

# Sexual Side-effects Associated with Antidepressants: A Clinical Guide



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This article discusses the sexual side-effects of the various antidepressants and what can be done about this issue.

## Introduction

It is not uncommon to have patients with depression whose mood symptoms improve with treatment, but who complain that their libido and ability to experience orgasm is impacted negatively by their antidepressant. Of course, sexual activity is complex and encompasses numerous domains. These include the quality of the relationship between sexual participants, their physical health, any alcohol or illicit substance use and general mental health issues. All of these factors need to be considered in the assessment and treatment of sexual problems, and sexual dysfunction should not automatically be attributed to an antidepressant. However, there is no doubt that certain antidepressants can cause sexual problems, notably decreased libido and delayed orgasm. There is also little doubt that the various classes of antidepressants have different propensities to induce such problems.

This article provides a clinically-focussed overview of the problem of antidepressant-associated sexual dysfunction and there is a particular emphasis on management. This is important, as sexual problems impact the individual and their partner and are also a common reason for patients to cease their antidepressant, thus increasing the risk of relapse of depression.

## Take Home Messages

- ✔ Sexual function should be seen within the context of the individual, the relationship and the culture. Physical health, drug and alcohol consumption and relationship issues should be excluded before deciding that antidepressants are the cause of sexual dysfunction.
- ✔ Sexual dysfunction is more likely with drugs that increase brain serotonin, notably SSRIs, SNRIs and certain TCAs.
- ✔ Generally, drugs that block 5HT<sub>2c</sub> receptors have lower reported rates of sexual dysfunction (e.g. mirtazapine, agomelatine). Moclobemide and vortioxetine are also associated with relatively low rates of sexual dysfunction.
- ✔ Sexual dysfunction associated with antidepressant use can be managed by switching to another with less propensity, or using an augmentation strategy. Only sildenafil and tadalafil (both for men only), and bupropion, have placebo-controlled trial support in this regard.

## Prevalence and mechanisms

Human sexual function is complex and impacted by individual attitudes and mores, as well as societal, religious and cultural factors. Relationship issues are paramount and the quality of the intimate partnership plays a vital role in determining sexual habits and enjoyment. All these factors need to be borne in mind when assessing sexual functioning and determining any change that could be associated with depression and antidepressants.

A number of factors at the biological level underpin the various stages of sexual function.<sup>1,2</sup> The parasympathetic and sympathetic nervous systems interact to establish and maintain penile erection in men, clitoral engorgement and vaginal lubrication in women, and ultimately orgasm. Dopamine seems to be the most important neurotransmitter in driving libido and physical arousal, whilst serotonin impairs orgasm and ejaculation, mostly through the 5HT<sub>2c</sub> receptors in the spinal cord.<sup>3</sup> Beta-adrenergic receptors play a role in maintenance of erections, countered by alpha-1 receptors.<sup>3</sup> Nitric oxide is also involved in erectile function.<sup>3</sup>

There are numerous causes of sexual dysfunction. An association between sexual dysfunction and depression is well described. However, reported rates depend upon whether the individual is specifically asked, as often there is reticence in volunteering such information spontaneously. Rates of approximately 50% have been reported for sexual impairment in patients with depression, but in some studies these are even higher.<sup>1</sup> It is also important to understand which aspects of sexual functioning are impacted. A lack of libido and a generally decreased interest in sex is not uncommon in patients who have depression, but the common antidepressant-associated delayed ejaculation is not usually a prominent issue in untreated depression.

**The overall pattern is that males suffer a higher adverse impact on desire and orgasm, whilst arousal is more affected in females.**

The rates and types of sexual dysfunction vary extensively with different antidepressants, as confirmed in the meta-analysis of Serretti and Chiesa.<sup>4</sup> These findings are summarised in Table 1. The rates of sexual dysfunction were highest in people taking medications that increase serotonin levels in the brain, notably selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline re-uptake inhibitors (SNRIs) and certain tricyclic antidepressants. Medications that block serotonin 5HT<sub>2c</sub> receptors post-synaptically had a generally lower reported rate of sexual

dysfunction (e.g. mirtazapine, and the melatonergic M1/M2 agonist, agomelatine). This pattern reflects what is known about sexual physiology. Bupropion, which acts through dopaminergic and noradrenergic mechanisms, had a relatively low rate of sexual dysfunction, as did the reversible selective monoamine oxidase A inhibitor, moclobemide.

