

Sexual Dysfunction and Psychotropic Medications: Review and Management

Allen SN*

Department of Pharmacy, Philadelphia College of Osteopathic Medicine, USA

***Corresponding author:** Shari N Allen, PharmD, BCPP, Associate Professor of Pharmacy Practice, Philadelphia College of Osteopathic Medicine, School of Pharmacy, USA, Email: sharial@pcom.edu

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Abstract

Sexual dysfunction is a disturbance in sexual function that may be experienced by both males and females. It may be caused by mental health disorders, namely depression, anxiety, schizophrenia, and bipolar disorder. It may also be caused by the pharmacologic treatments used to treat the common mental health conditions. Antipsychotics increase the risk of sexual dysfunction in relation to their affinity to dopamine as well as acetylcholine, histamine, and the alpha receptors. The antidepressants that have an affinity for serotonin, have a greater risk of sexual dysfunction. Of the mood stabilizers, lithium is considered to have the highest incidence of sexual dysfunction this may be attributed to its relaxation of the corpus cavernosa and is seen even more so when combined with a benzodiazepine. When sexual dysfunction is a concern the psychotropic choice should be evaluated for its potential to contribute. Other appropriate options are to adjust the dose of the agent or use adjunct medication to help address the dysfunction while still utilizing the psychotropic of choice.

Keywords: Sexual Dysfunction; Hypersexuality; Antipsychotics; Antidepressants; Mood Stabilizers

Introduction

Sexual dysfunction is a disorder characterized by a disturbance in sexual desire and the physiological changes associated with the sexual response cycle (excitement, plateau, orgasm, and resolution). While more commonly recognized as a male dominated disorder, sexual dysfunction may occur in both males and females with a higher prevalence being reported in the female population. The prevalence in males is reported to be between 10-52% while females report an occurrence of sexual dysfunction between 25% and 63% [1]. There are many different types of sexual dysfunction recognized and defined by bodies of work such as the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition, International Classification of Diseases – 10, and the International Consultation on Sexual Medicine.

Mental health disorders may be a cause of sexual dysfunction, both the disorder itself and the pharmacologic treatment of the disorder. They each may cause difficulty with sexual function and satisfaction. In patients with a diagnosis of schizophrenia or other psychotic disorders, sexual dysfunction may be secondary to the negative symptoms (anhedonia, avolition) associated with the disease. Patients who have depressive symptoms have a high prevalence of sexual dysfunction. When compared to individuals without a diagnosis of depression the prevalence in those with is 50% compared to 24% [2]. Recurrent episodes of depression further increases the risk of sexual dysfunction. In patients with a diagnosis of bipolar disorder, during the manic phase hypersexuality or increased risk of risk sexual behavior may be a defining characteristic. During the depressive phase, sexual dysfunction may present similar to that of major

depressive disorder. The pharmacologic medications used to treat these common mental health disorders namely; antipsychotics, antidepressants, and mood stabilizers may further exacerbate sexual dysfunction in these patients. It is important to communicate to patients, that sexual dysfunction may be a cause of the disease state and not solely the pharmacologic treatment. If patients are under the impression that the medication is the only reason for sexual dysfunction this may lead to non-adherence to treatment. This is something to communicate when weighing the benefits and risk of initiating a medication for a mental health disorder.

Antipsychotics

Antipsychotics are most commonly used to treat disorders such as schizophrenia and bipolar disorder. They may also be used as augmenting agents with antidepressants to treat major depressive disorder. Antipsychotic medications may exacerbate sexual dysfunction due to their activity on the dopamine, cholinergic, histamine and/or alpha receptors. It is the ability of the antipsychotics to cause hyperprolactinemia that is the major area of focus as it relates to the pathophysiology of sexual dysfunction secondary to antipsychotic use. Evidence of this is further discussed by

