Sex Boosters and Busters: Making Sense of Sexual Pharmacology

James K. Childerston

Childerston & Associates, Hagerstown, Maryland

In an effort to make sense of the complex interaction of biology and emotion in sexual chemistry, this article systematically evaluates drugs that can cause impotence, block orgasm, or affect sexual functioning in other ways (e.g. antihypertensives, psychotropics, and drugs for internal medicine). It will also address the sexual responses of the human body as it is influenced by hormones and adjunctive hormonal therapies as well as describing the effects of alcohol, nicotine, marijuana, and supposed aphrodisiacs. Lastly, an overview of the clinical management of medication-induced sexual dysfunction is provided.

Hundreds of commonly prescribed medications produce side effects that impact sexual function. On the other hand, a smaller, but growing group of drugs has the potential to improve sexual dysfunction. Of clinical concern is that medication-induced sexual dysfunction can reduce patient compliance and thus jeopardize treatment, but it can also impact one's quality of life in that it may lead to depression, divorce, and even suicide.

Twenty years ago, approximately 80% of sexual problems were considered psychological in origin, with the other 20% having medical or pharmacological causes. Today, these figures are almost the reverse (Crenshaw & Goldberg, 1996). The more we learn about sexual function, the more we are discovering an increasing number of medical conditions and pharmacological agents that contribute to sexual disorders.

Both prescribing and non-prescribing professionals need to increase their knowledge of sexual pharmacology. Without such information, they may misdiagnose sexual problems as a psychological condition that was actually caused by chemical interactions and easily treated with drug substitution. In such cases, even the finest therapy will fail to elicit the desired results, frustrating both therapist and patient alike. Professionals who treat sexual problems cannot arrive at a competent differential diagnosis without knowing how medications could be affecting their patients.

This article will focus on the medications associated with sexual dysfunction and provide a framework for evaluating medications based on their pharmacological properties that affect sexual function. It will also provide a very basic summary of the sexually effective drugs currently available and how they may be incorporated into the management of medication-induced sexual dysfunction.

The Neuropharmacology of Sexual Response

The brain is our most important sexual organ and sexual activity is modulated in the brain by a number of neurotransmitters and other naturally occurring endogenous substances (Table 1). These neurotransmitters influence three phases of sexual physiology including desire (libido), arousal (erection/lubrication and

engorgement), and orgasm/ejaculation (Meston & Frohlich, 2000). The neuroanatomic areas of the brain that principally 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 (Boyarsky and Hirschfeld, 2000). Sex hormones (e.g., estrogen, progesterone, and testosterone) significantly influence neurotransmitter actions that modulate sexual behavior, and account for intricate modulations of sexual arousal, functioning, and pleasure (Riley, Peet, & Wilson, 1993).

In the brain, dopamine and noradren-

Table 1

Mechanisms of Action Affecting Sexual Response

Endogenous Substance	Action	Positive Sexual Effects	Negative Sexual Effects
(1 adrenergic agonist	Excitatory	Enhances desire, arousal; facilitates action of DA, testosterone, Ach, vasopressin, prostaglandins	
(2 adrenergic agonist	Inhibitory (central and peripheral)		Decreases desire, arousal; peripheral vasoconstriction; decreases anxiety-related PME
(2 adrenergic agonist	Excitatory	Vasodilator; can enhance sexual arousal	Nervous reactions contribute to anxiety ("stage fright")
GABA	Inhibitory	Promotes receptive sexual response in females	Diminishes active sexual response in males & females
Acetylcholine (Ach)	Excitatory	Erection, lubrication, orgasm; mediates sexual thoughts, attitudes, and memories	
Cortisol	Excitatory Inhibitory	Acute effect	Chronic effect
DHEA/DHEAS	Excitatory	Increases sex drive in, females, less so in males	
Dopamine (DA)	Excitatory	Mediates pleasure, increases sex drive, promotes orgasm	In males, may promote PME
Estrogens	Excitatory & inhibitory in females	Desire, responsiveness in ; females lubrication, facilitates 5-HT, prolactin, oxytocin, opioids	Decreases desire in males
Histamine	Excitatory	Arousal, sensitizing, & blood flow facilitating properties	
Melatonin	Inhibitory		Serotonin-like substance; gonadal recession in animals

Table 1 (continued)

