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Management of and Counseling for Psychotropic Drug-Induced Sexual Dysfunction

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Abstract and Introduction

Abstract

Clinicians are increasingly faced with the need to identify, treat, and counsel patients regarding psychotropic drug-induced sexual dysfunction. Antipsychotic and antidepressant drugs have both rational mechanisms to explain their effects on sexual function and established literature documenting these effects. The agents have potential for causing decreased libido, delayed ejaculation, and anorgasmia. Management and counseling can be highly effective for patients taking these agents.

Introduction

Sexual response consists of three primary phases: desire, arousal, and orgasm (Table 1).^[1] Normal sexual response depends on the interplay of many hormones and neurotransmitters. Altogether, it is a delicate chain of events that is easily broken. Key hormones and neurotransmitters are dehydroepiandrosterone (DHEA), oxytocin, phenylethylamine (PEA), estrogen, testosterone, progesterone, prolactin, vasopressin, dopamine, serotonin, and acetylcholine. In addition to well-known effects of psychotropic drugs on various neurotransmitters, their effects on hormones and peptides may contribute to disruption of sexual function. The androgen DHEA, which is a precursor to testosterone, estrogen, and pheromones, has an excitatory role in limbic arousal in men and women. Drugs known to decrease DHEA include carbamazepine, phenytoin, cytochrome P450 (CYP) 3A4 inhibitors, and alcohol. Increases in DHEA may be caused by bupropion, digoxin, diltiazem, and cigarette smoking.^[2]

Oxytocin's role in sexual response is primarily to facilitate attraction and touch sensation, with levels increasing secondary to touch and spiking during orgasm. Oxytocin is also responsible for postorgasm inertia and refractory period, greater in men than in women. Drug effects on oxytocin are not well established, but estrogen and yohimbine increase its levels and alcohol decreases them. Amphetamine-like PEA is a stimulant whose levels spike at orgasm and ovulation and is believed to mediate feelings of romance and love. Its levels are increased by monoamine oxidase inhibitors. Prolactin directly inhibits sexual desire, arousal, and orgasm as well as erectile function in men. Its levels are increased by dopamine-blocking drugs (most antipsychotic drugs) and opiates and decreased by bromocriptine, testosterone, dopamine, and bupropion.

Understanding the mechanisms and neuro-transmitters responsible for each phase of sexual function allows clinicians to predict how psychotropic drugs may affect sexual response and provides the basis for developing pharmaco-logic treatments to manage drug-induced sexual dysfunction.

Sexual Desire

Sexual desire (libido) is dependent on both psychogenic stimuli, involving all five senses, and hormonal factors. In men, androgens are an essential determinant of sexual desire. Evidence shows that the threshold testosterone level required for sexual desire is lower than the normal circulating range, and levels beyond this range do not directly increase sexual desire. In both men and women, increased estrogen or an increased estrogen:testosterone ratio decreases libido. High prolactin levels decrease libido directly. Antipsychotic drugs with dopamine-blocking activity increase prolactin levels and are a common cause of reduced libido.

Sexual Arousal

Arousal in men and women requires vascular and neurologic components. Adequate arterial inflow is necessary for penile erection and, in women, pelvic vasocongestion. Penile erection requires at least a 6-fold increase in arterial inflow into the cavernosa. Changes in arteries seen with atherosclerosis, smoking, diabetes, and hypertension may lead directly to erectile dysfunction. In addition to the necessity for adequate arterial inflow, several neurophysiologic pathways mediate sexual arousal.

Penile erection results from relaxation of the arterial smooth muscle within the corpus cavernosa, allowing increased blood inflow and mechanical occlusion of venous outflow. Arteries dilate in response to peripheral cholinergic activity and release of nitric oxide from parasympathetic nerve endings onto vascular smooth muscle. Parasympathetic stimulation in women causes similar erectile tissue vasocongestion and also causes vaginal lubrication by secretion of mucus from Bartholin's glands.

