

# Drugs that cause sexual dysfunction

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## Abstract

Sexual dysfunction is a common and distressing side effect of many drugs, both prescribed and otherwise. In this brief overview, the normal biology of sexual function is outlined, together with the central and peripheral underlying chemical mechanisms. Knowledge of the normal biology of sexual function, along with knowledge of the mechanism of action of different drugs, helps one to predict whether a medication might cause sexual problems. Psychotropic drugs in particular can have both short- and long-term effects on sexual function, depending on length of exposure to an individual agent. This contribution provides an overview of those drugs which are most likely to be associated with sexual dysfunction, including not only prescribed medication but also recreational drugs and those commonly used by patients with mental health problems. The contribution ends with an outline of the management of drug-induced sexual side effects.

**Keywords** antidepressants; anti-epileptics; antipsychotics; antihypertensives; benzodiazepines; prostate medication; recreational drugs

Sexual dysfunction is a multifactorial problem with psychological, biological and social ramifications. As such, it is important to remember that, whatever the cause, treatment will require a holistic approach to achieve adequate resolution of the problem.

Sexual dysfunction is a common unwanted effect of many different types of drug therapy. It is important for clinicians to be aware of this, as sexual problems are often difficult for many patients to talk about. This is especially so when the original problem is unrelated to sexual function. Many patients will suffer in silence unless the issue is discussed with them first.

## The mechanism of drug-induced sexual dysfunction

Different drugs affect sexual function in different ways depending on their mechanism of action. Knowledge of the normal biology of sexual function allows one to predict whether a medication might cause sexual problems.

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## The biology of sexual function

Sexual function is divided into a number of different areas (see also pages 90–94):

- sexual interest or libido – mediated primarily by central nervous system (CNS) mechanisms
- arousal – mediated by CNS and parasympathetic system
- plateau
- orgasm/ejaculation – mediated by CNS and sympathetic system
- resolution.

In males, arousal is essentially the ability to achieve and maintain an erection. In females, there is relaxation, swelling and lubrication of the vaginal walls in readiness for penetration. The orgasm is the mental and physical phenomenon that signifies the climax of coital activity. In males, this is accompanied by the ejaculation of seminal fluid. Normal sexual functioning requires not only an ability to interact with others (i.e. a certain level of social skills) but also a variety of different physiological factors. The central and peripheral neurotransmitters, neuropeptides and hormones that come together to promote normal sexual reactions, are shown in Table 1.

Drugs that affect libido usually act centrally and may reduce desire by causing sedation or hormonal disturbance. Drugs that interfere with the autonomic system will have negative effects on erectile function, ejaculation and orgasm. Drugs interfering with hormones (e.g. tamoxifen) will also affect vaginal response.<sup>1</sup>

## Drugs that affect sexual function

**Benzodiazepines** act as hypnotics and cause drowsiness, thus reducing desire. In certain doses they can be disinhibiting and may increase libido.

## Antihypertensives

**β-blockers** are used to treat hypertension and anxiety. They are commonly associated with erectile dysfunction in men, owing to

### Factors affecting sexual function

	Excitatory	Inhibitory
Neurotransmitters	Dopamine Noradrenaline Acetylcholine Histamine	Serotonin GABA
Peripheral neurotransmitter	Nitric oxide	
Hormones	Testosterone Oestrogen (women) GnRH	Oestrogen (men) Progesterone Prolactin
Neuropeptides	Oxytocin Vasopressin Vasoactive intestinal peptide	

GABA, γ-aminobutyric acid; GnRH, gonadotrophin-releasing hormone.

Table 1

their autonomic effects. Many other antihypertensives, including ACE inhibitors and calcium channel blockers, can cause erectile disorders. Vasodilators and angiotensin-2 receptor antagonists are free of sexual side effects.

**Thiazide diuretics**, such as bendrofluzide, are associated with erectile dysfunction.

#### **Antidepressants**

Antidepressants are a well-known cause of sexual dysfunction.<sup>2</sup> This is primarily via activation of 5-HT<sub>2</sub> receptors, which inhibit both noradrenergic and dopaminergic transmission. Generally, antidepressants with fewer 5-HT<sub>2</sub> effects tend to cause less treatment-emergent sexual dysfunction.<sup>3</sup> Depression itself can cause sexual problems, thus it is sometimes difficult to tease out what is causing any sexual dysfunction that may be present.<sup>4</sup> It is therefore useful to try to get some idea of a person's sexual functioning prior to starting antidepressants.

**Tricyclic antidepressants** commonly cause sexual dysfunction, erectile failure in men and anorgasmia in women.

**Selective serotonin reuptake inhibitors (SSRIs)** are associated with even more sexual dysfunction than tricyclic antidepressants and cause loss of sexual interest, erectile dysfunction, ejaculatory delay or failure and anorgasmia, which remits in only one-third of patients who stop the medication. This appears to be dose-related.<sup>5,6</sup> It may be that the failure of two-thirds to experience remission is because their problems are due to the depression itself rather than a long-term effect of the medication. The ability of fluoxetine to delay ejaculation has been capitalized upon such that it is now sometimes used as a treatment for premature ejaculation (see also page 102).<sup>7</sup>

**Monoamine oxidase inhibitors (MAOIs)** such as phenelzine can affect erectile function and can delay ejaculation and female orgasm.

**Viloxazine and L-tryptophan** cause drowsiness and can thus affect libido.

**Nefazodone** (now withdrawn in the UK but available on a named-patient basis) is an analogue of trazodone and causes less sexual dysfunction than other antidepressants. Unlike trazodone it has not been associated with priapism.

