trials comparing the risk of sexual dysfunction with individual antidepressants are inadequate, but it is reasonable to conclude that the risk is greatest with selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), less with tricyclic antidepressants (except clomipramine) and mirtazapine, and least with moclobemide, agomelatine, reboxetine and bupropion.
- Management of antidepressant-induced sexual dysfunction requires an individualised approach (eg, considering other causes, dose reduction, addition of medication to treat the adverse effect, switching to a different antidepressant).
- Post-SSRI sexual dysfunction has been recently identified as a potential, although rare, adverse effect of SSRIs and SNRIs. Consider the possibility of post-SSRI sexual dysfunction in patients in whom sexual dysfunction was absent before starting antidepressants but develops during or soon after antidepressant treatment and still persists after remission from depression and discontinuation of the drug.

Incidence and prevalence

Between 50% and 70% of people with depression experience sexual dysfunction.[2,3] In some cases, sexual dysfunction itself can lead to depression.[4] The main type of sexual dysfunction that occurs as a result of depression is low sex drive, with disorders of arousal and orgasm or ejaculation occurring less commonly.[1] Adequate treatment of depression may improve sexual functioning (particularly libido) in some patients.[4]

However, many patients experience some disturbance of sexual function associated with antidepressant use.[3] Large variations in methodological approaches in clinical trials make it difficult to estimate the exact incidence, which is further complicated by the overlap between sexual dysfunction and depression.[5,6] The incidence of selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction has been suggested to be as high as 80%.[7]

Antidepressant-induced sexual dysfunction has been identified as a leading cause of medication non-adherence[8] and is one of the most under-reported adverse effects associated with the use of antidepressants. For example, in a small survey study, 62.5% of men and 38.5% of women believed that their psychiatric medications were causing sexual dysfunction, and 27.5% of patients reported that they had stopped medication due to perception of sexual adverse effects.[9] Among patients experiencing sexual dysfunction with psychotropics, 50% said they never or infrequently discussed this issue with their doctor.[9] Another study, which included 344 patients being treated with SSRIs, found that there was a significantly higher incidence of sexual dysfunction when physicians asked the patients direct questions (58%) compared with patients spontaneously reporting sexual dysfunction (14%).[10] Therefore, it is important that clinicians actively monitor for sexual dysfunction.[11,12]

Symptoms of antidepressant-induced sexual dysfunction

Antidepressant-induced sexual dysfunction affects all phases of sexual activity, including desire, arousal and orgasm, in both men and women.[3,11,13–15] The most commonly reported adverse sexual effects in women taking antidepressants are problems with sexual desire (72%), sexual arousal (83%) and orgasm (42%).[3] Men tend to more frequently report problems with desire and orgasm rather than arousal.[4]

However, not all effects of antidepressants on sexual function are unwanted. For example, men with persistent premature ejaculation, including those without depression, may benefit from treatment with an SSRI.[16]

Mechanism for antidepressant-induced sexual dysfunction

The pathophysiology of sexual dysfunction is complex and poorly understood.[1,13,17] Serotonin, noradrenaline, dopamine and acetylcholine all have effects on both the brain and genitalia. Serotonin appears to be the main neurotransmitter that has negative effects on sex drive and sexual function, both centrally and peripherally.[1] In particular, the activation of post-synaptic serotonin (5-HT) 2A receptors in the central serotonergic system is considered a significant contributor to antidepressant-induced sexual dysfunction.[17] In contrast, dopamine and noradrenaline agonism may have positive effects on sex drive and arousal.[1]

Comparing the risk of sexual dysfunction between antidepressants

To compare the incidence of sexual dysfunction between differing antidepressants, studies should ideally be prospective randomised controlled trials with detailed assessment of sexual function at baseline and follow-up.

Sexual dysfunction should be assessed with a reliable, valid and sensitive rating scale, such as the Arizona Sexual Experiences Scale,[18] the Sex Effects Scale,[19] the Changes in Sexual Functioning Questionnaire[20] and the Psychotropic-Related Sexual Dysfunction Questionnaire,[21] rather than relying on spontaneous reports or answers to open questions. In studies involving direct comparisons between drugs, they should be prescribed at doses of equivalent

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efficacy.[16] Very few studies to date meet these criteria. Most available evidence is from meta-analyses, which are limited in their ability to make adequate comparisons of sexual dysfunction incidence. There have been more studies investigating SSRI-induced sexual dysfunction compared with other classes of antidepressants.[7]

