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The Management of Medication-Induced Sexual Dysfunction

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Editor's Note

Most psychiatric illnesses are of long duration or of a relapsing nature. Increasing realization of this has resulted in a trend toward more prolonged treatment with psychotropic medications. One unwanted effect is the induction of abnormal sexual function. The advent of newer compounds such as the selective-serotonin reuptake inhibitors has focused attention on this problem. Psychotropic medications have always produced problems of this type, but there has been reluctance on the part of the patient to discuss it and oversight on the part of the clinician to enquire about such problems.

Medication-induced sexual dysfunction not only lowers the quality of life of the patient, but it may also jeopardize treatment adherence. It is thus important that the clinician take positive steps to counsel the patient before instituting a course of psychotropic medication and also enquires routinely about any possible change in sexual function.

In this article, Drs. Boyarsky and Hirschfeld deal in succinct detail with various aspects of the topic. Starting with the complex physiology and pharmacology of sexual functioning, they then review various types of psychotropic medication and describe the problems that may supervene. The incidence of such problems is often disquietingly high.

The management of this problem is very carefully described, and the various options are outlined. Although some patients manage to tolerate the problem, it is important that they be offered some remedial measures such as alternative medication, adjunctive therapy, or drug holidays. The reader will find many useful strategies in the management of this frequent but often overlooked adverse effect.

Introduction

Sexual dysfunction is a common side effect of psychoactive medications as well as a number of other frequently prescribed medications. Considerable attention has been focused on antidepressants recently, perhaps because of their widespread use and because they are often taken for long periods of time (e.g., months or years). This sexual dysfunction obviously interferes with the quality of life and may present the clinician with substantial compliance and management problems. Fortunately there are a number of options.

We focus on the management of medication-induced sexual dysfunction. It begins with neurotransmitter receptor actions at sites thought to affect sexual functioning and describes putative medication effects on receptor sites relevant to sexual functioning. Lastly, an overview of the clinical management of medication-induced sexual dysfunction is provided.

Basic Neuropharmacology of Human Sexual Response

Human sexual activity is modulated by a number of neurotransmitters (Table 1). **The principal neuroanatomic areas that control sexual behavior include the medial forebrain bundle, the medial preoptic-anterior region of the hypothalamus with its related limbic-hippocampal structures, and the ventral tegmentum of the midbrain.**¹ **Sex hormones** (e.g., estrogen, progesterone, and testosterone) **substantially influence the neurotransmitter actions that modulate sexual behavior.** These interactions, both on a central and a peripheral level, account for intricate modulations of sexual arousal, functioning, and pleasure.²

Centrally, dopamine and noradrenaline facilitate desire, arousal, and orgasm.³⁻⁷ **5HT-2 serotonin receptor stimulation in the brain results in inhibition of sexual function for both sexes.**^{1,8} Much less is known about the influence of other central neurotransmitters on female sexual function.

Peripherally, serotonin exerts an inhibitory effect on sexual arousal and orgasm in both sexes, while oxytocin facilitates these functions.^{1,6} **Acetylcholine, nitric oxide, and sex hormones facilitate male erection, while noradrenaline bal-**

ances these actions by exerting an inhibitory effect.^{1,9-11} Acetylcholine and norepinephrine modulate ejaculation and male orgasm, facilitating closure of the internal sphincter, relaxation of the external sphincter, emission of prostatic fluid, clonic contraction of the striated muscles of the penis, and resulting propulsion of semen. Again, little else is known about peripheral neurotransmission affecting sexual function in females.

Drugs That Induce Sexual Dysfunction

Many pharmacologic agents cause changes in sexual functioning, including, but not limited to, *antihypertensives*, *antibiotics*, *antihistamines*, *psychopharmacologic agents*, and *drugs of abuse*.¹² This article will focus specifically on psychoactive agents.

Psychoactive medications have long been known to affect sexual functioning, but reported rates of dysfunction vary greatly, depending on how the information was obtained from the patient. Montejo-Gonzalez et al.¹³ discovered a **44% increase in the incidence of sexual dysfunction in patients whose physicians asked their patients direct questions, compared with those patients who spontaneously reported sexual dysfunction. It became evident that when patients are not directly and specifically queried about treatment-emergent sexual dysfunction, they rarely report it in clinical trials.**

Psychiatric clinicians are thus becoming more aware of sexual difficulties caused by psychoactive agents, including lack of desire, impotence, difficulty gaining and sustaining an erection, and anorgasmia. Antidepressants, antipsychotics, mood stabilizers, anti-anxiety agents, stimulants, and drugs of abuse will be addressed.

