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Antidepressant-Induced Sexual Dysfunction

Introduction

Sexual dysfunction is an often overlooked effect associated with drug therapy of various psychiatric conditions. This problem not only negatively impacts on a patient's quality of life, but also leads to greater instances of medication noncompliance. In the treatment of depression, sexual dysfunction has become more prevalent, in part due to increasing use of selective serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs). As a group, these antidepressants are now often prescribed preferentially over the older tricyclic antidepressants (TCAs).

Epidemiology

Antidepressant drug monographs often report a low frequency that ranges between 2% to 27%. This underreporting of sexual dysfunction in part relates to the fact that surveys concerning sexual dysfunction may not always be conducted in clinical trials. The general population is generally reluctant to discuss issues pertaining to sexual problems with a physician. The actual incidence of sexual dysfunction is unknown, but as much as 50% (or more) of patients treated with antidepressants, in particular SSRIs, experience some degree of sexual dysfunction.

Ruling out other causes of sexual dysfunction

The risk for developing sexual dysfunction can be influenced by age, gender, lifestyle, relationship, and health. Even in the absence of medications, psychiatric patients are predisposed to experiencing sexual dysfunction. For example, a patient with schizophrenia can present with lack of volition and a depressed patient can often present with loss of libido. Various medical conditions such as endocrine disorders and cardiovascular diseases can be associated with sexual dysfunction. Various non-psychiatric medications are known to curtail sexual function. These include cardiovascular drugs, histamine$_2$-blockers, and lipid-lowering agents. In most cases, sexual function is restored upon discontinuation of the offending drug(s). In regards to drugs of abuse, the potential for alcohol and illicit drug use to adversely affect sexual function should not be underestimated.

Three phases of sexual response

The human sexual response is a complex function that incorporates a combination of physiologic, cognitive, and behavioral components. The first phase of the sex cycle is libido, or sexual drive, which is controlled primarily via the mesolimbic dopaminergic reward pathway. This is the same pathway that mediates other physiologic "highs", as well as artificial highs induced by illicit drugs. Next follows the arousal phase, which is characterized by erectile function in men and vaginal lubrication in women. The cycle culminates in the orgasm phase where sexual energy and tension are relieved.

Biochemical Factors that Affect Sexual Function

Cholinergic-adrenergic balance

Changes in sexual function can result through modulation of the cholinergic-adrenergic balance. Parasympathetic activity mediates spinal reflexes that are involved in vasodilatory effects that promote erectile function and clitoral engorgement. In theory, drugs with significant anticholinergic effects can decrease sexual arousal. Peripheral alpha$_1$-adrenergic activation is also important in maintaining sexual function. Evidence from animal studies suggests that stimulation of noradrenergic

tone increases sexual behavior and as such, drugs that exhibit alpha-adrenergic antagonism tend to cause a reduction in sexual function.

Dopamine

Stimulation of dopaminergic neurotransmission is important in maintaining libido and arousal. Dopamine antagonists have been documented to cause erectile dysfunction whereas dopamine agonists such as levo-dopa have been reported to cause increase in sexual interest and spontaneous erections.

Prolactin, estrogen, and testosterone

Testosterone and estrogen are believed to promote libido, whereas prolactin can cause a reduction. Aside from impairing sexual desire and/or performance, increased prolactin has been known to cause breast enlargement and galactorrhea. Dopaminergic stimulation decreases prolactin secretion whereas serotonergic stimulation can have the opposite effect. Many of the psychotropic medications such as neuroleptics and serotonergic antidepressants often cause an elevation in prolactin. Intuitively, drugs that elevate prolactin such as risperidone should cause stronger inhibition of sexual function than those that cause less prolactin elevation such as olanzapine and quetiapine.

Serotonin

Elevated central serotonin levels have the potential to inhibit all three phases of the sexual cycle. Serotonin excess can inhibit the spinal reflexes responsible in mediating sexual arousal. Serotonin affects the hypothalamic-pituitary axis and can impair the release of estrogen and testosterone, while enhancing the release of prolactin. Furthermore, a surge in serotonergic tone inhibits dopamine-related activation of sexual response. Serotonin receptors have been touted to influence sexual function. Stimulation of 5-HT_2 receptors is especially inhibitory to sexual function, while blockade or minimal effects on this receptor will likely cause fewer undesirable effects on sexual function. On the other hand, sexual function is facilitated through 5-HT_{1a} receptor stimulation and possibly through 5-HT_3 receptor blockade.

Nitric oxide (NO)

Nitric oxide causes smooth muscle relaxation to allow greater perfusion to mediate the vascular changes for erection and lubrication. By increasing arousal, NO is thought to indirectly enhance sexual desire and orgasm.

Antidepressants and Effects on Sexual Function

Antidepressants have been reported to impair all phases of sexual function. The mechanism for this effect relates in part to the pharmacological action of these drugs, including serotonergic activation, hormonal changes, disruption of the adrenergic-cholinergic balance, inhibition of alpha-adrenergic tone, and inhibition of NO.

SSRIs

Potent and selective serotonin reuptake inhibition results in a 5-HT_2-mediated decrease in norepinephrine and dopamine activity necessary for orgasm and ejaculation. Though the impact of SSRIs on sexual function varies considerably between individuals, orgasm-related dysfunction appears to be the most troublesome of the adverse sexual side effects. SSRI-induced sexual dysfunction generally occurs early in treatment and subsequently either remits, improves, or persists over time.

