

Serotonin and Sexual Dysfunction

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Editorial

Sexual dysfunction is a common side effect of psychotropic drugs and has received much attention because of its negative effects on quality of life and adherence to antidepressant agents. In patients with depression, sexual dysfunction can be attributed to the underlying disorder or to antidepressant drugs. Sexual dysfunction also can occur with first generation antipsychotic drugs and second-generation antipsychotic drugs (e.g., thioridazine and risperidone, respectively). In patients with schizophrenia, sexual dysfunction can be attributed to the underlying illness as well as to antipsychotic induced hyperprolactinemia due to dopamine blockade in tuberoinfundibular pathway [1].

Sexual behavior in humans is influenced by dopamine (DA) and serotonin (5-HT) neurotransmission [2]. In general, DA enhances, whereas 5-HT inhibits, sexual motivation and performance and thus may contribute to initiation and satiety, respectively. Dopamine has enabling effects on sexual motivation, copulatory competence, and genital reflexes. Dopamine in the nigrostriatal pathway influences motor activity and in the mesolimbic pathway it activates various motivational behaviors, including sexual activity. In the medial preoptic area (MPOA) it controls genital reflexes, sexual configurations, and specifically libido.

Serotonin generally inhibits sexual activity. Sexual behavior is impaired by many 5-HT agonists and agents that increase 5-HT [3]. Serotonin (5-HT) is primarily inhibitory, although stimulation of 5-HT_{2C} receptors increases erections and inhibits ejaculation, whereas stimulation of 5-HT_{1A} receptors has the opposite effects like facilitation of ejaculation and, in some circumstances, inhibition of erection. 5-HT is released in the anterior lateral hypothalamus at the time of ejaculation. Microinjections of selective serotonin reuptake inhibitors there actually delay the onset of sexual activity and delay ejaculation after sexual activity and begins elevating lateral hypothalamic area (LHA) 5-HT via reverse dialysis decreased extracellular DA during both normal conditions and during sexual activity. Together with these findings [4], suggest that LHA 5-HT exerts inhibitory control over sexual activity, in part, by inhibiting NAcc DA release after an ejaculation. This research has important clinical implications for those taking SSRI antidepressants, major side effects of which are impairment of ejaculatory and orgasmic ability and decreased libido.

Different subtypes of 5-HT receptors appear to mediate the inhibitory effects of 5-HT on erection and on ejaculation. Systemic administration of the 5-HT_{1B} receptor agonist anipriline impaired ejaculation in male rats [5]. Sexual side effects subsequent to antidepressant, antipsychotic or other serotonergic drugs have been illustrated almost exclusively in terms of serotonin receptor subtype activation or inhibition in the central nervous system.

The incidence of sexual dysfunction associated with antidepressants in controlled trials has been estimated to be between 30% and 60%; however, few trials measured baseline sexual functioning. Some clinicians estimate the actual incidence of antidepressant-induced sexual dysfunction to be as high as 85%. Sexual dysfunction is a common side effect associated with several antidepressants. The TCAs associated with the highest incidence of sexual dysfunction are clomipramine, amitriptyline, imipramine, and doxepin. The secondary amines, desipramine and nortriptyline, are associated with the lowest rates of sexual dysfunction among the TCAs. The incidence of SSRI induced sexual dysfunction is about 50-60% as measured by the rush sexual inventory scale and appears to be slightly more common in men where delayed ejaculation and anorgasmia are the most common complaints. Women report difficulty achieving orgasms or a decrease in sexual activity all together.

Pharmacological properties also may enable clinicians to select appropriate antidotes for the adverse effect. Neurotransmitters, hormones, and other molecules are involved in the three stages of sexual function. Drugs that alter the levels of these molecules may affect the various aspects of sexual function. For example, nitric oxide plays a role in arousal by causing vascular changes required for penile erection. Paroxetine reduces nitric oxide levels and inhibits sexual arousal. Antidepressants that have minimal 5HT reuptake blocking effects (e.g., bupropion, mirtazapine, and nefazodone) are associated with a significantly lower incidence of sexual dysfunction. Furthermore, agents such as mirtazapine and nefazodone have the additional benefit of 5-HT₂ antagonism resulting in increased dopamine activity.

Therapeutic Considerations

When a patient reports sexual dysfunction, the clinician should inform the patient that it may be a transient occurrence that will improve after several weeks. In some patients, decreased libido may persist and warrant management. Reports of difficulty with ejaculation or orgasm increases the likelihood that sexual dysfunction may be antidepressant-induced. Antidepressant-induced sexual dysfunction appears to be dose-related; therefore, if symptoms persist, the next step is to decrease the dose of the antidepressant. For patients taking a stabilized antidepressant dose, gradual reduction of the dose is recommended and monitoring for the re-emergence of depressive symptoms is especially important. For patients receiving short-acting SSRIs (e.g., paroxetine and sertraline), drug holidays may be an option. An open-label study with paroxetine and sertraline suggested that if patients skipped doses on Fridays and Saturdays, sexual function would return to normal on the weekends. However, this method may

promote treatment nonadherence resulting in depression relapses. The importance of adherence should be reemphasized to patients. Patients also need to be informed of antidepressant withdrawal symptoms during drug holidays (especially with paroxetine), such as gastrointestinal symptoms, dizziness, and paresthesias. This strategy is not recommended for patients who have a history of treatment nonadherence or only partial response to antidepressant treatment.

If the above strategies are not successful, many clinicians may choose to add an antidote to treat sexual dysfunction. Bupropion is usually the most preferred agent because of lack of serotonergic activity and its dopamine- and NE-enhancing properties. This may be the mechanism for improving SSRI-related sexual side effects that result from the suppression of these neurotransmitters. Studies and case reports suggest that the addition of bupropion can restore libido and also may relieve anorgasmia. Bupropion is a mild cytochrome P450 2D6 inhibitor and use of this drug may require an assessment for potential drug interactions, as well as precautions regarding seizures at high doses and past history of eating disorders. Bupropion also may aggravate symptoms of anxiety and jitteriness associated with depression, other agents, such as amantadine, buspirone, cyproheptadine, dextroamphetamine, ginkgo biloba, methylphenidate, sildenafil, and yohimbine, have been used to manage SSRI-induced sexual dysfunction; however, evidence regarding efficacy is limited [5]. Buspirone is a partial agonist of the 5-HT_{1A} receptor that decreases 5-HT transmission and increases dopamine activity. Although some reports suggest efficacy in improving libido and delayed orgasm, a randomized, controlled trial failed to confirm this finding. Cyproheptadine is an antihistamine with potent anti-serotonergic properties; however, the agent is sedating, which limits its intended use just before sexual intercourse. Ginkgo biloba increases peripheral blood flow to the genital organs and may have beneficial effects on arousal, but clinical results are variable. In a randomized, controlled

trial, sildenafil effectively improved erectile function and other aspects of sexual dysfunction associated with the use of SSRI antidepressants.

Switching to an antidepressant associated with less sexual side effects may be effective, especially when patients are having less than full response to the initial antidepressant. Studies showed improvement in sexual functioning when patients were switched to bupropion, mirtazapine, or nefazodone. However, clinicians should be aware that switching antidepressants may result in other side effects and possibly relapse of depressive symptoms. The decision on whether to add an antidote or to switch to another antidepressant may depend on the patient's preference and response to the initial antidepressant. Some patients may resist switching therapy for fear of relapse.

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