Mechanisms of Action Affecting Sexual Response

Endogenous Substance	Action	Positive Sexual Effects	Negative Sexual Effects
Monoamine Oxidase B	(central)		Decreases sex drive, responsiveness
Nitric Oxide	Excitatory	Vasodilates	
Opioids	Inhibitory (central)	Disinhibits at low doses	Inhibits orgasm, ejaculation, diminishes sex drive
Opioids	Inhibitory (central)	Disinhibits at low doses	Inhibits orgasm, ejaculation, diminishes sex drive
Oxytocin	Excitatory	Facilitates attraction & touch sensation, spikes during orgasm	
Progesterone	Inhibitory (central)		Sexual depressant, lowers testosterone
Prolactin	Inhibitor (central)		Decreases sex drive, orgasm; causes impotence
Prostaglandins	Excitatory	Facilitates vasodilation, (peripheral) tissue sensation, erection, lubrication	
Serotonin 1a (5-HT)	Inhibitory	Inhibits arousal, orgasm; decreases anxiety, aggressiveness	
Serotonin 1c (5-HT)	Excitatory	Increases penile erections in rats (Simon, 1993)	
Serotonin 2a (5-HT)	Inhibitory (central & peripheral)		
Substance P	Excitatory (peripheral)	Increased sensation, blood flow	
Testosterone	Excitator (central & peripheral	Increases sex drive, assertiveness, aggressiveness; facilitates DA, epinephrine, vasopressin;inhibits 5-HT, opioids, prolactin, MAO	
Thyroid Hormone	Inhibitory		Both hyper and hypo undermine sexual drive & response
Vasoactive Intestina Peptide (VIP	Excitatory	Mediates genital vascular and smooth muscle relaxation	
Vasopressin	Excitatory (central)	Facilitates focused sexual arousal; modulates adrenergic sexual excitation	

Developed and adapted, in part, from Crenshaw and Goldberg, 1996; Schiavi and Seagraves, 1995; & Boyarsky and Hirschfeld, 2000.

aline facilitate desire, arousal, and orgasm (Harvey & Balon, 1995), whereas serotonin receptor (5HT-2) stimulation results in inhibition of sexual function for both sexes (Schiavi & Seagraves, 1995). At the periphery, serotonin has an inhibitory effect on sexual arousal and orgasm in both sexes, while the neuropeptide hormone oxytocin facilitates these functions (Meston & Frohlich, 2000). Acetylcholine, nitric oxide, and sex hormones facilitate male erection, while noradrenaline (or norepinephrine) balance these actions by exerting an inhibitory effect (Boyarsky and Hirschfeld, 2000).

Acetylcholine and norepinephrine are also the neurotransmitters involved in sending the sexual messages from the brain and down the spinal cord to the nerves in the pelvis (Lyles, 2001). In addition, they perform roles in modulating ejaculation and male orgasm (Boyarsky and Hirschfeld, 2000). Much less is known about the influence of central neurotransmitters or of peripheral neurotransmission on sexual function in females. We do know, however, that anything that interrupts the cascade of signals and reflexes in neurotransmission can cause sexual dysfunction.

Drugs Associated with Sexual Dysfunction

Many medications and drugs of abuse can cause changes in sexual functioning, including, but not limited to antiandrogens, antiarrhythmics, anticancer agents, anticholinergics, antihistamines, antihypertensives, diuretics, hormones (e.g. corticosteroids, progestins), illicit and nonprescription drugs (e.g. alcohol, cocaine, nicotine, amphetamines, marijuana), opiates (e.g. Demerol, Methadone) and psychotropics (e.g. anxiolytics, anticonvulsants, antidepressants, antipsychotics, sedatives/hypnotics, stimulants). This article will briefly discuss each category, and focus more specifically on the psychotropic medications.

Reported rates of dysfunction vary greatly, often depending on what information is actually obtained from the patient. Obviously, not everyone will experience sexual dysfunction as a side effect of taking these drugs, and the dysfunction can vary in severity depending on the individual patient, the particular medication, the dosage, the number of medications prescribed for that patient, and their particular medical condition.

Every drug has certain chemical mechanisms of action that can influence any or all aspects of sexual desire and activity. These mechanisms of action will involve the neurotransmitters, neuropeptides, and endocrine factors referred to in Table 1 with their inhibitory and/or excitatory actions and result in positive or negative sexual effects. Some drugs will have mixed effects and/or impact the nervous system differently, e.g. centrally versus peripherally. There is no simple or "cookbook" approach to this incredibly complex process. However, some understanding of the mechanisms involved can inform our decision making as to diagnostic and therapeutic interventions.

The possible psychological factors of sexual dysfunction should only be evaluated after all medical and pharmacological factors have been considered. One must be careful not to reverse the roles of cause and effect, assuming that if psychological factors such as relational stress or an impending divorce are present, may be responsible for the sexual problem, when in fact, it may be an indirect consequence of a drug induced sexual dysfunction. As a result, the relational stress and conflict could, in this case, be the consequence of the sexual dysfunction (Crenshaw & Goldberg, 1996).

Side Effects and Sexual Function

In examining the impact of medications, there are a number of sexual problems that can result. These effects can be the direct result of the chemical mech-

anisms the drug has on the body, or the sexual side effects can be indirect in nature in that they result from some other drug side effect. The most common sexually related effect of medication is diminished desire, which applies rather equally to both sexes. The next most frequent direct sexual side effect is erectile difficulties, followed by orgasmic difficulties in both males and females. The most common orgasmic dysfunction in women is delayed orgasm (Crenshaw & Goldberg, 1996). Symptoms of gynecomastia, lactation, priapism, dyspareunia, infertility, and hypogonadism are less frequent, but still quite disturbing when they occur. Females can experience lubrication difficulties and menstrual disorders, which can interfere with sexual appetite, function, and frequency. Certain drugs can induce states of psychoses, which can initially manifest as hypersexuality.