Tricyclic antidepressants (TCAs) decrease desire, decrease ability to gain and sustain erection, and inhibit orgasm and ejaculation (Table 2).¹⁴ **The tricyclics causing the greatest amount of sexual dysfunction** (decreased drive, lubrication, inhibited ejaculation, and orgasm) **are clomipramine** (Anafranil), **amitriptyline** (Triavil), and **doxepin** (Sinequan). Rates of 41% to 96% of sexual dysfunction were reported in two studies of clomipramine.^{15,16} *Clomipramine has been used successfully in the treatment of patients with premature ejaculation.*¹⁷ Imipramine affects sexual function as well, but to a lesser extent than clomipramine. **Desipramine** (Norpramin) and **nortriptyline** (Pamelor) **induce the least sexual dysfunction of the tricyclic antidepressants.**¹⁸ The TCAs increase central serotonin and prolactin levels and decrease cholinergic and beta adrenergic activity.¹⁹

The heterocyclic antidepressant *amoxapine* (Asendin) has been associated with inhibition of ejaculation, painful ejaculation,²⁰ and retrograde ejaculation.¹⁸ Its mechanism of action is similar to that of the tricyclic agents.

Table 1
SEXUAL EFFECTS OF NEUROTRANSMITTERS

Neurotransmitter Action	Positive Sexual Effects	Negative Sexual Effects
α 1 adrenergic agonist	Excitatory	Enhances desire, arousal facilitates action of DA, testosterone, Ach Vasopressin, prostaglandins
α 2 adrenergic agonist	Inhibitory (central and peripheral)	Decreases desire, arousal Peripheral vasoconstriction Decreases anxiety-related premature ejaculation
GABA and females	Inhibitory	Diminishes active sexual response in males sexual response in females
Ach	Excitatory	Erection, lubrication, orgasm
Cortisol	Excitatory Inhibitory	Acute effect Chronic effect
DHEA/DHEAS	Excitatory	Increases sex drive in females, less so in males
Dopamine	Excitatory (central and peripheral)	Mediates pleasure, increases sex drive, promotes orgasm
Estragens	Excitatory and inhibitory in females	Desire, responsiveness in females Lubrication, facilitates 5-HT, PRL, oxytocin, opioids
Monoamine Oxidase A	Inhibitory	Decreases NE, 5-HT, DA
Monoamine Oxidase B (central)		Decreases sex drive, responsiveness
Nitric Oxide	Excitatory	Vasodilates

Opioids	Inhibitory (central)	Disinhibits at low doses	Inhibits or gasm, ejaculation, diminishes sex drive
Progesterone	Inhibitory (central)		Sexual depressant, lowers testosterone
Prolactin	Inhibitory (central)		Decreases sex drive, or gasm Causes impotence
Prostaglandins	Excitatory (peripheral)	Facilitates vasodilation, tissue sensation, erection, lubrication	
Serotonin 1a	Inhibitory		Inhibits arousal, or gasm Decreases anxiety, aggressiveness
Serotonin 1c	Excitatory	Increases penile erections in rats (Simon, 1993)	
Serotonin 2a	Inhibitory (central and peripheral)		
Substance P	Excitatory (peripheral)	Increased sensation/blood flow	
Testosterone	Excitatory (central and peripheral)	Increases sex drive, assertiveness, aggressiveness Facilitates DA, EPI, Vasopressin Inhibits 5-HT, opioids, PRL, MAO	
Vasopressin	Excitatory (central)	Facilitates focused sexual arousal Modulates adrenergic sexual excitation	

Adapted in part from Crenshaw and Goldberg, 1996, and Schiavi and Seagraves, 1995.