A 2014 meta-analysis, including 58 randomised controlled trials and five observational studies, found it difficult to quantify comparative risks of sexual dysfunction with specific antidepressants.[2] The authors were only able to conclude that escitalopram and paroxetine had a higher risk of sexual dysfunction than some other antidepressants — escitalopram had a higher risk than fluoxetine and mirtazapine; paroxetine had a higher risk than fluoxetine, mirtazapine and venlafaxine — and that bupropion had a lower risk than some other antidepressants — escitalopram, paroxetine and sertraline.[2] The limitations in this meta-analysis include differences in how sexual dysfunction was assessed and the short term nature of included trials. Thus, the authors rated the overall strength of evidence for their findings as low.[2]

Box 1 provides a comparison of risk of sexual dysfunction with antidepressants based on currently available, although limited, evidence.

1 Risk of sexual dysfunction with antidepressants[2,4,7,8,11,13,14,22–38]

Class	Drug name	Risk
SSRIs	• Citalopram • Escitalopram • Fluoxetine • Fluvoxamine • Paroxetine • Sertraline	All SSRIs have a **high risk**. Limited evidence suggests that paroxetine and escitalopram may have the highest risk in this group
SNRIs	• Desvenlafaxine • Duloxetine • Venlafaxine	SNRIs have a **high risk**. Insufficient evidence to compare the risk between individual SNRIs, and between SNRIs and SSRIs. Duloxetine has been suggested to have a lower risk compared with venlafaxine, but further evidence is needed to clarify this
TCAs	• Clomipramine • Amitriptyline • Dosulepin (dothiepin) • Doxepin • Imipramine • Nortriptyline	Clomipramine has a **high risk** (similar to SSRIs) **Medium risk** with other TCAs; however, very few studies have evaluated risk with TCAs and how the incidence compares with SSRIs. Results to date have been inconsistent
RIMA or MAOI	• Moclobemide • Phenelzine • Tranylcypromine	**Low risk**; comparable to placebo. Data are limited These are associated with SD, but the incidence compared with SSRIs is unclear due to a lack of trials. Limited data suggest phenelzine has a greater risk than tranylcypromine
Others	• Agomelatine • Bupropion • Mirtazapine • Reboxetine • Vortioxetine	**Low risk**; comparable to placebo in trials **Low risk**; comparable to placebo in trials **Low to medium risk**; less than SSRIs **Low risk**; comparable to placebo **Medium to high risk**; less than duloxetine at doses of 5–10 mg, but not different to duloxetine at higher doses. Data are limited

MAOI = monoamine oxidase inhibitor; RIMA = reversible inhibitor of monoamine oxidase; SNRI = serotonin and noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant. ◆

Management of antidepressant-induced sexual dysfunction

It is important to assess sexual functioning before and after antidepressant initiation, at initial and subsequent visits.[3,39] Repeated measures provide important information about either decline in sexual function (due to medication adverse effects) or improvement (due to a reduction in depression).[3]

There are a number of strategies, listed below, that have been suggested for managing antidepressant-induced sexual dysfunction.

Consider other causes

Other causes or contributors to sexual dysfunction include the depression itself, alcohol use, diabetes, atherosclerosis, cardiac disease, and central and peripheral nervous system conditions. Other medications could also be associated with changes in sexual response (eg, antipsychotics, lithium, mood stabilisers, diuretics, β-blockers).[4,13]

Wait

In some cases, sexual dysfunction remits spontaneously over time.[3,4,7,10,40] Resolution, or at least moderate improvement, occurs in 6–12% of patients within 4–6 months despite continuing the antidepressant.[10] As it may take several months for the sexual dysfunction to improve with watchful waiting, this may not be practical for many patients, and medication non-adherence is a potential concern.[3,4] Consider this approach for patients with mild sexual dysfunction.[7]

Reduce dose

Sexual dysfunction is associated to some degree with antidepressant dose.[4,10] In a descriptive study of 344 patients taking an SSRI, 30 patients underwent a dose reduction (by 50%), resulting in sexual dysfunction improvement to some extent in 73% of patients.[10] Evidence for this approach is limited and reducing doses may result in decline of the condition being treated.[3,7,13,15,16] This approach could be considered if the condition being treated is well controlled, particularly if patients are taking high antidepressant doses and/or have other adverse effects.[3,7,16] Dose reductions should be small and slow, and not be reduced below the minimum recommended therapeutic dose.[7]