It is also important for the therapist to recognize possible indirect sexual side effects that result not from the chemical properties of the drug, but from some other drug effect, such as sedation, changes in mood and energy levels, weight loss or gain, body image, etc. These indirect effects can make a person too sleepy, too unhappy, too tired, or too confused for sex to be appealing or possible. These effects may be the result of neurological factors (e.g. headaches, dizziness, pain, analgesia), physical levels of comfort (e.g. constipation, dryness, nausea, indigestion, rash) endocrinological in nature (e.g. alterations in insulin metabolism or thyroid function), or a function of vascular problems (e.g. arrhythmias, headaches, vasoconstriction).

Sexual Effects of Hormonal Therapies

Estrogen, progesterone, and testosterone are the chief hormones involved in cyclical female sexuality. All three are used in various hormone replacement regimens for females, with testosterone supplementation most used with men.

In humans, levels of estrogen and sexual desire do not seem to be correlated and fluctuations across the menstrual cycle do not seem to be related to estrogen levels. Estrogen Replacement Therapy (ERT) can provide relief from the psychological problems associated with menopause, and thus enhance sexual response indirectly. Improvements appear to be related to an overall improved well being, a decrease in anxiety, and a reduction in climacteric symptoms (Crenshaw & Goldberg, 1996). The full benefits of ERT in relation to improved sexual desire are reliably achieved only with the addition of testosterone (Greenblatt, 1987). Studies have shown that estrogens are usually effective in resolving sexual dysfunction due primarily to dyspareunia and secondarily to vaginal dryness (Sarrel, 1988). Estrogens promote REM sleep during which time secretions may "irrigate" the vagina. Progesterone supplementation, however, may impede or prohibit the facilitation of sleep lubrication.

Progesterone is utilized in replacement therapy and in certain oral contraceptives. An increase in progesterone levels throughout the cycle has been associated with decreased sexual desire, primarily due to its tendency to reduce testosterone levels (Gottesman & Schubert, 1993). Progesterone increases monoamine oxidase (MAO) activity, while estrogen decreases it, so progesterone has the propensity to cause depression. Progesterone also has the potential to inhibit orgasm, and may lower DHEA/S in addition to lowering testosterone. It is associated with reduced physical sensitivity, and it functions as a sedative in moderate doses and as an anesthetic at high doses (MacDonald, Dombroski, & Casey, 1991).

Medroxyprogesterone is used in the treatment of sexual offenders by providing a "chemical castration" which within 1 month can cause testosterone levels to drop by more than 90% (Cooper, 1988).

This chemical treatment, widely used in Europe, is only now being applied cautiously in the Untied states, due to several legal challenges by offenders opposed to its application.

In the female, the ovaries produce testosterone with additional testosterone being derived from the adrenal steroids. Removal of the ovaries will decrease sexual desire to a certain extent, but removal of the adrenal glands had an even more deleterious effect on sexual desire (Meston & Frohlich, 2000). With natural menopause, androgen levels are positively correlated with sexual interest. While desire is influenced by androgen levels, androgens alone are not sufficient for the experience of sexual desire. Testosterone treatment seems to be useful in facilitating sexual desire in a subset of women with hypoactive sexual desire, but it requires monitoring, and currently there are not clearly defined dosage levels for females. However, women with higher testosterone levels reported less depression, experienced more sexual gratification with their husbands, and showed a "greater capacity to form good interpersonal relationships" (Persky, Lief, et al, (1978).

Testosterone appears to influence both men and women to be more self-focused sexually. However, masturbation without interpersonal sexual interaction does not increase testosterone levels, while intercourse with a partner usually does (Keverne, 1979). In men, the primary effect of lowering testosterone is to reduce sex drive rather than sexual potency. In fact, testosterone is clinically effective for sex drive only in hypotestosterone males (O'Carroll, Shapiro, & Bancroft, 1985). It is important to note that testosterone is not the only "chemical switch" that governs sexuality. Sexual desire and response are increased or decreased by a complex interaction of body chemicals, including peptides, neurotransmitters, and hormones. The notion that sex hormones exclusively control sexual behavior is out-of-date today (Crenshaw & Goldberg, 1996).

Sexual Effects of Abused Drugs

Alcohol stimulates sexual desire at low doses, due to disinhibition, but sexual responsiveness is blunted and erection and orgasm are decreased with intoxicating doses. It seems to share inhibitory properties with GABA, benzodiazepines, opiates, and serotonin. With chronic use, gynecomastia, atrophied testicles, infertility, and feminization may occur in males because testosterone decreases and estrogen increases. It would not be inaccurate to explain to male alcoholics that alcohol goes directly to their testicles, causing damage, so that their genitals age before they do. In female alcoholics, menstrual disorders, pelvic inflammatory disease, and bleeding disorders are common due to decreased vasocongestion and decreased vaginal lubrication (Crenshaw & Goldberg, 1996).

Nicotine is a vasoconstrictor and diminishes blood flow to the brain and to the penis, and causes increased blood flow out of the penis, which results in damage to vascular and genital tissue. It can cause impotence and increases arteriosclerosis (Virag, Bouilly, & Frydman, 1985). Smoking may actually improve sex drive, due to increased DHEA, dopamine, and decreased serotonin, but it also increases cortisol and progesterone, which impairs sexual function. Smoking impedes reproduction in both sexes and eliminates the protective effect ERT has on osteoporosis (Kiel, Baron, et al., 1992).