Dr. Richard Balon's review summarizing available studies on antipsychotic induced sexual dysfunction [3]. Testosterone, in both males and females, is needed for the sexual response. Prolactin inhibits testosterone. Due to their activity at the dopaminergic receptors in the tuberoinfundibular tract, antipsychotic medications may inhibit or block dopamine which increases prolactin and lowers testosterone. This hyperprolactinemia also increases activity at the GABA receptor and endogenous opioids, both of which can decrease libido and interfere with erection [4]. The parasympathetic nervous system has a role in male erection and female excitation. Acetylcholine is an activator or major component of the processes of the parasympathetic nervous system, it helps to facilitate vasodilation of the erectile tissues. Antipsychotics may inhibit acetylcholine or have anticholinergic effects and may then be a cause of sexual dysfunction. By inhibiting the alpha receptor, antipsychotics, may lower vasodilation leading to erectile dysfunction and decreased lubrication in females. Antagonizing the histamine receptor causes sedation which may impair arousal [5]. All of the antipsychotics have activity at these receptors at varying degrees. Their affinity for each receptor may be an indicator of the risk of sexual dysfunction with each antipsychotic (Table 1).

	D1	D2	H1	5HT1A	5HT2A	M1	M3	$\alpha 1$	$\alpha 2$
Olanzapine	++	++	+++		+++	++	++	++	+
Clozapine	+	+	+++	+	++	+++	++	+++	++
Chlorpromazine	++	+++	+++		+++	++	++	+++	+
Iloperidone	+	+++	+	++	+++			+++	+
Risperidone	+	+++	+++	+	+++			+++	++
Quetiapine	+	+		++	++	+	+	++	+
Paliperidone	+	+++	++	+	+++			+++	+++
Asenapine	+++	+++	+++	+++	++++			+++	+++
Aripiprazole		+++	++	+++	++			++	++
Brexpiprazole	+	++++	++	++++	++++			++	++
Cariprazine		++++	++	+++	++			+	
Haloperidol	+	+++			+			++	+
Lurasidone	+	+++		+++	+++			++	++
Ziprasidone	+	+++	++	+++	++++			++	+

Table 1: Receptor Binding Profile of Antipsychotics [6].

There are two broad classes of antipsychotics, first generation or typical antipsychotics and second generation or atypical antipsychotics. Their ability to cause or exacerbate sexual dysfunction is related to their affinities to the discussed receptors. There is limited research on the comparative incidence of sexual dysfunction amongst the antipsychotics.

From what data is available, risperidone, olanzapine, and haloperidol have shown the highest prevalence [7]. Quetiapine, ziprasidone, perphenazine, clozapine and aripiprazole have been associated with a lower rate of sexual dysfunction [8].

To address sexual dysfunction caused by antipsychotics, the first step is to identify which antipsychotics have a greater risk and which have a reduced incidence. This allows clinicians to initiate a therapy that has a lower risk, if that is a concern to the patient. Some clinicians may find it beneficial to watch and wait, or see if the adverse effect of sexual dysfunction will resolve on its own. Other appropriate strategies include lowering the dose. However there is a risk of the symptoms not being well controlled or increasing when the dose is lowered. Switching to an antipsychotic that has a lower risk of sexual dysfunction is typically the most well tolerated option. Additionally, adjunct medications such as PDE5 inhibitors (i.e. sildenafil, tadalafil) may be used in appropriate patients [9]. A dopamine agonist (i.e. bromocriptine) may be utilized, however patients with a diagnosis of schizophrenia started on a dopamine agonist should be monitored closely and frequently as these medications may exacerbate the symptoms of schizophrenia and other psychotic disorders.

Antidepressants

There are 5 broad classes of antidepressants, selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), and atypical antidepressant. Antidepressants are the mainstay of treatment of depression and have an indication for other disorders such as anxiety disorders and neuropathic pain. All of the antidepressant classes have been associated with some degree of sexual dysfunction. Of the antidepressants, it is the selective serotonin reuptake inhibitors (SSRIs) that have the highest reported prevalence (up to 71%) of sexual dysfunction [10]. This may be attributed to the large role that serotonin plays in sexual function. Serotonin is thought to have an inhibitory effect on sexual function. Serotonin may alter dopamine levels and affect the smooth muscle of the sexual organs. This results in alterations in sexual arousal and orgasm [11]. More specifically, stimulation of the 5HT₂ and 5HT₃ receptors is the proposed mechanism for sexual dysfunction [12]. Serotonin also inhibits nitric oxide production. Nitric oxide relaxes smooth muscle including the reproductive organs. This allows for vasodilation and increased blood supply to the reproductive organ. Inhibiting nitric oxide contributes to the incidence of sexual dysfunction. The mechanism that results in sexual dysfunction secondary to SSRI use, and the other antidepressants, is not solely attributed to serotonin. The SSRIs have varying activity at other neurotransmitters (i.e. dopamine, acetylcholine, norepinephrine) which also contribute to sexual dysfunction.

