

Antidepressant induced sexual dysfunction Part 1: epidemiology and clinical presentation

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Abstract

Sexual dysfunction is a common side effect of treatment with antidepressants, particularly those with a predominantly serotonergic mechanism of action. Although there has been an increasing awareness of the problem in recent years, it is still probably true to say that sexual side effects often go undetected. Antidepressant induced sexual dysfunction has significant implications for a patient's quality of life and that of their family unit. The issue cannot be ignored because it is likely to impact on a patient's sense of wellbeing, their compliance with medication and ultimately the prognosis of their illness. This review will be presented in two parts. The first part focuses on the prevalence of antidepressant induced sexual dysfunction and its clinical presentation both generally and in the case of individual classes of antidepressants. The second part will focus on the assessment and management of the problem. The aim of this review is to improve overall awareness of sexual side effects and to suggest a rational approach to their detection and management. It is not intended to be a detailed exploration of underlying causative mechanisms and receptor neurochemistry.

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Introduction

Sexual dysfunction has been reported in 26% of the normal subjects and 45% of untreated depressed patients.¹ In addition to being a common symptom of depression, the use of antidepressant medication is also associated with difficulties in sexual functioning. Indeed, the association of sexual side effects with the use of antidepressants has been conclusively demonstrated and antidepressants can clearly both aggravate and precipitate sexual problems.^{2,3,4}

The additional burden of antidepressant induced sexual dysfunction (AISD) exacerbates an already difficult situation.

As antidepressant treatment is usually a long-term undertaking, the presence of sexual dysfunction is likely to adversely affect the quality of life of patients, their partners and indirectly their families. Although there is not currently any reliable data on the subject it is estimated that a significant proportion of patients who suffer from severe AISD will discontinue treatment because of that side effect.⁵ Sexual dysfunction is likely to have a significant impact on a patient's compliance with medication and, by implication, their prognosis and the likelihood of relapse or recurrence.

It is therefore important that clinicians appreciate the extent of the problem. They should also be aware of how antidepressant induced sexual side effects present clinically. If they are not then AISD will continue to go under reported, inadequately assessed and poorly managed. Part 1 of this review focuses on the epidemiological and clinical aspects of the problem. Some reference is made to the likely aetiology of sexual side effects in individual classes of antidepressants, but a detailed exploration of the underlying neurochemistry and physiology is not included. Part 2 will focus on the assessment and management of AISD.

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Epidemiology

The exact prevalence of AISD is not clear. Early estimates that were based on spontaneous self-reporting substantially underestimated the frequency of the condition.⁶ Later estimates that specifically looked for this side effect reported rates from 20% to 40% and 10% and 50%.^{4,7} A prospective Spanish study in 2001 found that the overall incidence of sexual dysfunction in 1022 outpatients was 59.1% when all antidepressants were considered as a whole.⁵ A 2003 study of 4557 depressed patients in France reported that the frequency with which antidepressant drugs aggravated the sexual dysfunction associated with depression was even higher.⁸ It found that the frequency of sexual dysfunction was 71% amongst patients treated with antidepressants and 65% in untreated patients. Although estimates of the extent of the problem vary widely for various methodological reasons, the fact remains that AISD is a common problem. It is also true that more recent studies that have looked more aggressively for AISD have tended to report higher prevalence rates. Furthermore, there is some evidence that AISD has a greater prevalence in females (38.7%) compared to males (24.9%).¹

Sexual dysfunction has been reported as a side effect of all antidepressants, but there is a certain amount of variation from one antidepressant to another in terms of the prevalence, clinical presentation and likely underlying mechanism that produce the AISD associated with their use. These differences are highlighted in the discussion that follows, but an emphasis is placed on those with serotonin re-uptake inhibition as their predominant mechanism of action.