Table 2
ANTIPSYCHOTIC EFFECTS ON SEXUAL FUNCTION

Typical Antipsychotics	Effect on Sexual Function
Typical antipsychotics in general	galactorrhea, gynecomastia menstrual irregularities dyspareunia secondary to vaginal atrophy
chlorpromazine	ejaculatory disturbance decreased libido and arousal erectile dysfunction
fluphenazine	ejaculatory disturbance decreased libido and arousal erectile dysfunction changes in quality of orgasm in men orgasm dysfunction and decreased libido in women
haloperidol	decreases in libido and arousal ejaculatory disturbances
maprotiline	decrease in arousal orgasm disturbance
molindone perphenazine pimozide thioridazine, mesoridazine	priapism ejaculatory and orgasm disturbances decrease in arousal difficulties with libido, arousal, erection, ejaculation, orgasm changes in quality of orgasm in men orgasm dysfunction and decreased libido in women
thiothixene	decreases in libido and arousal ejaculatory and orgasm disturbance
trifluoperazine	orgasm dysfunction ejaculatory disturbance orgasmic dysfunction and decreased libido in women
Atypical Antipsychotics	
clozapine	impotence breast pain/discomfort vaginal itching reported priapism
olanzapine	abnormal ejaculation breast pain impotence
risperidone	abnormal ejaculation ejaculation failure male breast pain

(Sullivan and Lukoff, 1990; Thompson, et al., 1990; Schiavi, 1996; PDR, 1999)

Sexual dysfunction with *monoamine oxidase inhibitors* (MAOIs) includes inhibition of desire, difficulty with erection, and a 20% to 40% incidence of delayed orgasm and inhibited ejaculation.^{22,23} There has been one case report of priapism related to **phenelzine** (Nardil).²⁴ The MAOIs increase serotonin and noradrenaline levels in synaptic nerve endings, increase prolactin,²⁵ decrease testosterone, beta adrenergic, and cholinergic activity.

Selective-Serotonin Reuptake Inhibitors (SSRIs) cause sexual dysfunction by decreasing libido and increasing time to orgasm. Reduced sexual desire, as well as difficulties in obtaining and maintaining an erection and inhibition of ejaculation, has been reported with all SSRIs. Orgasm is adversely affected in both sexes. Men and women taking SSRIs have 60% and 57% sexual dysfunction rates, respectively as measured by the Rush Sexual Inventory.²⁶ *Sertraline* (Zoloft) and *paroxetine* (Paxil) have been used with success in a placebo-controlled trial for premature ejaculation.²⁷⁻²⁷ *Citalopram* (Celexa) has also been reported to cause decreased libido.³⁰ The SSRIs increase synaptic levels of serotonin, thereby increasing cortisol, prolactin, and opioid levels, which adversely affect sexual function.³¹ Single cases of increase in sexual desire³² have also been reported.

Venlafaxine (Effexor) inhibits orgasm and ejaculation in 12% of male patients, less than conventional SSRIs but more than that of nefazodone (Serzone), trazodone (Desyrel), bupropion (Wellbutrin), or mirtazapine (Remeron).³³ There is one case report of increased libido and spontaneous erections.³⁴ Venlafaxine inhibits reuptake of serotonin and noradrenaline.

Trazodone and nefazodone are associated with very low incidences of sexual dysfunction. Trazodone may actually increase desire and erections and prolong time to orgasm.³⁵ Priapism has been documented in both males and females.^{33,36} Trazodone decreases peripheral alpha-1-adrenergic activity and blocks the serotonin 5-HT₂ receptor thought to be responsible for sexual dysfunction.³⁷ **Nefazodone was associated with significantly less sexual dysfunction than sertraline in a double-blind comparison of the two drugs.**³⁸⁻⁴⁰ There has been only one case report of spontaneous ejaculation and priapism reported.⁴¹ It is structurally similar to trazodone but lacks alpha-1-adrenergic antagonist activity and is less sedating. Trazodone and nefazodone both act as serotonin 5HT₂ receptor antagonists and serotonin reuptake inhibitors.⁴²

Clinical efficacy studies of bupropion estimate that treatment-emergent sexual dysfunction occurs in less than 3% of patients. There have been reports that bupropion increases desire and function, and also there are rare case reports of priapism in both men and women.⁴³ Crenshaw, et al.⁴⁴ conducted a double-blind, placebo-controlled study of 60 patients with psychosexual dysfunction who were not on other medications, and they found *a significant increase in sexual functioning by week 12 of bupropion therapy.* Walker, et al.⁴⁵ found that 84% of patients experiencing sexual dysfunction from fluoxetine had complete resolution of symptoms, with 81% experiencing an increase in libido after switching to bupropion. Bupropion has noradrenergic and dopamine activity, with no effect on neurotransmission of serotonin.⁴²

Mirtazapine also shows promise as an antidepressant with little or no adverse effect on sexual functioning. A small, open-label pilot study of depressed patients has reported increases in sexual functioning, especially in women.⁴⁶ This is probably due to its properties of post-synaptic blocking of 5HT₂ and 5HT₃ receptors.

