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.

Introduction
Perhaps not since Masters and Johnson published their pioneering work on the physiology of the human sexual response in 1966 has there been such lively interest in sexual functioning as today. The recent unabashed flaunting of sildenafil (Viagra) 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 hypothalamic-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.

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.

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.

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%).

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. 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. Antidepressants, antipsychotics, anticonvulsants, drugs with antimuscarinic effects, steroids, proton pump inhibitors, histamine receptor blockers and chemotherapeutic agents have also been implicated.

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.
**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.10 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.11 The causal relationship is far from clear and the precise effects of depression on sexuality are variable.

From a pathophysiological 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.12

In the 1980s, Derogatis13 and Schreiner-Engel11 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)14 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.15,16 Perlman and colleagues15 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 Casper16 and Osvath16 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 colleagues10 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.21,22 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.10

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.23,24 Efforts to establish the true prevalence of antidepressant-induced sexual dysfunction, to eke out significant differences between individual agents and compare vastly disparate clinical trials may leave methodology purists justifiably distressed. (See Table I.)

Nonetheless, the general consensus is, firstly, that there is a

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

* 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
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. 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.

The mechanism of SSRI- and SNRI-induced sexual dysfunction is thought to involve indiscriminate stimulation of post synaptic 5HT-2a and 5HT-2c receptors by the increased synaptic levels of serotonin. 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.

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.

Evidence-based recommendations for the pharmacological management of antidepressant-induced sexual dysfunction are in short supply. 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. 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.

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, and more recently – although not licensed for this group – in women with SSRI- and SNRI-induced sexual adverse effects. 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
whether this particular partnership is able to flourish or whether are untroubled by sexual dysfunction may ultimately determine the introduction of more alluring effective antidepressants that appears promising. However, unforeseen incompatibility issues or their eminent fields of erectile dysfunction and depression, ap-"