**Table 1: 'Ranking' of antidepressants in terms of overall rate of sexual dysfunction**

Highest	Middle	Lowest
Citalopram	Fluvoxamine	Agomelatine
Fluoxetine	Escitalopram	Bupropion
Paroxetine	Duloxetine	Moclobemide
Sertraline	Imipramine	Mirtazapine
Venlafaxine		
(data from Serretti and Chiesa) <sup>4</sup>		

An interesting aspect of the Serretti and Chiesa meta-analysis<sup>4</sup> lies in its ability to examine rates of dysfunction across the different phases of sexual desire, arousal and orgasm. In the main, those drugs associated with low rates of overall sexual dysfunction did not show specific effects on particular aspects of sexual function (albeit, mirtazapine has a small signal for desire dysfunction, and bupropion for arousal dysfunction). In terms of gender, the overall pattern was that males suffered a higher adverse impact on desire and orgasm, whilst arousal was more affected in females.

In terms of the newer antidepressants, the multimodal antidepressant vortioxetine has been shown in clinical trials to have a placebo-level or slightly higher rate of sexual dysfunction, with substantially lower rates than comparison agents, including duloxetine and venlafaxine.<sup>5</sup>

It is important also to appreciate that a range of other psychiatric medications can also impact sexual functioning. Notable amongst these are a number of antipsychotic agents, especially those that have a propensity to raise prolactin levels (e.g. risperidone, paliperidone, amisulpride, haloperidol).<sup>6</sup>

## Understanding sexual function and dysfunction at the individual level

Sexual function should be seen within the context of the individual, the relationship and the culture. Often there are sensitivities about discussing sexual issues, but clinicians dealing with people with mental illness need to establish an approach to such a discussion as a matter of routine.

One study reported that patients volunteered sexual dysfunction associated with antidepressant treatment in only 14% of cases,



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although 58% acknowledged problems in this regard when they were questioned directly.<sup>7</sup> There are established rating scales that can assist both in assessing cross-sectional sexual functioning and enjoyment, as well as longitudinal tracking. The two most commonly used are the Arizona Sexual Experiences Scale (ASEX)<sup>8</sup> and the Changes in Sexual Experience Scale (CSFQ)<sup>9</sup>.

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It is also important to understand the usual sexual activities and habits of the patient early during treatment. This will establish a baseline, as well as ensure that physical health or other factors are not contributing to any sexual dysfunction.

Balon<sup>10</sup> following Gitlin<sup>11</sup> suggests, inter alia, the following as important elements of a baseline assessment of sexual function in patients with depression. It should be noted that many of these questions are sensitive and the level of detail may be more appropriate to specialist psychiatric practice than to a general practice setting. Clinical judgement is required and should be made based on the entirety of the clinical scenario and the relationship between the patient and the doctor, notably regarding item 1. Items 2 and 3 should be considered part of the formal psychiatric assessment, but are important to consider in the context of sexual problems in particular.

1. Details of usual sexual functioning, pre-treatment and also pre-morbidly: A longitudinal history is useful, including first sexual experiences, enjoyment of sex, pattern of sexual partners, usual frequency of sex and masturbation.
2. Psychiatric issues that might contribute to sexual problems: These include not only depression, but also anxiety disorders,

post-traumatic stress disorder and body image disorders; particular problematic sexual problems are not uncommon in people who have experienced sexual abuse.

3. Alcohol and illicit drugs can have a profound effect on sexual function and are also important contributors to mental health problems; cigarette smoking can also affect sexual functioning.
4. Physical health requires careful assessment. Diabetes mellitus and other endocrine disorders, as well as cardiovascular risk factors (such as obesity and hypertension) can impair sexual function. A number of medications used for physical health problems can contribute to this issue as well (e.g. some antihypertensive agents and antiarrhythmics, antiandrogens and other hormonal preparations).
5. Details of sexual functioning during the current (and past, if relevant) depressive episode; note that some people, when depressed, actually increase their sexual activity, but this does not provide the normal satisfaction. This could be referred to as akin to 'comfort eating'.
6. The personal importance of sexual activity, and the impact that any changes in sexual function associated with the depression has had upon the current relationship.