As antihypertensive drugs lower blood pressure, the resulting decreased arterial inflow explains the primary mechanism of their potential to cause erectile dysfunction. Drugs with significant anticholinergic effect also may negatively influence sexual arousal, and selective serotonin reuptake inhibitors (SSRIs) reduce nitric oxide synthesis, explaining their potential to impede arousal. These early findings are being investigated in clinical trials to determine the role of treatments such as sildenafil. Dopamine-blocking antipsychotic drugs also decrease nitric oxide synthesis, and dopamine agonists enhance it.^[3]

Detumescence requires both sympathetic and α -adrenergic activity to contract arterial smooth muscle, whereas β -adrenergic activity increases venous outflow. Trazodone, the agent most commonly associated with drug-induced priapism, is a potent α -adrenergic-blocking agent without significant anticholinergic effect.

Orgasm

Orgasm in both men and women is primarily under adrenergic control. In men, released norepinephrine acts on α -adrenergic receptors of smooth muscle of the vas deferens, prostate, and seminal vessels to contract and propel seminal fluid into the bulbar urethra (emission). Ejaculation, as well as orgasm in women, is a sacral spinal reflex mediated primarily by adrenergic activity. Oxytocin plasma levels are increased during orgasm in men and women, and oxytocin levels correlate with orgasmic intensity.

Neurotransmitters and Sexual Function

Although the effect of psychotropic drugs on various hormones is not certain, their effect on several neurotransmitters influencing sexual function is well established. Dopamine is the neurotransmitter in the mesolimbic "pleasure center." Increasing dopaminergic activity may enhance sexual response, and blocking it may compromise response. Among psychotropic drugs, many antipsychotic agents are dopamine blockers, whereas the antidepressant bupropion has mild dopamine-agonist activity. A reciprocal relationship exists between serotonin and dopamine, in that serotonin can diminish the release of dopamine in the mesolimbic area, thus decreasing sexual response. Drugs that increase serotonergic activity are most commonly associated with delayed ejaculation in men and anorgasmia in men and women. In addition, the serotonin 5-HT₂ receptor may block descending pathways from the brain stem to spinal neurons and interfere with spinal reflex centers necessary for ejaculation and orgasm. This mechanism underlies the delayed ejaculation and anorgasmia seen so commonly with serotonin agonists and explains why some antidepressants with 5-HT₂-blocking effects (nefazodone, mirtazapine) do not cause anorgasmia.^[4]

Frequency of Sexual Dysfunction

Sexual dysfunction has many possible causes. Table 2 lists its frequency in the general population, in patients with untreated hyper-tension, and in those with major depression.^[5-7] In addition, arteriosclerosis, diabetes, and smoking are common etiologies of erectile dysfunction. The negative impact of smoking on circulation as a sole risk factor for erectile dysfunction was suggested to be equivalent to that of arteriosclerosis, hypertension, and diabetes.^[8] These naturally occurring high frequencies suggest great caution before identifying a drug as causing sexual dysfunction.

Baseline sexual function must be established before pharmacotherapy is prescribed. The exact type of dysfunction must be identified, since drugs differ in their likelihood of negatively affecting desire, arousal, and orgasm. Some patients complain of sexual problems but, on questioning, admit that erectile dysfunction or anorgasmia occurs with only one partner but not others, suggesting that it is not related to drug therapy. True drug-induced sexual dysfunction occurs after the agent is started or the dosage is increased, is not partner specific, is not lifelong or recurrent, and resolves when drug therapy is discontinued.

Psychotropic Drugs and Sexual Dysfunction

Given the very high frequency of sexual dysfunction in the general population and in persons with major depressive disorder, it is not surprising that virtually all psychotropic drugs have been reported to cause difficulties with desire, arousal, and orgasm. Distinguishing true drug-induced sexual dysfunction from the many other possible causes is difficult.

Decreased Libido

At least 30-60% of men and women who take a typical antipsychotic drug with potent dopamine-blocking activity (chlorpromazine, thioridazine, haloperidol, fluphenazine, thiothixene) experience adverse sexual effects due to increased prolactin levels.^[9] Decreased libido is the most common symptom, which also indirectly inhibits sexual arousal. Anticholinergic agents given to treat extrapyramidal effects further contribute to the dysfunction. The newer atypical antipsychotic drugs have much less dopamine-blocking effect and thus should have a reduced likelihood of causing sexual dysfunction.