Clinical presentation and aetiology

The specific types of sexual dysfunction associated with antidepressants include decreased libido, erectile dysfunction, delayed ejaculation or orgasm, anorgasmia and decreased genital sensation.⁹ The commonest complaints are those of decreased libido, impaired erection and difficulties with ejaculation or orgasm.¹⁰ Increased libido, improved or spontaneous erections or orgasms, priapism and altered sexual sensations and sensitivity have been less commonly reported. There is also evidence to suggest that the direct effect of an antidepressant on diminishing libido and orgasm can have indirect adverse effects on sexual arousal over time.⁸ All sexual side effects, with the possible exception of rare cases of priapism, are thought to be reversible. It is important to note that not every sexual side effect is undesirable.² For example, serotonergic antidepressants are often effective in the treatment of premature ejaculation and may also be beneficial in the control of paraphilias.

Unfortunately, because both depression and its treatment can disturb the desire, arousal and orgasm phases of the human sexual response cycle, determining which of them is actually causing the sexual problems can be very difficult. Obviously, the temporal relationship between the onset of the sexual dysfunction and the onset of other depressive symptoms or antidepressant treatment may provide a clue. The precise nature of the sexual dysfunction may also suggest whether it is depression or its treatment that is the more likely cause. It has been reported that between 40% and 50% of people with depression complain of diminished libido and problems with arousal in the month before diagnosis, while in comparison only 15% to 20% of patients

Table I: Factors that may contribute to sexual dysfunction during treatment with an antidepressant

| | FACTORS |
|----------------------|---|
| BIOLOGICAL | Psychiatric illness Other psychiatric treatment Medical illness Medical treatment Neurological insult Substance use Hormonal change |
| PSYCHOLOGICAL | Developmental issues Lifecyle issues Sexual trauma Concern about sexually transmitted diseases Sexual identity issues Poor self esteem |
| SOCIAL | Cultural issues Religious issues Environmental issues Interpersonal conflicts Partner specific Sexual activity specific Pregnancy and child bearing |

experience difficulties with orgasm prior to taking an antidepressant.¹¹ Complaints of orgasmic dysfunction with relatively little impairment in desire and arousal are therefore more likely to be caused by the antidepressant. However, it may in many cases be impossible to discern the underlying cause, and in reality it is likely that multiple factors are involved. Some of the factors that can potentially contribute to sexual dysfunction during antidepressant treatment are listed in Table I.¹²

As a group the antidepressants can cause a variety of side effects including sedation, hormonal changes, disturbances of cholinergic-adrenergic balance, peripheral α -adrenergic antagonism, inhibition of nitric oxide and increased serotonergic activity.¹³ All of these side effects and indeed most antidepressants have been associated with the development of sexual dysfunction. However, the actual mechanisms that produce AISD are varied and generally poorly understood. A number of newer antidepressants with different mechanisms of action appear to be less likely to cause sexual side effects.⁸ These antidepressants with a lower incidence of sexual dysfunction are invariably either relatively free of serotonergic effects or have highly selective receptor activity at central serotonergic synapses.

Tricyclic antidepressants

The approximate prevalence of sexual dysfunction with tricyclic antidepressants is about 30%.¹⁴ Specific problems include decreased libido, erectile dysfunction, delayed orgasm and impaired ejaculation. Painful ejaculation has been reported very rarely. These side effects can probably be best explained by the anticholinergic properties of tricyclic antidepressants, with the possible exception of decreased libido where their dopamine antagonist properties are likely to be involved.¹⁵ In addition, to a greater or lesser extent tricyclics also produce serotonin re-uptake inhibition. There appears to be some correlation between this and their propensity to cause sexual dysfunction. For example, the prevalence of delayed orgasm with

clomipramine may be double that of other tricyclics.¹⁴ Indeed, sexual dysfunction was reported in 95% of subjects involved in a trial of clomipramine for obsessive-compulsive disorder.¹⁶ This is possibly as a result of its strongly serotonergic mechanism of action. The tricyclic antidepressants are a diverse group of compounds and their lack of receptor selectivity means that a combination of neurotransmitter systems are likely to be involved in the production of their sexual side effects.

