Sexual adverse effects with new antidepressants

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Sexual dysfunction is a widely recognised adverse effect of many psychotropic agents. Older antidepressants such as monoamine oxidase inhibitors and tricyclics, particularly clomipramine, are known to engender sexual adverse effects. In depression, this problem is exacerbated by the occurrence of impotence and lowered libido as part of depressive illness itself. We examined evidence relating to more recently introduced antidepressants: selective serotonin reuptake inhibitors, moclobemide, venlafaxine, nefazodone, mirtazapine and reboxetine. We reviewed published trials and case reports collated from searches of Medline, PsychLit and Micromedex from 1985 to December 1997, and contacted manufacturers of new antidepressants and requested information from them.

The true incidence of antidepressant-induced sexual dysfunction is difficult to establish. For instance, people may be understandably reluctant to voluntarily report such information. Direct questioning regarding sexual side-effects may then produce a higher estimate of the level of sexual dysfunction than by allowing individuals simply to volunteer the information. Also, psychogenic factors such as anxiety and depression are known to contribute to impairment of sexual function. Furthermore, few prospective controlled studies of sexual dysfunction have been performed, and so the literature available mainly reports single cases.

Selective serotonin reuptake inhibitors

There are a number of case reports associating SSRIs with sexual dysfunction. Indeed there are more than with other new antidepressants. However, this probably reflects more widespread use rather than a greater propensity to cause such effects. Nevertheless, it is accepted that all SSRIs cause a variety of sexual adverse effects (Gitlin, 1994). The most commonly reported effects are reduced libido, ejaculatory delay, erectile failure and anorgasmia (Hawley & Smith, 1994).

Fluoxetine seems to be the most widely reported of the SSRIs to cause sexual impairment (it is, however, the most prescribed). In men prescribed fluoxetine there have been reports of prolonged erection (Murray & Hooberman, 1993), involuntary sperm emission (Benazzi, 1995) and delayed ejaculation (Hong *et al*, 1996). Ejaculatory abnormalities (failure or delay) have also been reported with paroxetine (Charles *et al*, 1993, Waldinger *et al*, 1997), fluvoxamine (Dorevitch & Davis, 1994), sertraline (Doogan *et al*, 1988) and citalopram (Baldwin & Johnson, 1995).

In women, antidepressant-induced sexual adverse effects seem more varied. Morris (1991) reported spontaneous orgasm with fluoxetine, whereas Herman *et al* (1990) described delayed orgasm and anorgasmia. Fluvoxamine has been linked with an increase in libido and multiple orgasms (Dorevitch & Davis, 1994). Citalopram appears to be the only SSRI reported to cause clitoral priapism (Berk & Acton, 1997).

Clinical studies of the SSRIs report the incidence and nature of sexual adverse effects. However, incidence figures for the same drug vary considerably (perhaps because different methods of evaluation were used) and there are few direct comparisons between drugs. Nevertheless, given that the SSRIs by definition have the same mode of action, differences in the incidence or nature of sexual dysfunction are likely to be small, if indeed they exist.

Moclobemide

Moclobemide is a reversible inhibitor of monoamine oxidase-A (RIMA). Philipp *et al* (1993) describe how moclobemide led to an increase in libido in 18% of patients compared with 6.3% on doxeprin. They also described a case of moclobemide-induced sexual hyperarousal in one woman. Lauerma (1995) reported a similar case of hyperorgasmia and sexual hyperactivity in a female patient taking moclobemide. Despite relatively widespread use, particularly in Europe, we could find no other case reports linking moclobemide with sexual dysfunction. This and clinical experience suggests the incidence of sexual side-effects caused by moclobemide to be very low. Of particular note is that delayed orgasm or anorgasmia seem not to occur.

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Venlafaxine

Venlafaxine inhibits the reuptake of both noradrenaline and serotonin. The manufacturers of venlafaxine have received reports of anorgasmia, increase or decrease in libido, ejaculation disorders, impotence and priapism; most of which could be causally linked to venlafaxine. In their efficacy and safety study, Mendels *et al* (1993) found the difference in incidence of sexual side-effects between placebo and the highest dose of venlafaxine (200 mg a day) to be statistically significant. This may suggest a dose-related effect, further supported by Michael & Owen (1997), who described increased libido and spontaneous erections in a man taking the maximum daily dose of venlafaxine. The number of reports of sexual side-effects with venlafaxine is fairly high considering the drug's recent introduction to the market.

Nefazodone

Nefazodone is a relatively recently marketed antidepressant. It appears to lack sexual side-effects (Dubovsky & Thomas, 1995); this is thought to be because of its antagonist activity at $5HT_2$ receptors. Preskorn (1995) compared information from different databases and found that sexual dysfunction with nefazodone was less common than with other antidepressants. For example, the placebo adjusted incidence for abnormal ejaculation/orgasm with nefazodone was 0.6% compared with paroxetine (12.9%), sertraline (13.3%) and venlafaxine (12%). Indeed, intermittent nefazodone has been used in one case to treat sertraline-induced anorgasmia in a man (Reynolds, 1997), although caution is required with such a combination of drugs because of the potential of serotonin syndrome. We could find no reports associating nefazodone with sexual dysfunction. However, it is difficult to establish whether or not nefazodone is completely free from sexual side-effects as it has only been introduced to the market recently and therefore has not been widely used.