**Venlafaxine** is also reported to cause less sexual dysfunction than SSRIs.<sup>8</sup>

**Reboxetine** is a selective noradrenaline reuptake inhibitor which causes little sexual dysfunction except when used in high doses.<sup>9</sup>

**Mirtazepine** is also associated with a low incidence of sexual dysfunction.<sup>10</sup>

**Trazodone** has moderate to high affinity for  $\alpha$ -1 and  $\alpha$ -2 receptors and this may account for its purported positive effects on libido and erectile function. However, although it has been used as a treatment for erectile dysfunction, double-blind

placebo-controlled studies have not found it to be superior to placebo.<sup>11</sup> Trazodone has been associated with priapism.

**Duloxetine** causes less sexual dysfunction than paroxetine, but more than placebo.<sup>12</sup>

**Anti-epileptics:** hyposexuality is common in epilepsy; however, anti-epileptic medications worsen the situation, usually via hormonal effects on the hypothalamic-pituitary-adrenal (HPA) axis. This is particularly true of the hepatic-enzyme-inducing anti-epileptic drugs carbamazepine, phenytoin and sodium valproate. Lamotrigine, which does not induce hepatic enzymes, appears not to affect sexual function.<sup>13</sup>

**Antipsychotics:** there is increasing evidence that antipsychotic medications are associated with marked sexual dysfunction via autonomic and hormonal mechanisms. Thioridazine, aliphatic phenothiazines (e.g. chlorpromazine), sulpiride and the atypical antipsychotic risperidone have all been particularly associated with problems.<sup>14,15</sup> Prolactin-raising antipsychotics are more likely to cause sexual and reproductive dysfunction whereas quetiapine, aripiprazole and olanzapine have been reported to produce less sexual dysfunction. Although relatively prolactin-sparing, clozapine has been associated with sexual dysfunction probably via adrenergic mechanisms.<sup>16</sup>

**Prostate medications:** drugs used to treat benign prostatic hypertrophy (e.g.  $\alpha$ -blockers) may cause ejaculatory problems. Finasteride (5- $\alpha$  reductase inhibitor) reduces sexual desire. Drugs used to treat prostatic cancer include anti-androgens (e.g. cyproterone acetate and flutamide) and gonadotrophin-releasing hormone analogues (e.g. goserelin and leuprorelin). These impair the action of testosterone, thus causing reduced libido and erectile dysfunction.

**Anti-parkinsonian drugs:** L-dopa may cause hypersexuality as a side effect in some cases.

#### **Recreational drugs**

**Psychostimulants** tend to increase sexual desire in the short term, but long-term use may result in reduced sex drive.

**Amphetamine** use is also associated with ejaculatory disturbance in the long term. Long-term *cocaine* abuse is associated with reduced sexual sensations in both men and women and reduced sexual performance in men.<sup>17</sup>

**Ecstasy** alters libido and can increase sex drive at the expense of impaired sexual performance (delayed orgasm and erectile dysfunction), possibly due to increased prolactin secretion.<sup>18,19</sup>

**Crystal methamphetamine** use is growing in the UK. Like ecstasy, it is associated with a significant disinhibiting effect and has been implicated in an increase in sexual risk-taking behaviour. Unlike ecstasy, it appears not to be associated with negative effects on sexual function.<sup>20</sup>

**Alcohol** is disinhibiting and even in small doses may lead to increased sexual desire. Intoxication can result in erectile failure

and long-term alcohol abuse interferes with the HPA axis, resulting in reduced testosterone and feminization in men, and thus reducing sex drive and performance.<sup>21</sup>

**Anabolic steroids** reduce sexual interest, testicular size and fertility in men. In women they may increase or reduce sex drive and may be masculinizing.

**Cannabis** may cause sexual dysfunction in the long term in high doses.

**Opiates:** heroin reduces sexual feelings and may decrease desire, and cause erectile and ejaculatory dysfunction. High-dose methadone is well known to be associated with sexual dysfunction. Buprenorphine is also associated with sexual dysfunction.<sup>22–24</sup>

**Poppers (alkyl nitrates)** increase sexual arousal by increasing blood flow to the genital region. If used in conjunction with sildenafil, these drugs can cause severe lowering of blood pressure.

**Tobacco** in the long term may damage the lining of blood vessels in the genital region and thus cause erectile dysfunction.

### Management of drug-induced sexual dysfunction

Before starting patients on medications known to cause sexual dysfunction, it is necessary to obtain a sexual function history; change in sexual function should be monitored on subsequent visits. Open discussion of the problem may help to reduce non-adherence later on. This will also help to distinguish disease-induced sexual dysfunction from drug-induced sexual dysfunction. A number of approaches have been tried to relieve drug-induced sexual dysfunction, including behavioural strategies to modify sexual technique, delaying the intake of the drug until after sexual activity. In many cases, drug-induced sexual dysfunction is dose-related; thus reduction of medication may improve any dysfunction. However, if this does not help, a 'drug holiday' or changing to a different medication that has fewer sexual side effects may be necessary. It may take up to 6 weeks following the switch for improvement to be seen. For patients who cannot tolerate a reduction of dose or a switch, it may be necessary to institute a drug to treat the sexual dysfunction (adjuvant therapy), such as sildenafil (*Viagra*), tadalafil (*Cialis*), vardenafil (*Levitra*) or yohimbine (see pages 100–101). In appropriate cases, psychosexual therapy should be offered and, with all patients, attention should be paid to the effects on the whole person. ♦

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