Caffeine is the most widely used drug in the world. Its activating effect is due to antagonism of adenosine. However, a decrease in adenosine - induced vasodilation results in decreased resting penile tone and decreased erectile tumescence rigidity (Karaki, Ahn, & Urakawa, 1987). As a strong diuretic it can increase urinary incontinence, which will decrease urinary-

genital sensitivity (Crenshaw & Goldberg, 1996).

Opioids decrease sexual responsivity in that, while they provide a sense of relaxation and well being, they have an analgesic effect on sexual sensations because they inhibit oxytocin release, which mediates touch behavior (Racke et al., 1991). Opioids also decrease testosterone and nocturnal penile tumescence. In fact, sexual dysfunction is a notable cause of methadone treatment discontinuation in males (Boyarsky and Hirschfeld, 2000). The chief sexual benefit of opioids appears to be the delay of orgasm/ejaculation in men (but it may prolong female orgasm). So it is not surprising then, that Naloxone and Naltrexone (opiate antagonists used in facilitating opiate withdrawal), can also be used to treat impotence and retarded orgasm (Crenshaw & Goldberg, 1996).

Marijuana at low doses appears to intensify sexual experience in that it increases relaxation and pleasurable touch between partners already comfortable with each other (Kolodny, Masters, & Johnson, 1979), but intoxication severely dampens interest, participation, and performance (Halikas et al. 1982). It has not been found to change concentrations of testosterone, luteinizing hormone (LH), or follicle stimulating hormone (FSH) in controlled studies (Mendelson et al. 1974).

Cocaine can increase sex drive through increased dopaminergic activity and inhibit orgasm at low to moderate doses, but with chronic use, impotence and anorgasmia are predictable because dopamine becomes depleted. Hallucinogens have little direct impact on sexual function, but can impair focus and coordination. Amphetamines provide acute pleasurable effects, but repeated use "burns out" these pleasure neurons, leaving behind a reduced capacity for pleasure, sexual arousal, and sexual function (Crenshaw & Goldberg, 1996). Ecstasy (the "hug" pill) increases sexual desire, but results in decreased sexual performance, in addition to impairing memory and causing brain damage (Kuhn, et al., 1998).

Sexual Effects of Antihypertensive Medications

Antihypertensive medications were the first drugs recognized to cause sexual dysfunction as part of their side effect profile. However, since a common cause of hypertension is atheroschlerosis (narrowing of the arteries throughout the body), which can cause impotence without the addition of any medication, there is higher incidence of sexual problems among untreated hypertensives than among the general population. There are essentially six classes of medications used to treat hypertension: diuretics, beta-blockers, alpha1 blockers, alpha2 agonists, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers. The following medication information is summarized from Crenshaw & Goldberg's text on Sexual Pharmacology: Drugs That Affect Sexual Functioning.

Diuretics are used for hypertension, congestive heart failure, and edema and are often used in combination with other antihypertensives. There are four different sub-classes of diuretics, but as a general rule, they tend to increase estrogens and prolactin and decrease zinc and as a result are quite sexually toxic. This chemical mechanism results in desire disorders (in both sexes), erection difficulties, and breast disorders (gynecomastia). However, they may be useful for lubrication problems. Of the diuretics, the preferred alternatives to minimize sexual dysfunction are the Thiazide type - Indapamide (Lozol), Hydrochlorothiazide (Hydrodiuril) or the Loop diuretic - Furosemide (Lasix). A preferred alternative drug class would be the calcium channel blockers.

Beta-Blockers are used for hypertension, arrhythmia, angina, migraine, and acute MI. They tend to increase serotonin and decrease beta-adrenergic activity. This

may result in desire disorders (in both sexes), infertility (due to decreased sperm motility), and erection difficulties (decreased quality of erection and Peyronie's disease). Alternatives would be the ACE inhibitors, alpha1 blockers, or calcium channel blockers. Avoid Propranolol (Inderal) if possible as it is the most sexually toxic, whereas the best beta-blocker choice may be Bisoprolol (Zebeta).

Alpha1 Blockers are used for hypertension. They act to decrease adrenergic (alpha1) activity which may result in erection difficulties (priapism, impotence) and retarded ejaculation. Alternatives would be the ACE inhibitors, calcium channel blockers, or the diuretic Indapamide (Lozol). Doxazosin (Cardura) and Terazosin (Hytrin) may be best of alpha1 blockers to minimize sexual dysfunction, but sexual problems are exacerbated when used with diuretics.

Alpha2 Agonists are used for hypertension and opiate/alcohol withdrawal. The positive mechanism of action is that they tend to increase growth hormone and decrease cortisol. However, on the negative side they function to increase adrenergic (alpha2) activity and opioids, and decrease alpha1 activity, cholinergic activity, prostaglandins, substance P, and vasopressin. This may result in desire disorders (in both sexes), erection difficulty, and retarded ejaculation. Alternatives are the ACE inhibitors, alpha1 blockers, calcium channel blockers, or the diuretic Indapamide (Lozol). The transdermal clonidine patch is preferable to oral clonidine.