Change administration times

Planning sexual activities around times when serum drug levels are at their lowest, such as shortly before a dose or immediately after taking a medication, may be effective for some patients taking antidepressants with short half-lives.[3] Evidence for this is approach is lacking.[3,13,41]

Drug holidays

This involves stopping or reducing the dose of a short half-life antidepressant for 1–3 days per week. This was beneficial in some patients in one small study of 30 patients with paroxetine- or sertraline-related (but not fluoxetine) sexual dysfunction.[42] However, this approach may be associated with withdrawal reactions and worsening or return of the condition being treated, and may foster non-adherence. Drug holidays may be considered in patients with mild depression and

in those who would discontinue treatment because of sexual dysfunction.[3,7,13,16]

Switch to a different antidepressant

There are no trials comparing switching antidepressants with use of an augmentation or adjunctive treatment (see below) for antidepressant-induced sexual dysfunction. Switching antidepressants is often preferred over use of an augmentation or adjunctive treatment to improve adherence, to reduce the risk of adverse effects and drug interactions, and to reduce cost to the patient.[7] This approach is reasonable for patients who have only achieved modest benefit with the implicated antidepressant, or for patients with severe sexual dysfunction.[7] When switching antidepressants, it is important to consider whether a washout and/or tapering period is necessary.[16]

Switching between the same class

Few studies have evaluated the approach of switching between the same class (eg, switching from one SSRI or serotonin and noradrenaline reuptake inhibitor [SNRI] to another), and it is only likely to be of benefit in a small number of patients given that all SSRIs and SNRIs are associated with sexual dysfunction.[7,10] Escitalopram and paroxetine may have a higher risk, so switching from these agents to a different SSRI or SNRI could be considered.

Switching to an antidepressant with less risk of sexual dysfunction

Antidepressants that appear to have the lowest risk of sexual dysfunction are moclobemide, agomelatine, bupropion and reboxetine. Mirtazapine and possibly vortioxetine appear to have a lower risk of sexual dysfunction than SSRIs and SNRIs.[4,7,11,22,23] A small randomised controlled trial found improvement in sexual dysfunction when switching from an SSRI to vortioxetine compared with switching to escitalopram.[14] A case series and a descriptive study found sexual dysfunction resolved when switching from an SSRI to moclobemide (300–600 mg per day).[10,43] A small open study found benefit when switching from fluoxetine to bupropion for management of fluoxetine-induced sexual dysfunction.[44] Note that some of these agents are not subsidised through the Pharmaceutical Benefits Scheme and cost may be prohibitive for many patients.

Use an augmentation or adjunctive treatment

Adding in a second antidepressant may be reasonable in patients who have had only a partial response to an antidepressant but are experiencing sexual dysfunction, as adding a second antidepressant may also be effective in improving depression symptoms. However, this approach requires expert knowledge and close follow-up.[1] The risk of drug interactions and adverse effects (in some cases potential for serotonin toxicity) needs to be considered.

The addition of a non-antidepressant adjunctive treatment would be most reasonable for patients who have obtained substantial clinical benefit from the implicated antidepressant, and where sexual dysfunction is of moderate severity.

A Cochrane systematic review[45] that evaluated evidence for adjunctive pharmacotherapy in patients with antidepressant-induced sexual dysfunction concluded that, for women, the addition of bupropion at higher doses (ie, 150 mg twice daily) was the most promising approach studied to date.[45] Bupropion is not subsidised through the Pharmaceutical Benefits Scheme for this indication, and cost may be prohibitive for many patients. For men with antidepressant-induced erectile dysfunction, the addition of sildenafil or tadalafil appears to have the best evidence.[45]

Box 2 outlines the evidence for various augmentation and adjunctive treatments that have been investigated for antidepressant-induced sexual dysfunction.