Monoamine oxidase inhibitors

Overall, approximately 40% of patients taking irreversible monoamine oxidase inhibitors experience sexual dysfunction.⁵ Specific side effects are similar to those of the tricyclic antidepressants.² The inhibition of monoamine oxidase is neither a neurotransmitter nor receptor selective mechanism of action. Consequently, the cause of sexual side effects with these agents is likely to involve numerous factors and all the monoamine neurotransmitters. The reversible monoamine oxidase inhibitor, moclobemide, appears to be much less likely to cause sexual dysfunction. The prevalence of sexual dysfunction with moclobemide has been reported to be only 3.9%.⁵

Selective serotonin re-uptake inhibitors

AISD is particularly common with serotonergic antidepressants.¹⁷ Overall, it appears that the prevalence of sexual difficulties in clients on serotonergic antidepressants is likely to be between 58% and 73%.⁵ Although this section refers to the selective serotonin re-uptake inhibitors (SSRIs) it is important to remember that a number of other antidepressants also have a predominantly serotonergic mechanism of action.

The specific sexual problems most strongly associated with SSRIs include decreased libido and delayed orgasm. In a major study of 1022 subjects citalopram and paroxetine emerged as the worst offenders.⁵ Furthermore, significant differences in the prevalence of specific sexual side effects appeared to exist between the individual SSRIs. In this study the overall incidence of sexual dysfunction for citalopram was 72.7%. The specific problems associated with its use included decreased libido (62.1%), delayed orgasm or ejaculation (63.6%), anorgasmia or no ejaculation (51.5%) and erectile dysfunction or decreased vaginal lubrication (34.8%). The overall incidence for paroxetine was 70.7%, while 63.9% experienced decreased libido and delayed orgasm or ejaculation, 52% anorgasmia or no ejaculation and 41.4% difficulties with erection or vaginal lubrication. For sertraline the overall incidence was 62.9%, with 54.7%, 56.6%, 47.1% and 28.9% complaining of decreased libido, delayed orgasm or ejaculation, anorgasmia or no ejaculation and erectile dysfunction or decreased vaginal lubrication respectively. Fluvoxamine (62.3%, 48.1%, 54.5%, 37.6% and 20.8%) and fluoxetine (57.7%, 50.2%, 49.5%, 39.1% and 21.8%) emerged from this study with the lowest incidence of sexual dysfunction. However, the overall incidence of sexual dysfunction with this class of antidepressants was found to be so high that individual differences are of limited clinical usefulness. Head-to-head comparative studies are needed, as conclusions drawn from comparisons across trials are relatively meaningless.

These results seem to suggest that paroxetine is associated with higher rates of erectile dysfunction and decreased vaginal lubrication, both of which represent a disturbance in the arousal phase of the sexual response cycle. This may be an exception to the rule or possibly due to selective reporting. Delayed ejaculation and impaired arousal have been reported previously with fluoxetine.¹⁸ However, it is generally accepted that the SSRIs predominantly affect sexual desire and orgasm. Although they can and do impair arousal, this is a less common finding and it may in many cases be the indirect result of impairments in other phases of the sexual response cycle. Difficulties with orgasm have been particularly strongly associated with SSRIs, and have been present in approximately two-thirds of patients in a number of other studies.^{19,20}

Complaints of decreased genital sensation are encountered in clinical settings, but this side effect has received little attention in the current literature. Penile anaesthesia has been reported with fluoxetine in rare cases, but this remains an unclear and controversial AISD.²¹ The role of serotonin in the peripheral nervous system may represent a plausible explanation of this side effect.

