

# Antidepressant-induced sexual dysfunction

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## Abstract

Depression and sexual dysfunction are both common in the general population. When they co-exist they have the potential to impact negatively on each other in a bidirectional manner. Medication used to treat depression may cause additional problems with the sexual response cycle; although no drug is completely innocent, serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are most frequently implicated in antidepressant-induced sexual dysfunction. Adherence to long-term treatment may be compromised, which may have serious consequences. Various psychological and pharmacological strategies, including the ad hoc use of sildenafil, may offer some respite.

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## Introduction

Perhaps not since Masters and Johnson<sup>1</sup> published their pioneering work on the physiology of the human sexual response in 1966 has there been such lively interest in sexual functioning. The recent unabashed flaunting of sildenafil (Viagra<sup>®</sup>) and other phosphodiesterase type 5 inhibitors by pharmaceutical giants has greatly facilitated changing attitudes to sexual health globally. Erectile dysfunction in particular is no longer taboo and is increasingly viewed and treated as a medical issue.

## The physiology of sexual functioning

The normal sexual response cycle is generally divided into four successive phases (desire, arousal, orgasm, resolution) and is controlled by a multifaceted interplay between the hypophyseal-pituitary-adrenal (HPA) axis, the autonomic nervous system, circulating sex hormones (testosterone, oestrogens and progesterones), neurotransmitters (serotonin, dopamine, noradrenaline, GABA and acetylcholine) and vasoactive peptides such as nitric oxide.<sup>2</sup>

It has been postulated that *desire* is facilitated mostly by a combination of hormonal factors and noradrenaline, *desire and arousal* by dopamine, and *orgasm* by oxytocin and acetylcholine. Prolactin's role might be to deter arousal and studies have shown serotonin to hinder *desire and arousal*, possibly by indirect means (by inhibiting noradrenaline and dopamine) as well as by influencing peripheral effects (decreasing sensation, and inhibiting the vasodilator, nitric oxide). It may thus play a role in the *resolution* phase of the sexual cycle.<sup>3</sup>

## Sexual dysfunction

Whilst a *sexual complaint* is an expression of discontent or pain associated with the sexual experience, *sexual dysfunction* is pain associated with sexual activity (vaginismus or dyspareunia) or a disturbance (either psychogenic or organic) in sexual functioning, involving one or more of the phases of the physiological sexual response cycle. When this is accompanied by marked distress, it becomes a *sexual disorder*.<sup>4</sup>

Approximately 34% of men and 41% of women in the general population experience some form of sexual problem, which may range from decreased libido, vaginal dryness (28%) and erectile problems (26%) to premature ejaculation (14%) and anorgasmia (27%).<sup>5,6</sup>

Many aetiologies have been linked to the disruption of the normal sexual response cycle. These include psychological causes (psychiatric illness, particularly anxiety and depression), pathological states (vascular disease, diabetes, neurological disease) and pharmacological effects of drugs.<sup>6</sup> It has long been recognised that certain antihypertensive agents, notably centrally acting sympatholytic agents, beta antagonists, and diuretics, have an adverse effect on sexual functioning.<sup>7</sup> Antidepressants, antipsychotics, anticonvulsants, drugs with antimuscarinic effects, steroids, proton pump inhibitors, histamine receptor blockers and chemotherapeutic agents have also been implicated.<sup>8</sup>

Increasing age, poor physical health, smoking more than six to 20 cigarettes a day, recreational drugs including alcohol and opioid use, loss of or low income and distressing previous sexual experiences may increase the likelihood or risk of encountering sexual problems.<sup>6,9</sup>

## Sexual dysfunction and depression

Depression is a common, serious and disabling illness. Besides depressed mood and reduced energy, it is characterised by loss of interest, diminished self-esteem and the inability to experience pleasure, which may often impede the establishment or maintenance of intimate relationships.<sup>10</sup> It is hardly surprising therefore that depression may negatively impact on sexual function. Equally, it is plausible that sexual dysfunction may impact adversely on depression. It has even been suggested that these two disorders may share a common aetiology.<sup>11</sup> The causal relationship is far from clear and the precise effects of depression on sexuality are variable.