Thirty percent to 60% of patients receiving typical antipsychotics experience disturbances in sexual function.⁴ The sexual side effects of typical antipsychotics include **erectile, orgasmic, and sexual-satisfaction problems.**^{47,48} Primary mechanisms include antagonism at the D₂ dopamine receptor site. (Table 2).

To date, there have been no controlled studies on sexual dysfunction using the new atypical antipsychotic medications, although they appear to be associated with less sexual dysfunction than the typical antipsychotics.⁴⁹ Case studies report sexual dysfunction with several atypical agents, however. **Clozapine** (Clozaril) **has been associated with retrograde ejaculation.**⁵⁰ **Risperidone** (Risperdal) **can cause ejaculatory dysfunction,**⁵¹ **gynecomastia, and other sexual difficulties,** all of which may result from increased prolactin levels and depressed testosterone levels.⁵² **Olanzapine** (Zyprexa) **has the fewest reports of sexual dysfunction to date,** including one case report of olanzapine-induced priapism.⁵³

Lithium (Eskalith) **can interfere with libido and erection in some males,**^{54–56} although **Ghadirian**⁵⁷ found that sexual dysfunction was evident in **22% of patients who were on a combination of lithium and benzodiazepines, not lithium alone.** **Twenty percent of women taking lithium or lithium combined with psychotropics had increased sexual desire and orgasm in this study.**

Carbamazepine (Tegretol) **decreases desire, arousal, and erection.** It inhibits dehydroepiandrosterone and dehydroepiandrosterone sulfate, which are adrenal androgens essential to sexual well-being, and it decreases free testosterone and thyroxine.⁵⁸

Valproate does not appear to affect sex drive or cause impotence. Unlike other anticonvulsants, it does not inhibit adrenal androgens or thyroxine⁵⁹ and may increase free testosterone.

Chlordiazepoxide (Limbitrol), **lorazepam** (Ativan), **alprazolam** (Xanax) **and other benzodiazepines decrease excitement and cause ejaculatory delay in males and delay of orgasm in females.**^{1,23,60} Lydiard et al.⁶¹ found that one half of male subjects with panic disorder experienced decreased sex drive and orgasmic dysfunction while taking alprazolam, while 44% indicated difficulties with erection.

Buspirone (BuSpar) may enhance desire and orgasm in both sexes and has few reported sexual side effects; there has been one case report of priapism.⁶² Buspirone has been shown to reduce the amount of copulatory stimulation required for ejaculatory behavior in rats, while increasing the copulatory rate.⁶³ It acts to increase serotonin through downregulation of the 5HT1a receptor and increased alpha 1 adrenergic activity.⁴²

Amphetamines and other stimulants heighten or reduce sexual response in a dose-dependent fashion⁶⁴ Low doses of amphetamines create a general feeling of well-being and stimulate sexual response. Higher doses cause anxiety and nervousness. Amphetamines act to increase adrenergic activity.

Methylphenidate (Ritalin) also causes increased or decreased sexual desire in a dose-dependent fashion. At higher doses, it may aggravate premature ejaculation and impotence and cause anxiety. Methylphenidate increases alpha 1 adrenergic activity, dopamine, and cortisol.

The halogenated amphetamine derivative, fenfluramine (Pondimin), appears to have an overall adverse effect on sexual function,⁶⁵ despite research indicating it stimulates erections and copulatory behavior in rats by increasing oxytocin levels.⁶⁶ It stimulates central serotonin, prolactin, and cortisol release and inhibits dopamine release.