Angiotensin-Converting Enzyme (ACE) Inhibitors are the antihypertensive drugs of choice at this time. They are indicated for hypertension and congestive heart failure. The positive mechanism of action is that they tend to decrease angiotensin II and increase cholinergic activity, prostaglandins, and substance P. On the negative side, they function to decrease alpha1, LHRH, and vasopressin, and they increase opioids. This may result in erection difficulties and possible birth defects. Alternatives would be the calcium channel blockers, with the best options appearing to be Amlodipine (Norvasc), Felodipine (Plendil), Nicardipine (Cardene), or Isradipine (DynaCirc).

Calcium Channel Blockers are used for hypertension, angina, congestive heart failure, and arrhythmia. The positive mechanism of action is that they tend to increase DHEA and decrease serotonin. On the negative side, they function to increase prolactin and decrease alpha1, dopamine, oxytocin, vasopressin, and substance P. This may result in desire disorders (in both sexes), erection difficulties (occasional impotence), retarded ejaculation, menstrual disorders (menorrhagia), infertility (decreased sperm motility), and breast disorders (gynecomastia). The alternatives would be the ACE Inhibitors, alpha1 blockers, and the diuretic Indapamide (Lozol). ACE inhibitors and calcium channel blockers are currently the most effective antihypertensive medications for patients wishing to avoid sexual dysfunction.

Sexual Effects of Psychotropic Medications

Antianxiety Agents:

Buspirone (Buspar) is a 5-HT1A agonist used for anxiety and depression. It acts to increase serotonin through downregulation of the 5-HT1A receptor and increased alpha1 activity (Stahl, 1996). There are no adverse sexual side effects with Buspar with the exception of possible quickened ejaculation, which could worsen PME. It may enhance desire and orgasm in both sexes. Buspar is often not very effective alone, but can be a useful adjunct.

Benzodiazepines are used for anxiety, panic/phobia disorder, OCD, pain (chronic, back, muscle spasm), insomnia, alcohol withdrawal, and jet lag. The positive mechanism of action is that they tend

to decrease cortisol and serotonin levels, while increasing cholinergic activity. On the negative side, they function to decrease alpha1, LHRH, substance P, and testosterone, while increasing GABA/BZD and progesterone (Schiavi and Seagraves, 1995). This results in decreasing excitement, which causes ejaculatory delay in males and delay of orgasm in females. The sexual effects are similar to alcohol and other substances used to decrease inhibitions, but with chronic use they can be sexually disabling. However, benzodiazepines may be useful for dyspareunia due to vaginismus. Alternatives include SSRIs for OCD and anxiety or Venlafaxine (Effexor) for anxiety.

Antidepressants:

Serotonin Selective Reuptake Inhibitors (SSRIs) are the first line of drugs used for depression, as well as for OCD, panic/phobia, PTSD, and premenstrual dysphoric disorder (PMDD). Their mechanism of action involves an increase in serotonin, cortisol, opioids, and prolactin. This results in sexual dysfunction by decreasing desire and libido, causing difficulties in obtaining and maintaining an erection, and increasing time to orgasm. Orgasm is adversely affected in both sexes. Research with Rush Sexual Inventory demonstrated sexual dysfunction rates of 60% for men and 57% for women for those taking SSRIs (Zajecka, et al., 1997). Paroxetine (Paxil) appears to be the most potent SSRI in inhibiting orgasm and therefore can be used to treat PME (Waldinger, et al, 1994). Vaginal and penile anesthesias have been reported during Fluoxetine (Prozac) treatment (King & Horowitz, 1993).

Tricyclic Antidepressants (TCAs) are used for depression, bulimia, panic/phobia, anxiety, PTSD, enuresis, and ADHD. The positive mechanism of action is that they tend to increase alpha1 and decrease cortisol. On the negative side, TCAs function to increase prolactin and serotonin, and decrease beta-adrenergic and cholinergic activity, histamine, and oxytocin. This results in decreased desire, decreased ability to gain and sustain an erection, and inhibited orgasm and ejaculation (Elmore & Quattlebaum, 1997). The most sexually toxic tricyclics are Clomipramine (Anafranil), Amitriptyline (Elavil) and Doxepin (Sinequan) (DeVeaugh-Geiss et al., 1989). Clomipramine has been used successfully to treat PME. Desipramine (Norpramin) and Nortriptyline (Pamelor) cause the least sexual dysfunction of the TCAs (Noyes, et al., 1989). Due to their anticholinergic side effect, tricyclics tend to interfere with most body fluid secretions (salivation, lubrication, precoital fluid, and ejaculatory volume).