Clozapine and quetiapine are different from other antipsychotic agents in that they do not increase prolactin levels.^[10, 11] Risperidone and, to a lesser extent, olanzapine increase prolactin levels,

although much less than typical anti-psychotics.^[12, 13] The increase with risperidone is dose related, with dosages greater than 6 mg/day producing consistent and significant elevations.

The antipsychotic-induced sexual dysfunction most commonly seen with thioridazine is "dry" or retrograde ejaculation.^[2, 6] Whereas most men experience lack of ejaculation on orgasm, semen may be expelled backward through the internal sphincter into the bladder, leading to its presence in urine.

Management

Since these conditions due to antipsychotic drugs are dose related, reducing the daily dose should be the first consideration.^[9] When possible, drugs with anticholinergic effects should be discontinued or dosages decreased. When dosage reduction is not clinically feasible, switching the patient to olanzapine or quetiapine may be preferred.

Patient Counseling

Because sexual dysfunction is so common with the conventional antipsychotics, patients should be encouraged to report changes in sexual functioning to their physician, and be reassured that it can be treated.

Delayed Ejaculation and Anorgasmia

Serotonergic antidepressants are the most common cause of delayed ejaculation and anorgasmia. Early reports of antidepressant-induced sexual dysfunction were anecdotal case reports or open trials with few patients. Concurrent drugs, alcohol, and cigarettes were typically ignored, as were underlying psychiatric and organic diseases, and the status of the relationship with, or sexual dysfunction of, the partner. Thus evidence regarding sexual dysfunction from all tricyclic antidepressants (TCAs) except clomipramine and from monoamine oxidase (MAO) inhibitors is not reliable. Fortunately, evidence regarding effects of SSRIs and newer antidepressants is much more reliable.

When treated for major depression, many patients are not aware of SSRI-induced anorgasmia; while they are depressed, sexual desire and arousal are naturally greatly diminished. Most patients become aware of delayed ejaculation and anorgasmia only after the depressive episode is successfully treated. Thus, clinical trials of SSRIs for 4-6 weeks will not detect a true frequency of anorgasmia. This explains why early rates of SSRI-induced sexual dysfunction in premarketing clinical trials were so low and now have been adjusted upward.^[7] Evaluation of the relevant literature must include awareness that methods used to detect and identify sexual dysfunction greatly influence the reported frequency.

In a trial of SSRIs, 58% of 344 patients acknowledged sexual dysfunction developing after therapy was begun when directly asked by their physician, but only 14% spontaneously reported the symptoms.^[14] In a trial of clomipramine, 30% of men and women spontaneously reported anorgasmia, 60% admitted to it when given a questionnaire, and 96% acknowledged it when directly asked by a clinician.^[15] These studies suggest that sexual dysfunction due to antidepressant drugs will be greatly underestimated and underreported if clinicians wait for patients to mention it spontaneously.

Clomipramine

As the most serotonergic TCA, clomipramine has the greatest potential to cause delayed ejaculation and anorgasmia. In a trial of 111 men given a mean dosage of 200 mg/day (100-300 mg/day), the drug was associated with delayed ejaculation in 41%, compared with 2% given placebo.^[16] In patients given a mean dosage of 140 mg/day (25-200 mg/day), difficulty achieving orgasm began within the first few days with doses of 25-50 mg, and anorgasmia commonly occurred once the daily

dose reached 100-150 mg. Total lack of orgasm occurred in 70% of patients, and in 96%, orgasm was either more difficult or was absent, with equal occurrence among men and women. Anorgasmia persisted for the 6 months of the trial but disappeared within 3 days of discontinuing clomipramine.^[15]

Serotonin Agonist Antidepressants.