## Management

The management of sexual dysfunction associated with antidepressants requires a good understanding of the issues outlined above, followed by a full and frank discussion with the patient about therapeutic options. The offer should be made to include the patient's partner in at least some of these discussions. It is particularly useful for partners to understand the impact of antidepressants on libido, as they might otherwise believe that the patient has lost interest in sex because of issues to do with sexual attraction, specifically towards their partner.

Some patients report benefit from simple explanation and psychological strategies, but many do not. Approaches such as 'drug holidays' (that is, stopping the antidepressant for the day or two before sex), are not usually very effective and have the disadvantage of removing the spontaneity of sex, as well as sending potentially conflicting messages about regular medication adherence.<sup>2</sup>

In those individuals in whom such simple approaches do not work, some will 'accept' a degree of sexual dysfunction as a 'price

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**References:** 1. Valdoxan Approved Product Information. 2. Malhi G et al Aust N Z J Psychiatry 2015;49:1087–1206. 3. Serretti A et al. J Clin Psychopharmacol 2009; 29:259–66. 4. Sapetti A. J Sex Marital Therapy 2012; 38:190–7. 5. Montejo A et al. Hum Psychopharmacol 2011; 26:537–42. 6. Kennedy et al. CNS Drugs 2010;24:479–99. 7. Martinotti G et al. J Clin Psychopharmacol 2012; 32:487–491. 8. Guillena S et al. Eur Neuropsychopharmacol 2014; 24(Suppl2): S461. 9. Gargoloff PD. Hum Psychopharmacol Clin Exp 2016; 31:412–418. 10. Montgomery S et al. Int Clin Psychopharmacol 2004; 19:271–280. 11. Lemoine P et al. J Clin Psychiatry 2007; 68:1723–32. 12. Quera Salva et al. Hum Psychopharmacol Clin Exp 2010 ;25:222–229. 13. Quera Salva M et al. Int J Neuropsychopharmacol 2007; 10:691–696.

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worth paying' for their mood being better, and are reluctant to countenance a change in antidepressant medication and risk relapse. Others will be willing to take this risk, and so will need to be offered a range of options. Table 1 details the relative propensity of sexual side-effects associated with commonly used antidepressants. Switching needs to be done in a controlled manner, mindful of the relative receptor pharmacology of the agent being switched 'from' and 'to'. For example, switching from a sedating agent to a non-sedating agent can result in insomnia, so slow transition and/or the short-term use of a hypnotic agent should be considered. Also, if the initial agent is used at a high dose, a slower cross-titration is usually preferred. Attention also needs to be given to potential pharmacokinetic interactions between the two agents. Certain combinations are potentially dangerous and require wash-out periods, notably monoamine oxidase inhibitors. It is important to refer to the product information regarding the changing over of particular medications.

In terms of which agent to 'switch to', agomelatine has the virtue of a generally low side-effect burden and has no major interactions with other antidepressants (except fluvoxamine). It does carry a risk of hepatic dysfunction (0.8% 25mg and 1.9% 50mg, >3x ULN, placebo-adjusted in the clinical trials) and liver enzymes should be measured at baseline, followed by three, six,

twelve and twenty four weeks after initiation, and after any dose increase. This antidepressant is not available on the Pharmaceutical Benefit Scheme (PBS) in Australia, but many private insurers offer part-reimbursement. Bupropion is also not available on the PBS in Australia for depression and it is rather costly. It also can cause nausea and is associated with a risk of seizures, so should not be used in patients with a history of fitting. Mirtazapine has sedative effects that can be useful, but some patients may find these excessive; it also commonly increases appetite and can result in weight gain. Moclobemide is generally well tolerated and may be worth considering in patients sensitive to side-effects generally, as well as specifically those experiencing sexual side-effects. Vortioxetine is also useful in some patients who have experienced sexual dysfunction with an SSRI or SNRI and in whom a serotonergic medication is required, but it is also not available on the PBS.