Non-pharmacological treatments

Psychotherapy, including cognitive behavioural therapy and couples therapy, may be helpful.[15] Exercise before sexual activity may be effective in some patients, based on a single study involving 52 women with antidepressant-induced sexual dysfunction. In this study, 30 minutes of moderately intense exercise three times a week, scheduled immediately before sexual activity, improved sexual desire and global sexual function but had no effect on orgasm function or sexual satisfaction.[39]

Sexual dysfunction persisting after using serotonergic antidepressants

Sexual adverse effects of antidepressants usually persist for as long as medication is taken and it is generally presumed that they will resolve after it is discontinued.[66] However, recent literature has raised the possibility of antidepressant-induced sexual dysfunction occurring or continuing beyond SSRI and SNRI treatment cessation.[67–69]

Post-SSRI sexual dysfunction (PSSD) was first reported in the medical literature in 2006.[70] Following this, there have been a number of publications, including case reports, case series and possible cases reported to pharmacovigilance centres.[66–68,71–74] While PSSD has been largely unrecognised in research trials and professional communities, it is being increasingly identified in online communities.[71] The European Medicines Agency have recently acknowledged the potential for this adverse effect with SSRIs and SNRIs.[74]

PSSD includes decreased libido, genital anaesthesia, pleasureless or weak orgasm, erectile dysfunction, delayed ejaculation, loss of lubrication in women, and anorgasmia.[68–70,72,73] Of these symptoms, the most characteristic triad consists of genital anaesthesia, loss of libido, and erectile dysfunction. The incidence of PSSD is unknown.[69] The symptoms may be very distressing to patients and there are some documented cases of PSSD leading to attempted or completed suicide.[69,71,72]

The antidepressants that have most often been associated with PSSD are the SSRIs and SNRIs.[66] The time to onset of PSSD has ranged from days to years, and the duration of treatment with SSRIs and SNRIs has varied from a few weeks to a few years.[66] There appears to be no difference in likelihood of PSSD with abrupt compared with gradual discontinuation of the treatment.[73]

The diagnosis of PSSD is often very difficult, as sexual dysfunction is commonly associated with depression and other factors.[69] However, PSSD should be considered when patients report that sexual dysfunction was absent before starting antidepressants, still persists after remission from depression and discontinuation of the drug, and no other physical contributors linked to sexual dysfunction are present.[73]

Pathophysiology

The pathophysiology of PSSD is unclear; however, the following mechanisms have been suggested:[69]

2 Augmentation and adjunctive strategies for managing antidepressant-induced sexual dysfunction (SD)

Agent	Evidence	Comments
Bupropion	Adding bupropion to the offending antidepressant is the approach with most evidence and appears to be particularly helpful for women. There is some evidence of benefits in men, but it is not as robust as the evidence in women. Evidence includes a small open study and two small RCTs (with two studies finding a benefit of bupropion added to the SSRI).[44,46,47] A larger RCT that compared adding bupropion sustained release 150 mg twice daily with placebo in 218 women with SSRI-induced SD found bupropion to be significantly better than placebo for improving desire, arousal, lubrication, orgasm and sexual satisfaction.[17]	Combining bupropion with another antidepressant is associated with a number of risks (drug interactions, increased seizure risk and possibly a risk of serotonin toxicity). Bupropion inhibits reuptake of noradrenaline and dopamine without direct effects on serotonin (possibly explaining its low risk of SD). Bupropion is a strong inhibitor of CYP2D6 and it may increase blood levels of antidepressants metabolised by this enzyme (eg, fluoxetine, fluvoxamine, paroxetine, venlafaxine). Bupropion is not approved or subsidised through the PBS in Australia for this indication and is expensive on private prescription.
Phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil)	Multiple RCTs have found an improvement in antidepressant-induced SD with these drugs in both men and women.[1,4,7,13,48–52] Patients in these studies to date have had a mean age below 60 years. Studies in older adults are needed.[13] The benefit of these drugs for women is most pronounced for delayed orgasm and less so for decreased libido.[40]	A Cochrane systematic review concluded that for men with antidepressant-induced erectile dysfunction, the addition of sildenafil or tadalafil appears to have the best evidence of all adjunctive strategies.[45] Trials have used these agents on demand rather than regular dosing.[49]
Mirtazapine	One small open label study found that 48% of patients with SSRI-induced SD had resolution of SD following augmentation with mirtazapine.[53]	Mirtazapine may improve antidepressant response and sexual adverse effects, but the evidence is limited. Consider the potential for increased risk of adverse effects with such combinations (there are inconclusive reports suggesting a small potential for serotonin toxicity when adding mirtazapine to an SSRI or SNRI).[54] Weight gain and sedation are common adverse effects with mirtazapine.[54]
Second generation antipsychotics	A small RCT found that giving olanzapine 1–2 hours before usual time of sexual activity on a daily basis, in female patients with fluoxetine-induced SD, was more effective than placebo for overall sexual satisfaction but not on other measures of sexual function.[55] Aripiprazole improved sexual interest and satisfaction (but not orgasm or sexual arousal) in women with depression (but not men) in a post hoc analysis of data from three RCTs (total of 1092 patients), which were designed to assess efficacy of aripiprazole augmentation in patients with major depression who failed to respond to standard antidepressants.[56] The improvement appeared independent of improvement of depressive symptoms.[56]	Evidence is limited. Careful consideration of risks associated with antipsychotics is essential.
Testosterone cream or gel	One small RCT in men with SD taking an SSRI or SNRI found a benefit of testosterone gel over placebo, with morning total testosterone levels ≤ 350 ng/dL (which is considered to be low/low–normal). Only patients with partial response to their antidepressant were included.[57] A small RCT in 44 women with SSRI or SNRI-induced loss of libido found improvements in the frequency of satisfactory sexual events with a testosterone 300 µg/day patch versus a placebo patch. However, there was no difference between groups for overall score on a sexual self-rating scale.[58]	Further studies are required, particularly in men with normal testosterone levels. Consider measuring and correcting for low testosterone levels in men with SD. Testosterone may provide benefit for women with loss of libido, but further trials are warranted.
Others	Case reports and a post hoc analysis of a small RCT suggest possible beneficial effects of dexamfetamine or methylphenidate in patients with SSRI-induced SD.[59–61] There is conflicting information from small RCTs regarding whether buspirone may be effective for improving SSRI-induced SD.[62,63] A small open study and case reports have suggested a possible benefit with cyproheptadine when given daily or as needed (4–16 mg 30 min to 2 h before sexual activity).[13,64] One small RCT found benefit (particularly improved arousal, lubrication and pain) with saffron treatment (15 mg saffron twice a day) for female patients with fluoxetine-induced SD.[65]	Evidence is limited, making it difficult to advocate these treatments. Regular dosing of cyproheptadine could reduce the antidepressant effects of an SSRI or SNRI, as it is a serotonin antagonist.[64] Sedation is a common adverse effect with cyproheptadine.