Drugs with prominent serotonin agonist effects, particularly on postsynaptic 5-HT₂ receptors, frequently cause delayed ejaculation and anorgasmia. The five SSRIs marketed in the United States (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram), as well as venlafaxine, have potent serotonergic agonist effects that include 5-HT₂-receptor agonist effects. Sexual dysfunction associated with 5-HT₂ activity is directly dose related. Delayed ejaculation is more commonly reported in men, but anorgasmia in women is usually more severe. At least 30-60% of men and women will experience some delay or difficulty in achieving orgasm during therapy with an SSRI.^[14, 17]

Because sexual dysfunction is dose related, it is difficult to identify one serotonin agonist as either more or less likely than others to cause these problems. The very limited information that exists suggests that paroxetine is associated with more delay in orgasm and ejaculation than other SSRIs, possibly due to its greater anticholinergic effect.^[14] Citalopram and venlafaxine are newer agents, so comparative data are unavailable, but their common mechanism suggests that dose-related sexual dysfunction is a common and expected effect.

Antidepressants Unlikely to Cause Sexual Dysfunction

Three antidepressants -- bupropion, nefazodone, and mirtazapine -- have mechanisms that specifically minimize the risk of sexual dysfunction.^[17] In addition, their mechanisms may reverse such symptoms caused by serotonin agonists. Unlike most antidepressants, bupropion has no significant effect on serotonin. As a mild dopamine agonist, it has the potential to affect sexual desire and arousal positively.^[2] Nefazodone and mirtazapine are serotonin agonists, but in addition, have postsynaptic 5-HT₂-blocking effects that maintain the ability to achieve orgasm.^[18, 19]

Management

Possible options to manage and treat serotonin agonist-induced sexual dysfunction include decreasing the dosage, giving drug holidays, adding another agent, switching to an alternative antidepressant without these effects, or waiting for tolerance to develop.^[17] Most evidence, however, suggests that tolerance does not develop.^[20, 21]

Decreasing the dosage is a reasonable concept, as the condition is dose related. Clinically, however, it is rarely possible to do so without compromising efficacy of maintenance therapy. Patients being treated for depressive disorders require the same dosage for maintenance as for immediate therapy, or the risk of relapse greatly increases, so dosage reduction is not recommended.^[22] Patients receiving serotonin agonists for obsessive-compulsive disorder or panic disorder require even higher dosages than those taken for depression, so dosage reduction is rarely an option.

Drug holidays are a possible method to allow normal sexual functioning on occasion while maintaining the benefit of drug therapy. Discontinuing either sertraline or paroxetine on Fridays and Saturdays improves sexual function without a significant return of depressive symptoms.^[23] Weekend drug holidays were not effective for patients taking fluoxetine due to its much longer elimination half-life. Although the concept is appealing, concern about SSRI withdrawal syndrome, which often follows abrupt discontinuation of therapy, dampened interest in this strategy.^[24, 25]

The two most realistic and effective management options are adding another drug and switching to

an alternative antidepressant. The decision to add or switch should be based primarily on the agent's clinical efficacy. If efficacy is not adequate, or the patient is unlikely to continue taking the drug due to sexual dysfunction, switching to bupropion, nefazodone, or mirtazapine is the most appropriate option.^[26] A more common clinical situation, however, is a patient with good clinical response to an antidepressant but in whom sexual dysfunction is significant and threatens adherence. In this case, continuing the antidepressant and adding a drug to manage the sexual dysfunction is preferred. Many treatments have been tried, based primarily on understanding the mechanisms involved.

Cyproheptadine, a nonspecific serotonin antagonist, is effective in reversing SSRI-induced delayed ejaculation and anorgasmia in doses of 4-12 mg. Continuous therapy with the agent, however, carries the risk of reversing the antidepressant effect, so it is generally limited to dosing as required 2-4 hours before sexual activity.^[21] Significant sedation also limits its potential value as adjunctive treatment. Yohimbine, a presynaptic α_2 -adrenergic antagonist, known to be effective for erectile dysfunction, has shown effectiveness against anorgasmia. It is given in doses of 2.7-16.2 mg 2-4 hours before sexual activity. Sweating, elevated blood pressure, anxiety, and tachycardia limit its value as an adjunctive treatment.^[21, 27]

Dopamine agonists, including amantadine and dextroamphetamine, are reported to have some efficacy in reversing serotonin agonist-induced anorgasmia. Amantadine, given intermittently at 200 mg twice/day for 48 hours before sexual activity, successfully treated ejaculatory delay in six patients receiving paroxetine.^[28] In a 4-week open trial in 63 patients taking antidepressants, ginkgo biloba improved sexual function.^[29] Women were more responsive to its effects than men, with success rates of 91% and 76%, respectively. Mean dosages of ginkgo biloba extract were 209 mg/day (range 60-240 mg/day), with gastrointestinal distress, headache, and central nervous system activation the most common adverse effects.