Monoamine Oxidase Inhibitors (MAOIs) are used for depression, atypical (hypersomnia, hyperphagia, and mood reactive) depression, panic/phobia, OCD, and bulimia. The positive mechanism of action is MAOIs increase alpha1 and monoamine oxidase. On the negative side, MAOIs function to increase prolactin and serotonin, and decrease beta-adrenergic and cholinergic activity, as well as testosterone. This results in inhibition of desire, difficulty with erection, and a 20% to 40% incidence of delayed orgasm and inhibited ejaculation (Harrison, et al., 1986). Tranylcypromine (Parnate) causes far less weight gain and sexual dysfunction of all the MAOIs.

Trazodone (Desyrel) and Nefazadone (Serzone) are used for depression and pain. They have been associated with very low incidences of sexual dysfunction. Trazodone has somewhat unpredictable effects on erectile function. It has been reported to increase desire and erections and prolong time to orgasm, but has also been associated with priapism in both men and women (PDR, 1999). Trazodone blocks peripheral alpha1 activity and blocks the serotonin 5-HT2 receptor thought to be responsible for sexual dysfunction. Nefazadone is structurally

similar to trazodone, but lacks the alpha1 antagonist activity which is less sedating.

Venlafaxine (Effexor) inhibits reuptake of serotonin and noradrenaline and is used for depression and anxiety. It inhibits orgasm in 12% of male patients, which is less than the SSRIs, but more than that of Nefazadone (Serzone), Trazodone (Desyrel), Bupropion (Wellbutrin), and Mirtazapine (Remeron) (PDR, 1999). There is one reported case of increased libido and spontaneous erections (Owen, 1986). Mirtazapine (Remeron) also appears to cause very little sexual dysfunction probably due to its blocking of the postsynaptic serotonin 5-HT2 and 5-HT3 receptors. However, its side effects can include fairly significant sedation and weight gain.

Bupropion (Wellbutrin) is used for depression, smoking cessation, and bipolar disorder. Its sexual mechanisms of action are generally positive and include increases in adrenal androgens (DHEAS), alpha1 and dopamine and decreases in prolactin. Studies have estimated that treatment emergent sexual dysfunction occurs in less than 3% of treated patients (Boyarsky and Hirschfeld, 2000). Bupropion appears to improve sexual desire and function, as well as improve erectile difficulty and lubrication. However, it can aggravate hypersexuality and exacerbate nervousness, due to its stimulant action. It can also cause insomnia (delay of sleep onset and abnormal waking). It is not recommended for those with a potential for psychosis and those at risk for seizure. Bupropion's sexual action appears to involve activation of the limbic system, and it has an excitatory effect on the nucleus accumbens (Crenshaw & Goldberg, 1996). It has also been used successfully to treat SSRI-induced sexual dysfunction (Walker, et al., 1993).

Mood Stabilizers and/or Anticonvulsants:

Lithium (Eskalith) is used for bipolar disorder, alcoholism, and cluster headache prophylaxis. It acts to increase serotonin, cortisol, GABA/BZD, while decreasing thyroid hormone, vasopressin, and testosterone. Its sexual side effects are somewhat mixed, perhaps because Lithium is often used in combination with other psychotropics. Positive sexual effects are rare and only seen in women. It appears to interfere with libido and erection in some males (Aizenberg, et al., 1996) and may effect fertility due to birth defects, as well as decreased or malformed sperm (Crenshaw & Goldberg, 1996).

Carbamazapine (Tegretol) decreases DHEA (adrenal androgens essential to sexual wellbeing) and also decreases testosterone and thyroxine (MacPhee, et al., 1990). It is quite sexually toxic in that it decreases desire, arousal, and erection.

Gabapentin (Neurontin) and Lamotrigine (Lamictal) inhibit or regulate glutamate/excitatory amino acid activity in limbic areas of the brain that affect cognition and sexual desire. Their sexual effect seems promising but is not yet clear.

Valproic acid (Depakote) may be the best choice in this class due to its lack of inhibitory action on adrenal androgens. It does not appear to affect sex drive or cause impotence (Crenshaw & Goldberg, 1996).

Antipsychotics:

These types of medications are used for psychoses, schizophrenia, schizoaffective disorder, mania, Tourette syndrome, agitated depression, and psychotic dementia. Their sexual mechanism of action is primarily negative in that they increase prolactin, while decreasing dopamine, testosterone, alpha1 and cholinergic activity. Since dopamine is essential for sexual activation and function, blocking dopamine (D2 receptors) will have a sexually toxic effect. Dopamine also acts to inhibit prolactin, so when dopamine is blocked, one can have high levels of prolactin, which results in a decrease in testosterone. Thirty percent to 60% of patients receiving typical antipsychotics experience disturbance in sexual function

((Melis & Argolis, 1995). The sexual side effects include difficulties with erection, orgasm, and sexual satisfaction ((Sullivan & Lukoff, 1990).

As of this time, there have been no controlled studies on sexual dysfunction using the newer atypical antipsychotic medications, although they appear to cause less sexual dysfunction than the typical antipsychotics. (Boyarsky & Hirschfeld, 2000). The atypical antipsychotics block a higher ratio of serotonin (5-HT2) receptors versus dopamine, so there is not as great an increase in prolactin. Case studies report sexual dysfunction with these atypical agents, however. *Clozapine (Clozaril)* has been associated with retrograde ejaculation (Jeffries, et al., 1996). Risperidone (Risperdal) can cause difficulties with ejaculation and gynecomastia due to increased prolactin levels (Shiwach and Carmody, 1998). *Olanzapine (Zyprexa)* may be the most promising atypical to date, as it has the fewest reports of sexual dysfunction (Boyarsky & Hirschfeld, 2000).