From a patho-physiological perspective, a significant percentage of depressed patients exhibit overactivity of the autonomic system and dysregulation of the neuroendocrine hypothalamic-pituitary-adrenal

(HPA) axis. This is accompanied by changes in corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), beta-endorphins and catecholamines, which could increase the risks for not only cardiovascular disease, but also for sexual dysfunction.<sup>12</sup>

In the 1980s, Derogatis<sup>13</sup> and Schreiner-Engel<sup>11</sup> established a link between sexual dysfunction and mood disorders. They found that patients presenting with desire disorders had a strikingly elevated lifetime prevalence of psychopathology, particularly of depression, and that the mood disturbances almost always preceded or coincided with the development of inhibited sexual desire.

A decade or so later the Massachusetts Male Aging Study (MMAS)<sup>14</sup> revealed that depression and anger were highly correlated with erectile dysfunction. In other words, depressive symptoms were regarded as a strong predictor for erectile dysfunction.

Studies comparing the prevalence of sexual dysfunction in depressed patients and non-depressed controls have consistently shown higher levels of dysfunction (most commonly loss of interest or arousal) in the former group.<sup>15,16</sup> Perlman and colleagues<sup>17</sup> found that depression, co-morbidity (especially cardiopulmonary illness) and the use of antidepressants were all powerful risk factors for developing sexual dysfunction in the psychiatric inpatient setting. Moreover, both Casper<sup>18</sup> and Osvath<sup>19</sup> estimated the prevalence of sexual dysfunction in depressed patients to be in excess of 70%.

It has proved difficult to discern whether the prevalence of sexual dysfunction is related to, amongst others, depression itself or to the adverse effects of antidepressant treatment. Kennedy and colleagues<sup>20</sup> attempted to establish the baseline prevalence in an unmedicated sample of patients with major depressive disorder. Prior to initiating antidepressant medication, more than 40% men and 50% women reported decreased sexual desire and arousal, with 15–20% reporting ejaculatory or orgasm difficulties. No correlation with the severity of depression was found in the small sample.

### Antidepressant-induced sexual dysfunction

In the 1960s and 1970s, sporadic cases appeared in the literature of TCA- (tricyclic antidepressant) and MAOI- (monoamine oxidase inhibitor) induced erectile dysfunction, anorgasmia and retrograde ejaculation.<sup>21,22</sup> It wasn't until the introduction of selective serotonin reuptake inhibitors (SSRIs) in the latter half of the 1980s, however, that attention became more focused on the problem of antidepressant-induced sexual dysfunction. Widespread and first-line use of these agents highlighted their adverse effects on sexual functioning, and their negative impact on patients' quality of life (QOL) could not be ignored.<sup>10</sup>

The epidemiology of treatment-induced sexual dysfunction has been a thorny issue, due in part to confounding factors such as mental illness itself, cultural influences and co-morbidity.<sup>23,24</sup> Efforts to establish the true prevalence of antidepressant-induced sexual dysfunction, to eke out significant differences and to compare vastly disparate trials may leave methodology purists justifiably distressed. (See Table I.)

Nonetheless, the general consensus is, firstly, that there is a high incidence of sexual dysfunction attributable to SSRI and SNRI usage – the best estimate probably in the region of 30 to 50% – and that this is a dose-related class effect,<sup>25</sup> secondly, consensus is that drugs with different pharmacological actions are less inclined to affect sexual functioning.