Mirtazapine

Mirtazapine increases noradrenergic and serotonergic neurotransmission via α_2-auto-receptor blockade. The increased serotonergic neurotransmission is mediated only through postsynaptic $5\text{-}HT_{1A}$ receptors. This is because mirtazapine blocks $5\text{-}HT_2$ and $5\text{-}HT_3$ receptors. Thus, as with nefazodone one might expect a low incidence of sexual dysfunction. Indeed, clinical trials show mirtazapine to cause sexual dysfunction no more frequently than placebo and at lower frequency than amitriptyline (Montgomery, 1995). We could find no reports of sexual dysfunction related to the use of mirtazapine.

Reboxetine

Reboxetine acts as a specific noradrenaline reuptake inhibitor. Because of its lack of effect on cholinergic, adrenergic and serotonergic systems (see Table 1) a low incidence of sexual dysfunction might be expected. This seems to be borne out in clinical trials (Berzewski *et al*, 1997), especially at doses of 8 mg a day or less (Mucci, 1997).

Mechanism of sexual side-effects

It can be assumed that certain drugs can be associated with specific types of sexual side-effects. Observing which sexual side-effects are caused by a particular drug or class of drugs (not only antidepressants), and relating them to its

Table 1. Suggested mechanisms of drug-induced sexual dysfunction

Pharmacological effect	Adverse effect	Comments
Cholinergic blockade	May decrease or inhibit sexual function	Data inconclusive
α_1-adrenergic blockade	Inhibition of ejaculation	Orgasm achieved but without ejaculation, e.g. sertindole
	Retrograde ejaculation	Caused by prevention of complete closure of internal urethral sphincter
	Priapism in men and clitoral priapism in women	e.g. trazodone
Hyperprolactinaemia	Decreased libido in both men and women Impotence and azoospermia in men	e.g. typical antipsychotics, risperidone, amoxapine
Inhibition of serotonin reuptake (indirect stimulation of $5\text{-}HT_2$ receptors)	Spontaneous orgasm in women Impotence and delayed ejaculation in men Anorgasmia in both genders	e.g. SSRIs, venlafaxine, clomipramine

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pharmacology, allows one to suggest mechanisms of sexual dysfunction (see Table 1).

Treatment of drug-induced sexual dysfunction

Drug-induced sexual dysfunction can be managed in several ways. Wherever possible, the first step should be a dose reduction. If this fails or is not feasible, the use of another drug with a lower propensity to cause sexual dysfunction would be the next step. Before remedial drug therapy (for example cyproheptadine) is considered, a drug holiday (Rothschild, 1995) may be an appropriate option.

The choice of remedial drug therapy depends on the underlying mechanism of sexual dysfunction. For example, if the adverse effect is thought to be caused by enhanced serotonergic neurotransmission, cyproheptadine may be the drug of choice. Cyproheptadine is an antihistamine with 5-HT_2 antagonistic activity. Waldinger (1996) described an improvement in SSRI-induced sexual dysfunction with cyproheptadine. Aizenberg *et al* (1995) also conclude that cyproheptadine may be beneficial in those with SSRI-induced decreased libido and anorgasmia, and Lauerma (1996) reported the successful use of cyproheptadine in treating citalopram-induced anorgasmia. Oddly, Nelson *et al* (1997) report the first case of using a 5-HT_3 antagonist (granisitron) to treat fluoxetine-induced anorgasmia.

The use of yohimbine to treat impotence is widely recognised. Yohimbine is an α_2-adrenoceptor antagonist and an α_1-adrenoceptor agonist. Jacobsen (1992) has shown yohimbine to have some potential in the treatment of fluoxetine-induced orgasmic and erectile difficulties.

Unlike the remedial pharmacological treatments discussed above, the mechanism of action of amantadine in treating antidepressant-induced sexual dysfunction is not clear. Amantadine is a dopamine agonist and Shrivastava *et al* (1995) describe its successful use in treating SSRI-induced ejaculatory difficulties. Also, in one case amantadine has been used five to six hours before coitus to treat fluoxetine-induced anorgasmia (Balon, 1996).

Therapeutic uses of sexual side-effects

The sexual adverse effects of some antidepressants are so well known that they are used to relieve some sexual problems. For example, clomipramine and SSRIs can be used to treat premature ejaculation and trazodone is used for erectile dysfunction. Readers are directed to the review of Waldinger (1996) for a full discussion.

Comment

The true incidence and type of sexual dysfunction caused by antidepressants is difficult to establish. Furthermore, the incidence figures quoted for the same drug may vary considerably and there are few direct comparisons. Of the newer antidepressants, nefazodone and moclobemide appear to cause few sexual side-effects. The SSRIs and venlafaxine are more widely associated with sexual dysfunction. Such adverse effects, however, can have therapeutic uses. The treatment options available for antidepressant-induced sexual dysfunction are a dose reduction, changing to a different antidepressant, a drug holiday or remedial therapy. In clinical practice a dose reduction or change of drug therapy are the most common forms of treatment.

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