Sildenafil should be more effective for erectile dysfunction than for delayed ejaculation and anorgasmia since its direct effect is to increase vascular engorgement with direct stimulation. However, sildenafil was effective in two women with SSRI-induced anorgasmia and decreased lubrication.^[30] In both patients, a single 50-mg dose reversed anorgasmia. Further investigation is warranted since the drug is not the most logical option based on known mechanisms.

Bupropion as an adjunct to SSRIs in an open trial was effective for some patients with both as needed dosing and a continuous 2-week trial.^[31] Bupropion 75 or 150 mg taken as necessary effectively improved desire, arousal, or orgasmic difficulty in 38% of patients, and a 2-week trial of adjunctive bupropion 75 mg 3 times/day was effective in 57% of patients unresponsive to dosing as necessary. Anxiety and tremor were the most common adverse effects, causing 15% of patients to discontinue the agent.

The most logical approach to adjunctive therapy for serotonin agonist-induced sexual dysfunction is to administer 5-HT₂-blocking agents to reverse the cause of the dysfunction. Recognition of nefazodone and mirtazapine's selective blocking effect on 5-HT₂ receptors led to their inclusion as adjuncts for this indication. In several patients, nefazodone 150 mg taken as necessary 1 hour before sexual activity was effective in reversing sertraline-induced anorgasmia.^[32] Studies with both drugs are required to determine preferred dosage and duration of therapy.

Patient Counseling

Counseling patients about the possibility of sexual dysfunction due to an antidepressant is often uncomfortable and unfortunately avoided by too many clinicians. These conditions are common adverse effects of serotonergic drugs, they may negatively affect compliance, and they can be easily treated. For all these reasons, patients must be counseled about their likelihood. Specific

details regarding the type of sexual dysfunction or management options are not necessary unless the patient asks additional questions.

Premature Ejaculation

Although delayed ejaculation typically is viewed as an adverse effect of serotonin agonists, it can be advantageous in patients with premature or rapid ejaculation. In self-report studies, premature or rapid ejaculation occurs in 30-40% of adult men, and even when not identified as problematic, it limits the sexual satisfaction of both the man and his partner.^[33] Based on known mechanisms involved in ejaculation, drugs with central 5-HT₂-agonist activity should delay ejaculation by interfering with descending pathways to the spinal reflex center.^[34] Clomipramine, the most serotonergic TCA, and SSRIs have been successful in treating the condition.

Clomipramine

In one clomipramine trial, baseline time to ejaculation was 81 seconds, but 25 mg taken as necessary 4-6 hours before sexual intercourse increased the time to 202 seconds (249% increase), and 50 mg delayed it to 419 seconds (517% increase). Placebo had no significant effect in increasing ejaculatory latency (30% increase over baseline). Sexual satisfaction was increased for both the men and their partners in terms of partners attaining coital orgasm and greater emotional satisfaction. Withdrawal of clomipramine at the end of the study caused premature ejaculation to return to baseline levels.^[35] In other studies, 75 mg was necessary for successful response, but for some patients that dose caused complete inability to ejaculate.^[2] Individualized dosing is necessary when prescribing clomipramine for this indication.

SSRIs

Paroxetine 20 mg at bedtime for 8 weeks increased ejaculatory latency after 2 weeks of therapy in 32 patients.^[36] Three weeks after the end of the trial and cessation of paroxetine, premature ejaculation recurred in 90% of patients. In a placebo-controlled trial, paroxetine 40 mg/day for 6 weeks led to slight improvement during the first week of therapy and significant improvement after 3 and 6 weeks.^[37] Median intravaginal ejaculation latency time increased from a baseline of 30 seconds to 7.5 minutes after 3 weeks and 10 minutes after 6 weeks. No significant differences were found in placebo-treated patients compared with baseline.