SSRIs have demonstrated an effect on all phases of the sexual cycle, causing decreased libido, impaired arousal and erectile dysfunction. However, they are most commonly associated with delayed ejaculation and delayed orgasm.<sup>26</sup>

**Table I: Crude estimate of antidepressant-induced sexual dysfunction**

Class*	Drug	Prevalence range	Author / Year
TCA	amitriptyline	7.7–10%	Reimherr 1991; Montgomery 2002
MAOI	phenelzine	40%	Harrison 1986
SNRI	venlafaxine	16–65%	Kennedy 2008; Gregorian 2002
	duloxetine	33–46%	Clayton 2007; Delgado 2005
SSRI	escitalopram	9–44%	Hirschfield 2004; Clayton 2007
	citalopram	30–73%	Clayton 2002; Montejó 2001
	paroxetine	43–70%	Clayton 2002; Kennedy 2000
	sertraline	27–63%	Reimherr 1991; Montejó 2001
	fluvoxamine	59–62%	Montejó 1997; Montejó 2001
	fluoxetine	8–58%	Zajacka 1991; Montejó 2001
NaSSA	mirtazapine	1–24%	Behnke 2003; Montejó 2001
NARI	reboxetine	0–5%	Mucci 1997; Clayton 2003
RIMA	moclobemide	2–4%	Phillip 2000; Montejó 2001
MASSA	agomelatine**	0–3%	Rouillon 2006; Kennedy 2008
Others	nefazodone**	8–15%	Zajacka 2002; Modell 1997
	bupropion	0–7%	Thase 2006; Clayton 2006

\* Class:  
TCA: tricyclic antidepressant  
MAOI: monoamine oxidase inhibitor  
SNRI: serotonin and noradrenaline reuptake inhibitor  
SSRI: selective serotonin reuptake inhibitor  
NaSSA: noradrenergic and specific serotonergic antidepressant  
NARI: noradrenaline reuptake inhibitor  
RIMA: reversible inhibitor of monoamine oxidase type A  
MASSA: melatonin agonist and selective serotonin antagonist

\*\* not currently available in South Africa

The mechanism of SSRI- and SNRI-induced sexual dysfunction is thought to involve indiscriminate stimulation of post synaptic 5HT-2<sub>a</sub> and 5HT-2<sub>c</sub> receptors by the increased synaptic levels of serotonin.<sup>27</sup> Antidepressants that antagonise these particular serotonin receptor subtypes, e.g. mirtazapine, nefazodone and agomelatine, have a lower propensity to cause sexual dysfunction. The reversible inhibitor of monoamine oxidase, moclobemide, although showing an increased incidence of sexual arousal, has a very low incidence of sexual dysfunction per se, whilst the noradrenaline reuptake inhibitor, reboxetine, and the noradrenaline and dopamine reuptake inhibitor, bupropion, have little or no effect.

Gender, race and duration of treatment do not appear to predict sexual dysfunction. However, prior history of antidepressant-induced sexual dysfunction increases the risk of developing it again.<sup>28</sup>

### Management of antidepressant-induced sexual dysfunction

Antidepressant-induced sexual dysfunction impacts heavily on diagnostic issues, treatment planning and prescribing practices, patients' quality of life and their ultimate adherence to long-term medication. Non-adherence may lead to persistence, relapse or recurrence of depression, which may have serious consequences.

The overall treatment approach should be cognisant of the normal fluctuation of sexual functioning. Risk factors (co-morbid psychiatric, endocrine, vascular and neurological conditions and recreational drug, alcohol and nicotine use) should be noted and, if possible, addressed. It has been suggested that the promotion of a healthy lifestyle may lead to improved self-image, sense of well-being and general health, and consequently to a better physiological functioning of the sexual response cycle (thereby rendering the drug-induced sexual dysfunction

more manageable). Cognitive behaviour therapy, couple therapy and counselling may help the patient cope with the dysfunction, reduce symptom severity or help prevent symptom worsening. However, in the absence of psychogenic causes or relationship factors contributing to the sexual dysfunction, the impact of psychological treatment is currently unknown; no randomised studies assessing the benefits of psychological interventions in antidepressant-induced sexual dysfunction have been identified.