Alcohol use initially causes disinhibition and feelings of sexual well-being that are caused by transient increases in dopamine and estradiol and a luteinizing hormone (LH) surge secondary to luteinizing hormone releasing hormone (LHRH) potentiation. As blood alcohol levels rise, however, sexual responsiveness is increasingly blunted in both sexes: men find erection more difficult to obtain and sustain, and women are unable to experience orgasm. Male alcoholics develop reduced desire and function due to reduced levels of testosterone, which can return to normal after extended abstinence from alcohol. Female alcoholics experience decreased vasocongestion, resulting in decreased vaginal lubrication, despite perceived increases in sexual arousal.²³

Marijuana does not appear to improve sexual functioning, but it increases relaxation and pleasurable touch between partners already comfortable with each other.⁶⁷ It increases sexual pleasure and satisfaction in 70% of men and 76% of women, according to a longitudinal survey by Halikas.⁶⁸ It has not been found to change concentrations of testosterone, LH, or follicle stimulating hormone (FSH) in controlled studies.⁶⁹

Infrequent cocaine and crack use induces release of dopamine, which increases sex drive and delays time to orgasm and ejaculation in both sexes.^{4,23}

Chronic use depletes dopaminergic synaptic neurotransmission, causing impotence without decreasing sex drive.

Nicotine also initially increases sex drive and arousal. Chronic use, however, decreases sexual responsiveness. Atherosclerosis, a side effect of chronic nicotine use, decreases penile blood flow and increases venous penile outflow, ultimately causing impotence. Centrally, it increases dopamine and norepinephrine release and decreases serotonin neurotransmission. Nicotine also promotes the release of epinephrine, vasopressin, beta-endorphins, cortisol, progesterone, and dihydrocypianandrosterone (DHEA).²³

Opiates delay orgasm and ejaculation in men and may prolong time to orgasm in women. *Addicts may find the heroin rush more pleasurable than sexual orgasm.* Sexual dysfunction is a notable cause of methadone treatment discontinuation in males; dysphoric and uncontrolled spontaneous erection and ejaculation may occur in withdrawal. However, half of female patients who switch from heroin to methadone show improvement in sexual function.⁷⁰ Heroin increases dopamine release and suppresses LH secretion and testosterone.⁷¹

Guidelines for the Diagnosis of Medication-Induced Sexual Dysfunction

There are several reasons why patients neglect to tell their physicians about sexual dysfunction. Issues concerning self-esteem often arise with sexual discussion unless it is included as a usual part of the clinical interview. Patients may not realize the connection between sexual dysfunction and medication, may attribute it to other factors, or may simply be too shy to discuss it with a person of another gender. If the problem is not addressed, the clinician may find that his or her patient is not willing to give up sexual desire and pleasure in order to comply with the prescribed medications.

The clinician should **perform an assessment of baseline sexual functioning as it was prior to the onset of psychiatric illness, as well as current functioning before initiation of medication.** General medical illnesses such as diabetes and hypertension often result in difficulties with sex. The clinician should address any pre-existing sexual dysfunction and then **instruct the patient about the risks of sexual dysfunction,** as well as adverse effects that may begin with either initiation or continued use of the medication. The clinician should then **ask the patient to notify him or her of any effect, so that it may be specifically addressed at each visit.** When the dysfunction results in marked distress or interpersonal difficulty and is fully explained by the effects of the psychotropic medication, and not better accounted for by another disorder, drug-induced sexual dysfunction is diagnosed.⁷²

The physician can easily qualify and quantify the extent of the disorder. For example, the *Arizona Sexual Experiences Scale*⁷³ is a five-question, Likert-type questionnaire that takes 5 to 10 minutes to administer and has been perceived by pa-

Table 3

THE ARIZONA SEXUAL EXPERIENCES INVENTORY

A five-item, Likert-type rating scale for sexual functioning.
Each scale is rated from 1 (best sexual functioning) to 6 (worst).

1. How strong is your sex drive?

Very strong Somewhat strong Strong Somewhat weak Very weak

2. How easily are you sexually aroused (turned on)?

Very easily Somewhat easily Easily Somewhat weak Very weak

3a. (Female) How easily does your vagina become moist or wet during sex?

3b. (Male) Can you easily get and keep an erection?