Psychostimulants:

These amphetamine-oriented medications are used for ADD, ADHD, and off-label for weight loss. The positive sexual mechanism of action is that they increase alpha1 and dopamine, and the negative is that they increase cortisol. This can result in a heightened or reduced sexual response depending on the dose administered. A lower dose can create a general feeling of well-being and stimulate a sexual response, whereas higher doses cause anxiety and nervousness due to increased adrenergic activity (Boyarsky & Hirschfeld, 2000). At higher doses, *Methylphenidate (Ritalin)* may aggravate premature ejaculation and impotence and cause anxiety. An alternative to these medications is *Bupropion (Wellbutrin)*.

Sexual Effects of Drugs for Internal Medicine

This section will briefly comment on the sexual effects of antiulcer drugs (histamine-2 antagonists), cold/allergy medications, asthma medications, anticancer drugs, and cardiac drugs.

Histamine-2 antagonists are used for ulcer, reflux, and gastric hypersecretory states. *Cimitadine (Tagamet)* is sexually toxic due to its antiandrogenic effects (gynecomastia, impotence, and decreased sperm). It also increases estrogen metabolism, decreases DHEA, and interferes with testosterone metabolism. *Ranitadine (Zantac)* is the most widely prescribed drug in the world. *Ranitadine*, along with *Nizatidine* (Axid),and *Famotidine (Pepcid)* are relatively benign sexually. All Histamine-2 antagonists, except *Famotidine*, potentiate alcohol.

Cold /allergy medications include antihistamines (e.g. *Benadryl*), decongestants (e.g. *Sudafed*), or PPA products (*Ephedrine*). Anticholinergic and antihistiminergic effects can adversely affect sexual function (e.g. sedation, lubrication problems). Sympathetic stimulation from decongestants may cause constriction of blood flow which can negatively impact erection.

Asthma medications include beta2 agonists, xanthines, corticosteroids, and anticholinergics. Sexual dysfunction is frequent with pulmonary diseases. Of the available bronchodilators, the $beta_2$ agonists appear to be the least sexually toxic *(e.g. Albuterol (Proventil, Ventolin), Terbutaline (Brethine).*

Anticancer drugs focus on preservation of life, retarding cancer growth, and the prevention of pain and organ degeneration. Desire can be maintained, but orgasmic intensity can decrease and dry orgasm may occur. Irritability and occasional physical violence may accompany sexual dysfunction during chemotherapy. Sexual desire often shifts to a desire for intimate closeness, distinct from actual sexual activity. Certain cancers and the associated surgeries can cause sexual dysfunction without other adjunctive treatments.

Cardiac drugs - In men, long-term digitalis treatment causes increased estrogen and decreased testosterone and luteinizing hormone. There is little information on sexual side effects due to antiarrhthymic agents. Quinidine (Cardioquin, Quinidex) seems to be the antiarrhythmic drug of choice to minimize sexual dysfunction.

Sexually Effective Drugs

There are several types of medications that favorably affect sex including dopaminergic drugs, Bupropion (Wellbutrin), serotonin antagonists, Yohimbine (Yocon), vasodilators, and Sildenafil (Viagra). These drugs should not replace sex therapy, nor should anyone attempt to use them for that purpose. In many cases, however, they may be able to shorten therapy or contribute to its effectiveness (Crenshaw & Goldberg, 1996).

Dopaminergic Drugs - L-deprenyl (Eldepryl), a selective inhibitor of MAO-B may be helpful in the treatment of low sexual desire in the elderly. *Phenylethylamine (PEA)* somehow mediates feelings of love and romance, with levels generally found to be greater in females. *Bromocriptine (Parlodel)* inhibits prolactin, and corrects testosterone and luteinizing hormone deficits in hyperprolactemia. It is also used by 700,000 women a year in order to suppress lactation.

Serotonin Antagonists - P-Chlorophenyl alanine (PCPA) is a toxic drug that promotes aggression, insomnia, and aberrant sex in that it selectively depletes brain serotonin by inhibiting the metabolism of tryptophan to serotonin. The balanced interaction of testosterone, dopamine, and serotonin may be typical of natural sexual function. A deficiency in any of these can depress normal sex drive and behavior. Other serotonin inhibiting drugs, such as *Cyproheptadine (Periactin)* and *Methysergide (Sansert)* may have sexual benefits. Cyproheptadine can relieve the anorgasmia and lack of ejaculation caused by SSRIs.

Yohimbine (Yocon, YBRON) is used for impotence, orthostatic hypotension, and diabetic neuropathy. It helps by increasing alpha1, cholinergic, oxytocin, PEA, substance P, and vasopressin, and decreasing alpha2, GABA/BZD, opioids, and progesterone. On the negative side, it increases prolactin and cortisol with no adverse sexual effects (other than increased perspiration). It also seems to improve desire and erection.