Validated screening tools such as the Arizona Sexual Experience Scale (ASEX) and the Changes in Sexual Functioning Questionnaire (CSFQ) may be useful for evaluating baseline sexual functioning prior to initiating antidepressant medication as well as at intervals to determine the presence of adverse drug effects.<sup>24</sup>

Evidence-based recommendations for the pharmacological management of antidepressant-induced sexual dysfunction are in short supply.<sup>29</sup> Prescribers' intuition, experience and personal comfort zones therefore generally dictate their strategies. Some recommend *initiating* therapy with an antidepressant that has a lower propensity to cause sexual dysfunction, e.g. mirtazapine, reboxetine, nefazodone, bupropion or agomelatine. Others advocate *awaiting* spontaneous remission of sexual dysfunction or development of drug tolerance. The effectiveness of this "wait and see" strategy is considered low. *Reducing the dose* of the offending agent requires careful monitoring of the patient for relapse and recurrence of depression. Two to three-day *drug holidays* for agents with short half lives (paroxetine and sertraline) may elicit discontinuation reactions and encourage non-adherence.

There is some evidence that *switching* to an antidepressant such as nefazodone or bupropion is effective.<sup>30</sup> This may prove troublesome, however, if the offending drug is considered the only effective drug for alleviating the particular patient's depression.

Many *augmenting* agents have been described as useful, including the addition of bupropion, mirtazapine, nefazodone, granisetron (serotonin antagonist), yohimbine (alpha-1 agonist and alpha-2 antagonist), cyproheptadine (antihistamine with 5HT-2 blocking activity), amantadine and other dopamine agonists such as ropinirole. The evidence for bupropion augmentation is the most compelling.<sup>31</sup>

Finally, there is firm evidence that *remedial drug therapy with sildenafil*, the selective and competitive inhibitor of phosphodiesterase type 5 (PDE-5), has proved effective in men for antidepressant-induced erectile dysfunction,<sup>32</sup> and more recently – although not licensed for this group – in women with SSRI- and SNRI-induced sexual adverse effects.<sup>33</sup> Its characteristics of peripheral site of action, high efficacy, good tolerability, relatively short duration of action and administration only if and when required make this agent in some ways the ideal antidote. Common adverse effects include dyspepsia and those attributable to vasodilatation (headache and flushing). As with the routine prescription of sildenafil, a detailed medical and drug history should be undertaken prior to treatment.

## Conclusions and recommendations

When initiating therapy, prescribers should be aware that antidepressant drugs may cause sexual dysfunction and that this is particularly true of the SSRI and SNRI classes. Agents such as mirtazapine, reboxetine and the newcomer, agomelatine (not yet licensed in South Africa), do not currently enjoy the broad familiarity of the SSRI class. However, they are far less inclined to cause sexual side-effects and may be considered appropriate alternative first-line drug options for patients where normal sexual functioning is a priority.

The diagnosis of antidepressant-induced sexual dysfunction may be aided by baseline and periodic clinical monitoring of sexual function.

Delayed ejaculation and orgasm are most frequently associated with SSRIs and SNRIs, whereas diminished sexual desire is more commonly associated with either depression itself or with various psychological factors such as sorrow, relationship difficulties and anxiety.

Adjuvant supportive psychological therapy and the promotion of a healthy lifestyle may prove useful management options. Switching to a non-SSRI drug or augmenting with bupropion appear to be the best supported pharmacological strategies for managing antidepressant-induced sexual dysfunction, although they may be encumbered by the potential for discontinuation reactions and drug-drug interactions.

Finally, the liaison between PDE-5 inhibitors and SSRIs, the only two classes of pharmacological agents to have achieved superstar status (with their prototypes Viagra® and Prozac®) in their eminent fields of erectile dysfunction and depression, appears promising. However, unforeseen incompatibility issues or the introduction of more alluring effective antidepressants that are untroubled by sexual dysfunction may ultimately determine whether this particular partnership is able to flourish or whether it is brought to an emotional, celebrity-style conclusion.

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