Very easily Somewhat easily Easily With some difficulty With great difficulty

4. How easily can you reach an orgasm?

Very easily Somewhat easily Easily With some difficulty With great difficulty

5. Are your orgasms satisfying?

Very satisfying Somewhat satisfying Satisfying Somewhat unsatisfying Very unsatisfying

Table 4

**OVERALL STRATEGIES FOR THE TREATMENT OF
MEDICATION-INDUCED SEXUAL DYSFUNCTION**

1. Wait for spontaneous remission.
2. Decrease the medication to a lower dose.
3. Try partial or complete drug holidays.
4. Change to a different antidepressant medication with less sexual side effects.
5. Use a secondary agent to treat the sexual dysfunction.

tients as relatively nonintrusive (Table 3). Individual questions score desire, arousal, male erection or female lubrication, and satisfaction with orgasm. Total ratings range from 5 to 30, with a score of 15 to 18 indicating average sexual function. Changes in sexual functioning can be evaluated at each visit and correlated with changes made in dosing and/or changes to other medications.

The Treatment of Medication-Induced Sexual Dysfunction

If sexual dysfunction interferes with the patient's quality of life, treatment options should be discussed in detail. Non-pharmacologic interventions should be introduced first, because the addition of or change to other medications often involves additional expense, side effects, and/or the inconvenience of additional doses (Table 4). Here are guidelines to manage such situations.

1. Wait for Spontaneous Diminution of Side Effects Over Time

Side effects are often more severe in the initial weeks of medicating an illness, and later abate. *However, treatment-emergent sexual dysfunction tends to persist.*

2. Decrease the Medication to a Lower Dose

Sexual dysfunction tends to be dose-related, so lowering the medication dose may be helpful. Care needs to be taken, though, not to go below the therapeutic threshold.

3. Try Partial or Complete Drug Holidays

Fluvoxamine-, sertraline-, and paroxetine-induced sexual dysfunction has been successfully managed by partial or complete drug holidays (e.g., decreasing or holding the SSRI for a weekend).^{74,75} *Fluoxetine is not responsive to the drug holiday approach, because of its longer half-life.*

4. Change to a Different Antidepressant Medication With Fewer Sexual Side Effects

The antidepressants with the fewest effects on sexual function are nefazodone, trazodone, bupropion, and mirtazapine (Table 5). These may each serve as an alternate to SSRI- or TCA-induced sexual dysfunction. *Care must be taken, however, in the transition to nefazodone from fluoxetine or paroxetine. These SSRIs inhibit the 2D6 enzyme responsible for the metabolism of m-CPP, a metabolite of nefazodone. Increases in m-CPP can result in symptoms of anxiety or restlessness.*⁷⁶

Table 5
MEDICATION CLASSES FOR TREATMENT-EMERGENT SEXUAL DYSFUNCTION

Class	Example	Primary Agent	Adjuvant Agent
Norepinephrine Antagonist-Serotonin Antagonist	Mirtazapine	–	–
Norepinephrine-Dopamine Reuptake Inhibitor	Bupropion	–	–
Serotonin Antagonist Reuptake Inhibitor	Nefazodone, trazodone	–	–
Alpha-adrenergic antagonist	Yohimbine		–
Cholinergic enhancer	Neostigmine		–
Dopamine Agonist/Psychostimulant	Amantadine		–
Herbal remedy	Ginkgo biloba		–
Nitric oxide agonist	Sildenafil		–
Serotonin 1a partial agonist	Buspirone		–
5-HT ₂ Serotonin antagonist	Cyproheptadine		–

Trazodone is an effective antidepressant that does not decrease sexual drive or function. **Caution is advised due to the rare side effect of priapism, which is a medical emergency. Bupropion has no appreciable sexual dysfunction.** However, it is not recommended for patients at increased risk for seizures, including patients with alcohol or other drug use that results in a lowered seizure threshold.

Mirtazapine causes no appreciable sexual dysfunction, and augmentation or an immediate switch from an SSRI is well-tolerated.⁷⁷

5. Use a Secondary Agent to Decrease the Sexual Dysfunction

The following agents have been used as adjuvant therapy specific for drug-induced sexual dysfunction (Table 5):