A different approach to treating sexual dysfunction associated with antidepressants is to use an adjunctive agent to try to ameliorate the sexual side-effects of the initial medication. Again, care must be taken with potential drug-drug interactions and cumulative other side-effects. A summary of agents which might be used as adjuncts to SSRIs and SNRIs is shown in Table 2. It should be noted that most of these treatments have a very limited evidence base and none are approved for use as augmentation agents in patients with sexual

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Table 2: Selected augmentation agents with potential use for sexual dysfunction associated with SSRIs and SNRIs\*

AGENT	ACTION	EVIDENCE	COMMENTS
<b>Bupropion</b> <sup>15-18</sup>	DA, NA re-uptake inhibition	Efficacy at 150mg bd, but not 150mg daily	Potential for seizures
<b>Mirtazapine</b> <sup>19,20</sup>	Post-synaptic 5HT2 blockade and pre-synaptic alpha 2 agonism	No RCT evidence for efficacy as an augmenter, despite low sexual side-effects as solo agent	Sedation and weight gain can be problematic
<b>Agomelatine</b> <sup>21</sup>	Melatonin M1/M2 agonism and post-synaptic 5HT2c blockade	No RCT evidence for efficacy as an augmenter, despite low sexual side-effects as solo agent	Well tolerated side-effect profile; requires hepatic monitoring
<b>Cyproheptadine</b> <sup>22</sup>	Antihistamine with anti-serotonergic properties	Case reports only of efficacy at mean 8.6mg daily	Sedation can be problematic and may impede efficacy of SSRI/SNRI
<b>Buspirone</b> <sup>23</sup>	5HT1a partial agonist	Case reports of efficacy at 15mg to 60mg daily	Antianxiety effect can be helpful
<b>Amantadine</b> <sup>22</sup>	DA agonist	Case series report efficacy for anorgasmia at 100mg to 400mg daily	Potential DA agonist side-effects include psychosis
<b>Aripiprazole</b> <sup>24</sup>	Partial DA agonist	Post-hoc analysis of three RCTs support efficacy for sexual dysfunction in females only at 2mg to 20mg daily	Akathisia can be problematic; additional antidepressant effect can be helpful
<b>Methylphenidate</b> <sup>25</sup> <b>amphetamine</b> <sup>26</sup> <b>pemoline</b> <sup>27</sup>	Stimulants	Case reports of efficacy for SSRI-induced sexual dysfunction	Potential DA agonist effects, including psychosis; potential for dependence
<b>Yohimbine</b> <sup>28</sup>	Presynaptic alpha 2 blocker	Case series suggest efficacy for doses from 2.7mg to 16.2mg daily, but single RCT failed	Can cause anxiety, nausea, urinary retention
<b>Ginko biloba</b> <sup>29</sup>	Unknown	Case reports of efficacy at 60mg to 120mg twice daily	Can cause gastrointestinal upset, lightheadness and bleeding problems

\*NOTE: None of these agents are indicated or reimbursed in Australia for this indication. **DA** = dopamine; **NA** = noradrenaline; **5HT** = serotonin; **mg** = milligrams; **bd** = twice daily; **SSRI** = selective serotonin reuptake inhibitor; **SNRI** = serotonin noradrenaline reuptake inhibitor; **RCT** = randomised control trial

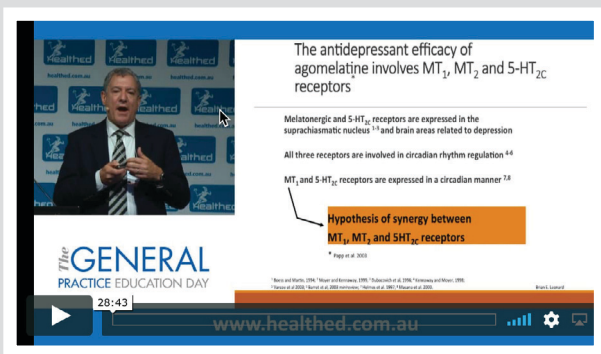
dysfunction associated with SSRIs and SNRIs. Indeed, a recent Cochrane review of treatments for sexual dysfunction associated with antidepressants found only twenty-two studies involving augmentation strategies.<sup>12</sup> Two studies<sup>13,14</sup> (n=255) found efficacy for the phosphodiesterase, sildenafil, for erectile function in males; the phosphodiesterase, tadalafil, was similarly effective in a single study of fifty-four patients. In a further three studies,<sup>15-17</sup> a benefit was shown for bupropion (150mg twice daily) in overall sexual function in both males and females, but this was not confirmed in a further two studies of bupropion (150mg once daily).<sup>17,18</sup>