In comparison to the other SSRIs, paroxetine has one of the highest potency for serotonin reuptake inhibition, has little or no dopamine reuptake inhibition, and has the most anticholinergic effects. Sertraline has comparable potency as paroxetine for serotonin reuptake inhibition, but also inhibits dopamine reuptake. A newer SSRI, citalopram is less potent than paroxetine and sertraline in terms of serotonin reuptake inhibition, but is the most selective of the SSRIs for serotonin reuptake relative to norepinephrine and dopamine.

On the basis of pharmacology alone, both paroxetine and citalopram should correlate with higher inhibition of sexual function relative to other SSRIs, whereas the opposite would hold true for sertraline. However, there is no conclusive evidence in the literature to support this claim. Until further data is made available,

there does not appear to be one SSRI that preferentially causes fewer sexual side effects. Not all effects of SSRIs on sexual function are undesirable. In the treatment of depression, these drugs improve depression-induced sexual dysfunction. They can correct premature ejaculation in addition to reversing sexual dysfunction secondary to phobic avoidance.

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)

TCAs and MAOIs have been known to cause sexual dysfunction, though likely less often in reported cases when compared to SSRIs. The predominant effect from TCAs on sexual function appears to be reduced libido and erectile dysfunction. In comparison to classical MAOIs, moclobemide seems to cause fewer sexual side effects.

Bupropion

This norepinephrine and dopamine reuptake inhibitor is virtually devoid of serotonergic activity. Adverse sexual side effects have seldom been reported. In fact, its dopaminergic effect may enhance sexual function. A standard daily dose of 75-150mg has been used as adjunctive therapy in combination with an SSRI in curtailing sexual dysfunction, though beneficial outcomes from this combination therapy have rarely been documented.

The potential for drug interaction further limits the usefulness of a bupropion/SSRI combination. Some SSRIs inhibit the cytochrome P450 3A4 and 2D6 isoenzymes (which are partially responsible for the metabolism of bupropion). As such, combination therapy with an SSRI can lead to increased serum bupropion levels.

Nefazodone and mirtazapine

Nefazodone blocks serotonin reuptake, but also blocks post-synaptic 5-HT_2 receptors. The latter effect is beneficial in term of causing less sexual dysfunction. However, recent reports of hepatotoxicity will limit its usefulness. Mirtazapine blocks the 5-HT_2, 5-HT_3 and $alpha_2$ receptors, as well as increase norepinephrine neurotransmission. Similar to nefazodone, mirtazapine has been touted to cause fewer sexual side effects than SSRIs, but the potential for this drug to cause weight gain may be problematic for some patients.

Venlafaxine

This drug is a dually acting antidepressant with both serotonin and norepinephrine activity. In addition to increased norepinephrine activity, dopamine reuptake inhibition has been described at the higher doses. Intuitively, this drug should cause fewer sexual side effects due to the compensatory norepinephrine and dopamine activity that offset the undesirable serotonergic effects on sexual function.

Management Strategies

Non-drug interventions

An individual's psychological state affects sexual performance. As such, acknowledgement and reassurance from the health care provider(s) can be beneficial. Watchful waiting for adaptation leading to natural resolution of the sexual dysfunction is a must for any individual affected. Minor medication adjustments from dosage reduction, to drug holidays, and to delay of drug administration until after coitus can help ease some of the problems. A drug holiday requires discontinuation of the antidepressant for a brief period of time, but involves medication compliance and advanced planning on the part of the patient and inherently carries with it the risk of discontinuation symptoms.

Treatment alternatives

Other more aggressive approaches include switching to an alternate antidepressant to inclusion of adjunctive drug or drugs to treatment regimen. However, in changing pharmacologic treatment relapse is possible, as is the emergence of new side effects. These considerations must be weighed into the decision making process.

Suitable alternatives that are associated with fewer sexual side effects include venlafaxine, mirtazapine, and bupropion. These along with nefazodone are summarized in the following table.

Antidepressant	Purported mechanism for alleviating sexual dysfunction
Bupropion	§ Potentiates dopamine neurotransmission § Devoid of serotonergic effect
Nefazodone	§ Blocks post-synaptic 5-HT_2 receptors
Mirtazapine	§ Blocks 5-HT_2 and 5-HT_3 receptors § Increases norepinephrine neurotransmission
Venlafaxine	§ Serotonin effect is offset by its stimulatory effects on norepinephrine and dopamine neurotransmission

Adjunctive treatments

A variety of adjunctive treatments for sexual side effects have been described medical literature. Yohimbine, an alpha$_2$-antagonist, can help restore sexual function by increasing norepinephrine activity. Amantadine is another agent that has been used for this purpose via its dopaminergic effect. This drug can be given 75 to 100mg BID or 100 to 400mg as needed, prior to coitus. Sildenafil (Viagra®) stimulates NO effects to alleviate sexual side effects. A dose of 25 to 100 mg given prior to coitus may be effective in correcting drug-induced erectile difficulties. In addition to these three drugs, other drugs that have been used include buspirone, the serotonin antagonist cyproheptadine and the cholinergic agonist bethanechol.

In clinical practice, these treatment options are seldom employed. Due to the complex nature of sexual function, these adjunctive agents may be effective only in select individuals.

Summary

While sexual dysfunction is an often overlooked effect from antidepressants, efforts should be taken to ensure recognition and adequate management of the problem. With a growing list of pharmacological choices, clinicians can now preferentially choose antidepressants that have lower potential to impair sexual functioning.

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