- a. **Norepinephrine-Dopamine Reuptake Inhibitors (NDRIs): Addition of bupropion 75 mg. t.i.d. or 75 to 150 mg. p.r.n. 1 to 2 hours before sexual activity can improve sexual dysfunction secondary to SSRI monotherapy.**^{78,79} However, isolated cases of spontaneous orgasm with the combined use of bupropion and sertraline have been reported.⁸⁰
- b. **5-HT₂ Serotonin Antagonists: Cyproheptadine 2 to 8 mg. q.d. or 4 to 12mg. p.r.n. 1-2 hours before sexual activity is effective in reversing imipramine-,⁸¹ MAOI-,⁸² clomipramine-,⁸³ and SSRI-induced^{47,84,85} decreased libido and anorgasmia.** Patients often experience next-day side effects of sedation when cyproheptadine is used in combination with tricyclic or MAOI agents, a result of the drug's antihistaminic properties. Return of depression, bulimia, and suicidal thoughts have been reported as well, however.⁸⁶
- c. **Alpha-Adrenergic Antagonists: Yohimbine 5.4 to 10.8 mg. p.r.n. before intercourse or t.i.d. has been effective in reducing sexual dysfunction secondary to SSRI monotherapy.** Side effects include nausea, shakiness, tension, and anxiety.⁸⁰ *Phentolamine* (Regitine) 20 to 60 mg. p.r.n. is useful in the treatment of erectile dysfunction.⁸¹
- d. **Dopamine Agonists and Psychostimulants: Amantadine** (Symmetrel) 100 to 200 mg. q.d. has been used successfully with fluoxetine-induced sexual dysfunction.⁸⁹ *Lisuride* has been used successfully in patients with erectile dysfunction secondary to diabetes or renal failure. However, the effect is prevented by centrally-acting dopamine antagonists.⁴ *Bromocriptine* (Parlodel) will correct decreased libido and sexual performance in patients with hyperprolactinemia, a side effect of antipsychotic medications.⁴ *Dextroamphetamine* (Dexedrine) or *methylphenidate* has been used in five cases of SSRI-induced sexual dysfunction and may be especially useful in patients with concomitant attention deficit hyperactivity disorder (ADHD). The women reported enhanced levels of arousal, orgasmic sensation, and resolution-phase excitement; men noted firmer erections.^{64,90,91}
- e. **Cholinergic Enhancers: Neostigmine** is a cholinesterase inhibitor that has been used to enhance libido and reverse ejaculatory difficulty in doses of 7.5 mg. to 15 mg., 30 minutes before sexual activity.³³ *Bethanechol* 10 to 20 mg. t.i.d., or 30 mg. 1 to 2 hours before coitus, is useful for erectile dysfunction caused by the anticholinergic effects of tricyclic antidepressants.⁹² *Both drugs should be prescribed cautiously in patients with Parkinson's disease, prostatic hypertrophy, peptic ulcer disease, or cardiovascular disease.*
- f. **Serotonin Antagonist Reuptake Inhibitors: Nefazodone** 150 mg. given 60 minutes before intercourse has resolved sertraline-induced sexual dysfunction.³⁸ *Trazodone* can increase libido when used as an adjunct to antidepressants or lithium.⁹³

- g. **Serotonin 1a Partial Agonists:** At doses above 30 mg per day, *bupirone* may reverse sexual dysfunction from SSRIs through one of its two major mechanisms. It is a partial serotonergic agonist and an alpha noradrenergic antagonist.⁹⁴
- h. **Norepinephrine Antagonist-Serotonin Antagonists:** *Mirtazapine* reversed SSRI-induced sexual side effects in 13 of 19 depressed patients without diminishing their response to an antidepressant.⁹⁵
- i. **Nitric oxide agonists:** *Sildenafil* facilitates erection by inhibiting phosphodiesterase-5, resulting in increases of nitric oxide with vasodilation of the corpus cavernosum.³³ It is *contraindicated in patients with cardiovascular disease or those taking nitrates*.
- j. **Herbal remedies:** *Ginkgo biloba* 60 to 180mg. b.i.d. may be effective in vasoconstrictive sexual dysfunction. Cohen⁹⁶ reported **an open trial of ginkgo in which 91% of the women and 76% of the men taking a variety of antidepressants had resolution of their sexual dysfunction**. There has also been a report of successful treatment of fluoxetine-induced genital anesthesia with ginkgo.⁹⁷ *Caution must be exercised, however, because of the lack of scientific information and reports of spontaneous bilateral subdural hematomas associated with chronic use.*⁹⁸ Side effects include gastrointestinal disturbances, headache, and general central nervous system activation.

Conclusion

A patient's compliance with medications is greatly influenced by the effect on his or her quality of life. Chronic psychiatric illnesses often require medications that can be taken for decades. This issue must be addressed. A collaborative working relationship between the clinician and the patient can help to determine which avenues to pursue in managing sexual dysfunction associated with psychotropic medications.

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