CYP = cytochrome P450; PBS = Pharmaceutical Benefits Scheme; RCT = randomised controlled trial; SNRI = selective serotonin and noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor. ◆

- Long term use of SSRIs or other serotonergic antidepressants may cause downregulation of 5-HT_{1A} receptors that persists after antidepressant cessation. The downregulation and desensitisation of 5-HT_{1A} receptors are involved in the regulation of sexual motivation.[69] The effect of SSRIs or other serotonergic antidepressants on serotonin levels in peripheral nerves

could lead to axonal damage (serotonergic neurotoxicity), similar to that seen with ecstasy, which has been associated with sexual dysfunction long after stopping the drug.[66,67,69,73]

- SSRI or other serotonergic antidepressant use could result in changes in other neurotransmitters and/or hormones. For example, dopamine is essential in sexual arousal, and SSRIs cause inhibition of dopamine transmission in the ventral tegmental area.[69]
- A high concentration of serotonin in the hypothalamus may cause downregulation of this axis and lower testosterone levels. PSSD appears similar to the persistent sexual symptoms that have been described in some patients with the use of 5-α-reductase inhibitors (eg, finasteride).[66,73]

Importantly, not all patients who use SSRIs or SNRIs develop PSSD, so individual vulnerability is likely to play a prominent role in this condition.[66]

Management of sexual dysfunction that persists after using serotonergic antidepressants

There is no definitive treatment for PSSD. Many drugs have been tried in patients for PSSD, including buspirone, trazodone, mirtazapine, pramipexole, cabergoline, phosphodiesterase type 5 inhibitors, testosterone, bupropion, dexamphetamine and other stimulants, with no or little benefit reported.[68,69,71]

Low power laser irradiation and phototherapy have shown some promising results, but this has only been tried in individual cases.[69] Psychotherapy may be useful for patients experiencing PSSD and their partners.[69]

It is important to record baseline sexual function and perform regular follow-up during and after SSRI or SNRI use.

Conclusion

Antidepressant-induced sexual dysfunction is common and distressing for many patients, and is associated with a high risk of medication non-adherence. Sexual function should be actively assessed at baseline, at regular intervals during treatment with an antidepressant, and after treatment cessation. Management of antidepressant-induced sexual dysfunction requires an individualised approach. Furthermore, there is the possibility of PSSD, which has been recently identified as a potential, although rare, adverse effect of SSRIs and SNRIs.

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