The SSRIs are thought to cause decreased libido and their other sexual side effects by increasing synaptic concentrations of serotonin and stimulating 5HT₂ and, possibly, 5HT₃ receptors.¹⁰ This results in decreased levels of dopamine activity in mesolimbic structures. SSRIs may cause delayed or absent ejaculation and orgasm by increasing serotonin release from neurones in the descending pathways between the brain and the dorsal horns of the spinal cord. Increased libido and spontaneous ejaculation or orgasm may be due to 5HT_{2A} receptor antagonistic effects, although this is a more likely occurrence with the use of trazodone and nefazodone.⁷ Priapism, although it has been reported with SSRIs, is not considered to be primarily a serotonergic effect; it is likely to be caused by blocking the α -1 adrenoceptor receptors that inhibit sympathetically mediated penile detumescence.²²

The impact of the SSRIs on sexual function is perhaps one of the most significant side effect of this class of drugs. It is certainly an important problem given their widespread and often long-term use. Unfortunately, the use of these agents is seldom accompanied by close monitoring for adverse events, particularly not for AISD.

Other antidepressants

The incidence of sexual dysfunction is high with venlafaxine, a serotonin and noradrenaline re-uptake inhibitor. It has been reported in 67.3% of patients using the agent.⁵ Specific problems associated with venlafaxine include decreased libido (60.0%), delayed orgasm or ejaculation (61.9%), anorgasmia or no ejaculation (41.8%) and erectile dysfunction or decreased vaginal lubrication (40.0%). Decreased libido and delayed orgasm are very common, but disturbances in other phases of the sexual response cycle are only somewhat less so. The mechanism involved is probably similar to that of the SSRIs at lower doses, although at higher doses other neurotransmitters are likely to contribute. This may explain the slightly different side effect profile which venlafaxine has in comparison with the SSRIs.

The extent of sexual dysfunction associated with the use of

trazodone has not been clarified.⁵ Impaired ejaculation and both increases and decreases in libido have been reported and trazodone has been used in some cases to promote erection. Priapism occurs in approximately 0.01% of subjects treated with trazodone.²²

Mirtazapine appears to have relatively low rates of sexual dysfunction with an incidence reported as 24.4%.⁵ The most common sexual side effects are decreased libido (20.4%) and delayed orgasm or ejaculation (18.4%). Anorgasmia or no ejaculation (8.2%) and erectile dysfunction or decreased vaginal lubrication (14.2%) are considerably less common. Mirtazapine's selective antagonism of 5HT₂ and 5HT₃ receptors is thought to be the main reason why it is associated with relatively little sexual dysfunction.²³

The incidence of sexual dysfunction with nefazodone has been found to be as low as 8.0%.⁵ Decreased libido (6.0%), delayed orgasm or ejaculation (2.0%), anorgasmia or no ejaculation (2.0%) and erectile dysfunction or decreased vaginal lubrication (0.0%) are all extremely infrequent side effects. Nefazodone is a potent antagonist of 5HT₂ receptors and this is likely to be the reason for its benign sexual side effect profile.²⁴

The approximate prevalence of sexual dysfunction with reboxetine is estimated to be between 5% and 10%.²⁵ Various abnormalities of orgasmic function have been described, but other phases of the sexual response cycle are thought to be relatively unaffected by this agent. Reboxetine is a noradrenaline re-uptake inhibitor with no serotonergic activity.

The dopamine enhancing antidepressant, bupropion, appears to have a very low likelihood of causing sexual dysfunction although reliable estimates of the frequency of the problem are lacking.²⁶ Bupropion does not enhance serotonergic activity at central synapses.

Conclusion

Major depression is a serious illness that is usually treated with antidepressant medication. Depression can place a significant strain on relationships in its own right and the further burden of AISD, in addition to impinging on a major area of most peoples lives, is likely to adversely affect compliance and the likelihood of relapse. This is particularly significant given the often long-term nature of the illness and its treatment. It is also important given the widespread use of antidepressants for depressive and anxiety disorders of sub-clinical severity.

More recent antidepressant drugs with different mechanisms of action appear to have less sexual dysfunction associated with their use. These agents have one of two things in common. Either their pharmacodynamic activity does not significantly involve serotonin, or, if they are serotonergic antidepressants, then they have selective 5HT₂ (and possibly to a lesser extent 5HT₃) receptor antagonist properties.

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