Another adjunctive approach is the use of a dopamine partial agonist antipsychotic. There is now widespread use of aripiprazole as an adjunct to antidepressants in major depressive disorder<sup>30</sup>

(again, it is neither indicated for this nor reimbursed in Australia) and there is support for a pharmacological mechanism regarding an additional benefit for sexual dysfunction (largely dopaminergic effects). Fava et al<sup>24</sup> pooled three placebo-controlled trials of aripiprazole used as an adjunct to a range of SSRIs and SNRIs (n= 737 female, 355 male) and reported benefits not only in mood but also (for women only) in sexual interest and sexual satisfaction. This effect was independent of improvement in mood and also was not correlated with prolactin levels.

Montejo et al<sup>6</sup> have summarised other 'add on' strategies, including transdermal testosterone (some efficacy in women)<sup>31</sup> acupuncture (efficacy more likely in men)<sup>32</sup>, saffron (women)<sup>33</sup> and macca root (women)<sup>34</sup>. Clearly these approaches are not 'mainstream' and

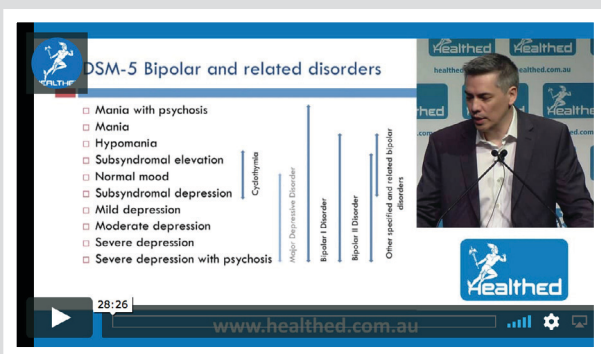
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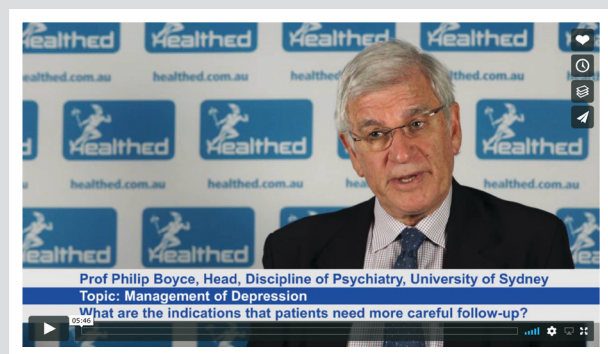
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side-effects and interactions need to be borne in mind if any of these therapies are considered. Of course, many patients use over-the-counter and herbal and other 'remedies', and these should be asked about in all patients.

### Conclusions

Sexual functioning is often impaired as part of a depressive process. Some antidepressants, notably SSRIs and SNRIs, whilst being effective in treating depression, induce sexual dysfunction. A full assessment of the individual to exclude other causes of sexual dysfunction, along with the offer to discuss the condition with the partner, when appropriate, is vital. Options for addressing the sexual dysfunction, if it is confirmed to be associated with the antidepressant, include switching to another antidepressant with less propensity to sexual dysfunction (e.g. agomelatine, bupropion, mirtazapine, moclobemide, vortioxetine), or using an augmentation strategy. In terms of augmenters, only the phosphodiesterases sildenafil and tadalafil, and the dopamine/noradrenaline antidepressant, bupropion, have placebo-controlled trial support (and for the phosphodiesterases, this is in males only). Some data support the benefits of the dopamine partial agonist aripiprazole for SSRI and SNRI-induced sexual dysfunction in women. The topic of

sexual side-effects associated with antidepressants clearly requires clinical common sense, careful questioning and a good therapeutic relationship with the patient.

### Further reading

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