When sertraline 50-200 mg/day or placebo was given to 52 men for 8 weeks, mean ejaculatory latency changed from a baseline of 1 minute to over 5 minutes; placebo caused no significant change.^[38] Mean ejaculatory latency returned to baseline within 2 weeks of discontinuing sertraline. In an open 8-week trial, fluoxetine 20-60 mg/day increased median ejaculatory latency from 0.9 minutes to over 9 minutes, but no information was provided regarding onset of effect.^[39] An open 8-week trial of fluoxetine 20 mg/day in patients with panic disorder found improvement in premature ejaculation after 2 weeks of therapy.^[40]

All trials of SSRIs involved 4-8 weeks of continuous therapy, and benefit for premature ejaculation required at least several weeks. Clomipramine is the only agent thus far to be effective with a single dose taken as necessary. Since SSRIs were given in usual antidepressant dosages, the expected adverse effects of sedation or activation, insomnia, headache, and nausea occurred. The beneficial effect is lost soon after SSRIs are discontinued, and no recommendations are available regarding long-term treatment.

Priapism

Priapus, the son of Zeus and Aphrodite, was a god with an enormous penis who symbolized the earth's fertility. Priapism is defined as a sustained, painful erection that can not be relieved by sexual

intercourse or masturbation, and that is frequently unrelated to sexual desire. Without intervention, it usually subsides within a few days, but 50-80% of men become permanently impotent. Stasis of blood for more than several hours leads to increased blood viscosity, deoxygenation, and, ultimately, irreversible fibrosis of tissue. Thus, priapism is a urologic emergency requiring immediate intervention.^[41]

Trazodone

About 30% of reported cases of priapism are drug-induced, with 80% of those cases involving trazodone. Other drugs associated with the condition are most antipsychotic agents such as risperidone, SSRIs, bupropion, phenelzine, prazosin, and intracavernosal injection of vasoactive drugs.^[41-45] Clitoral priapism has been reported as well and may be associated with either pain and discomfort or increased libido and orgasmic response.^[41, 46-48]

Trazodone-induced priapism is rare, occurring in less than 0.1% of patients. It typically is seen within the first month of therapy, occurs in all age groups, and may be caused even with low daily doses of 50 and 100 mg.^[41] Priapism from psychotropic drugs is related primarily to unopposed potent α_1 -adrenergic blockade.^[41, 49] This explains why trazodone is, and nefazodone is not, associated with the condition.^[50]

Management

Patients must be aware of the possibility of priapism when taking trazodone, and treatment must be given quickly to minimize the risk of permanent impotence. In the past, surgical intervention was routine practice, but it resulted in up to 50% of men being permanently impotent. Because trazodone-induced priapism is understood to be due to α_1 -adrenergic blockade, pharmacologic treatment is preferred since it carries no risk of permanent sequelae. Intracavernosal irrigation with an α -adrenergic agonist will successfully cause detumescence in most patients if the priapism is of less than 24 hours' duration. Since corporeal fibrosis is more likely after 24 hours, drug treatment is less effective.^[51] Typically, blood is removed from the penis and a solution of an α -adrenergic agonist is reinfused into the corpus cavernosum. Phenylephrine is preferred as the most selective and potent α_1 -adrenergic vasoconstrictor, with onset of action in less than 1 minute and duration of 7-20 minutes. Several intermittent injections of a 0.1 mg/ml solution may be necessary, with continuous monitoring of blood pressure and heart rate.^[51-53]

Patient Counseling

Although rare, priapism is a serious medical emergency that requires immediate intervention. Since most patients would not attribute the prolonged erection to trazodone, patient counseling about its possibility is necessary for all men beginning therapy with the drug. They should be advised to report prolonged or painful erections to their physician immediately.

Mood Stabilizers

Lithium monotherapy has not been associated with sexual dysfunction. Using a comprehensive sexual questionnaire in 36 men and women with bipolar disease and given lithium for 6 months or more, only 1 patient reported a change in sexual function.^[54] Most reports of lithium-associated sexual dysfunction are in patients who also take either antidepressants or antipsychotic drugs.^[2] Valproate has the most beneficial hormonal effects among anticonvulsant drugs, which theoretically suggests a very low likelihood of sexual dysfunction. Whereas phenytoin and carbamazepine increase prolactin and decrease DHEA and other adrenal androgen levels, valproate lacks an inhibitory effect on DHEA and does not increase prolactin levels.^[55, 56] This very limited information suggests that lithium and valproate are much less likely to cause sexual dysfunction than antipsychotic and anti-depressant drugs.