Among the SSRIs sexual dysfunction may be highest with paroxetine, fluvoxamine, sertraline, and fluoxetine. The incidence is considered to be dose related [13].

Antidepressants that may be associated with a lower incidence of sexual dysfunction include mirtazapine, bupropion, nefazodone, and trazodone.

If antidepressant use is problematic in regards to sexual dysfunction a switch may be indicated. Multiple studies have shown that bupropion has a lower incidence of sexual dysfunction. This is most likely attributed to its mechanism of action, inhibition of the reuptake of dopamine and norepinephrine. Because bupropion has no appreciable activity on serotonin, it is considered an appropriate alternative agent when experiencing sexual dysfunction due to another antidepressant with a higher incidence. The newer antidepressants, vilazodone and vortioxetine are another alternative antidepressant treatment. Vilazodone is similar in activity to a SSRI with additional activity at the 5HT_{1A} receptor (partial agonist). As a result of its activity at the 5HT_{1A} receptor it has minimal sexual adverse effects. Vortioxetine has antagonistic activity at the 5HT₃ receptor and inhibits the reuptake of serotonin. Vortioxetine at lower doses has been associated with less sexual adverse effects [13]. When achieving an erection is the cause of sexual dysfunction, the PDE5 inhibitors may be an appropriate adjunct medication. Other strategies to address antidepressant sexual dysfunction include lowering the dose of the antidepressant and a drug holiday.

Mood Stabilizers

Mood stabilizers are a class of medications that are used in the treatment of bipolar disorder and can also be used to augment therapy in patients with depression. The mood stabilizers have different mechanisms of action that are not all completely understood. The most common mood stabilizers utilized for the treatment of bipolar disorder include lithium, divalproex sodium, lamotrigine, and carbamazepine. Less information is known about the implication of sexual dysfunction as a result of mood stabilizer use. Of the mood stabilizers, lithium may have the higher incidence while lamotrigine has been associated with a lower risk [14]. Using lithium with a benzodiazepine further increased the risk of sexual dysfunction. Lithium may cause a degree of sexual dysfunction due to impairment of endothelial mediated relaxation of the corpus cavernosa. It is unclear why the combination of lithium and a benzodiazepine may result in more sexual dysfunction. It is proposed that lithium enhances the effect of the benzodiazepine. When used as monotherapy, the benzodiazepine does not result in significant sexual dysfunction [15].

There is fewer evidence for treatment strategies to address mood stabilizer induced sexual dysfunction. Switching mood stabilizers may be appropriate. Data from a controlled trial did indicate that aspirin 240mg daily was more effective

than placebo in reducing sexual dysfunction and helping with erectile dysfunction. The PDE5 inhibitors may also be a suitable treatment option [16].

Conclusion

Sexual dysfunction can present as a problematic result of both mental health disorders and the psychotropic medications used to treat the disorder. While most psychotropic medications have some degree of sexual dysfunction, identifying treatment options with higher risks and ideally avoiding those agents when able is preferable (Table 2). This may help to reduce the risk of non-adherence secondary to medication induced sexual dysfunction. Communicating the risk of sexual dysfunction to the patient, identifying concerns early on in treatment, and addressing appropriately is a standard of care that all clinicians should incorporate into their daily practice.

Drug Class	Higher Risk	Lower Risk
Antipsychotic	Risperidone	Quetiapine
	Olanzapine	Ziprasidone
	Haloperidol	Perphenazine
		Clozapine
		Aripiprazole
Antidepressant	Paroxetine	Mirtazapine
	Fluvoxamine	Bupropion
	Sertraline	Nefazodone
	Fluoxetine	Trazodone
Mood Stabilizer	Lithium	Lamotrigine

Table 2: Psychotropics and Risk of Sexual Dysfunction – Based on Available Data [8,13,14].

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