Benzodiazepines

Although relief of anxiety and disinhibition effects of benzodiazepines might suggest a beneficial effect on sexual function, the limited clinical literature suggests that the agents may aggravate sexual dysfunction in both men and women.^[2] There are few case reports of decreased desire and arousal in men and women taking benzodiazepines. Thus, widespread use of the drugs for over 3 decades, coupled with the paucity of clinical reports of sexual dysfunction, suggest that the overall risk of the disorders is low. The two exceptions may be high-dosage therapy and combination of benzodiazepines with other drugs. In an open survey of men and women taking alprazolam, in dosages of 3-10 mg/day, for panic disorder, almost one-half of patients reported decreased sex drive, reduced ability to achieve orgasm, and erectile dysfunction.^[57] In the study that found lithium monotherapy rarely caused sexual dysfunction, the combination of a benzodiazepine with lithium was associated with decreased sexual function in 60% of patients.^[54]

Summary

Although psychotropic drugs with serotonin agonist and dopaminergic-blocking effects commonly cause sexual dysfunction, many other potential causes must be considered first. Understanding the role of key hormones and neurotransmitters in normal sexual function allows clinicians to predict how drugs may affect sexual function and to select among effective options. Such knowledge must be communicated to patients taking psychotropic drugs with high potential to cause sexual dysfunction. Antipsychotic agents with dopamine-blocking effects consistently raise prolactin levels, leading to a variety of effects on both endocrine and sexual function. The most common clinical consequence of increased prolactin levels in men and women is decreased libido. Newer atypical antipsychotic drugs, notably clozapine and quetiapine, have minimal effect on dopamine and do not appreciably increase prolactin levels. Risperidone and, to a lesser extent, olanzapine increase prolactin levels, although less than older typical antipsychotics. Direct clinical comparison of atypical antipsychotic drugs' potential to cause sexual dysfunction is not yet available.

Serotonergic agonist antidepressants commonly cause delayed ejaculation and anorgasmia. Agents least likely to cause sexual dysfunction are bupropion, nefazodone, and mirtazapine. Management strategies for delayed ejaculation and anorgasmia include switching from the serotonergic antidepressant to bupropion, nefazodone, or mirtazapine, or prescribing adjunctive treatment. Tolerance usually does not develop to anorgasmia, and dosage reduction is not usually clinically possible. Drug holidays of SSRIs with shorter half-lives are possibly effective but raise concerns about overall compliance and SSRI withdrawal syndrome. Adjunctive treatment with either cyproheptadine or yohimbine may be replaced soon by either nefazodone or mirtazapine. The risk of patients independently decreasing their dosage or discontinuing treatment due to sexual dysfunction can be minimized by educating them about the possibility of the problem and assuring them that treatment can be successful.

Tables

Table 1. The Biology of Sexual Function

Phase	Description
Desire	Libido; interest in sex, sex drive; dependent on psychogenic stimuli, and cognitive and hormonal factors

Arousal	Subjective sense of sexual excitement and pleasure; penile tumescence, erection; vaginal lubrication, pelvic vasocongestion, swelling of external genitalia; dependent upon vascular and neurologic components
Orgasm	Climax of sexual pleasure associated with rhythmic contraction of perineal and reproductive organ structures, cardiovascular and respiratory changes, and release of sexual tension Male - emission and ejaculation mediated by different mechanisms Female - dependent on adrenergic, central cognitive arousal, and neuropeptides

Table 2. Frequency of Sexual Dysfunction

	General Population (%)	Untreated Hypertension (%)	Untreated Major Depression (%)
Decreased libido, men/women	16/22	21/ --	42-80/33-96
Erectile dysfunction	6-10 ^a	17-20	23-50
Ejaculatory dysfunction	6	7-10	--
Anorgasmia (women)	12-25	--	--

^a52% for men > 50 years.

Adapted from references 2, 6, and 7.

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