Vasodilators have largely been replaced by Sildenafil (Viagra) given that their primary mode of delivery is penile injection. These medications include *Papaverine, Phentolamine (Regitine) and Prostaglandin E1 (PGE1)*. Papaverine and Phentolamine are generally given in combination therapy. The failure of pyschogenically impotent men responding to pharmacological injection erection (PIE) therapy may be due to anxiety during the procedure, which produces excessive adrenergic sympathetic activity. Phentolamine, when taken orally or sublingually *(Vasomax)*, may also induce erections without direct injection. Prostaglandins are found naturally in the penis and PGE1 is available as injectable *Alprostadil.* Its FDA-approved indication is to aid in the treatment of pediatric heart attacks by keeping arterial ducts open. Its initial appeal was an apparent lack of priapism. PGEI is also available by penile injection as *Caverject* and *Edex* and transurethrally as Muse. PGE1 directly relaxes the penile corpus cavernosum muscle and inhibits alpha-adrenergic action in that muscle.

Sildenafil (Viagra) was released in 1998 and was designed to treat erectile dysfunction (ED). It takes about 50-60 minutes after ingestion to be effective. Sildenafil works in the context of sexual desire, in that it does not restore libido. It is generally initiated with a 50mg tablet, and titrated to 25 or 100mg depending on adverse effects or efficacy. It may inhibit phosphodiesterase, type 6 in the eye, with resultant difficulty in discriminating blue from green, bluish tones in vision, or difficulty seeing in dim light (Boyce & Umland, 2001).

Nitric Oxide (NO) is an essential component in the production of penile, and possibly, clitoral vasocongestion and tumescence. Sexual stimulation leads to NO production, which in turn stimulates the release of guanylate cyclase. Guanylate cyclase converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP), and cGMP produces smooth muscle relaxation of the penile arteries and increased blood flow, which results in an erection (or perfusion of the clitoris in females). Cyclic guanosine monophosphate (cGMP) is metabolized by cGMP PDE5. Sildenafil prolongs the action of cGMP by inhibiting its metabolism by PDE5 (Meston & Frohlich, 2000). Sildenafil is contraindicated in a patient taking nitrates in any form as it can result in a precipitous drop in blood pressure. The pharmaceutical company Eli Lilly is planning to release Cialis as a competitive PDE5 inhibitor drug if it is approved following clinical trials.

Treatment of Medication-Induced Sexual Dysfunction

The clinician should attempt to have an open discussion with the patient about the nature of the medications that they are taking and the risks of sexual dysfunction accordingly. Ask the patient to inform the clinician of any effect, so that it may be specifically addressed at each visit and discussed with the patient's prescriber if adjustments are needed. Non-pharmacologic interventions should be initially introduced in order to better minimize expense, additional side effects, and patient inconvenience. The following are clinical guidelines suggested by Boyarsky and Hirschfeld in their article, "The Management of Medication-Induced Sexual Dysfunction," and should be considered as the clinician approaches treatment in these situations.

1. Wait for spontaneous remission of side effects. Side effects are often more severe in the initial weeks of treatment, and later diminish. However, treatment emergent sexual dysfunction tends to persist.
2. Decrease the medication to a lower dose. Sexual dysfunction is often dose related, so lowering it may be helpful, as long as it is not lowered below a therapeutic threshold.
3. Try partial or complete drug holidays. This will not work for all medications or in all medical conditions. However, for SSRI induced sexual dysfunction, reducing or eliminating the medication for a weekend can reduce or delete the dysfunction during that time. This will not work for Fluoxetine (Prozac) because of its longer half-life, but does work for Paroxetine (Paxil).
4. Change to a different medication with fewer sexual side effects. For example, the antidepressants with the fewest effects on sexual function are Bupropion (Wellbutrin), Nefazadone (Serzone), Venlafaxine (Effexor), and Mirtazapine (Remeron). Be cautious in switching from Paroxetine or Fluoxetine to Nefazadone due to a significant drug interaction.
5. Use a secondary agent to decrease sexual dysfunction. Adding an adjunctive agent may be possible in many cases, but concern should be given to the possibility of additional side effects or interaction possibilities. The following are possible adjunctive agents:

   - a low dose of Bupropion (Wellbutrin) 75-mg q.d. or b.i.d.
   - Yohimbine 5.4-10.8 mg p.r.n. before intercourse or t.i.d (increases NE activity)
   - Viagra (50-75% response rates) - Be cautious here as it is contraindicated in patients with cardiovascular disease or those taking nitrates.
   - Cyproheptadine (Periactin) 4-

12mg 1-2 hrs prior to intercourse (serotonin antagonist)

- Dopamine agonists and Psychostimulants: Amantadine (Symmetrel) 100-200 mg q.d., Lisuride, Bromocriptine (Parlodel), Dextroamphetamine (Dexedrine), and Methylphenidate (Ritalin) have all been used with varying success.
- a low dose of Bupropion Ginkgo Biloba - 60-180mg b.i.d. may be effective in vasoconstrictive sexual dysfunction. Side effects include gastrointestinal disturbances, headache, and general central nervous system activation (Cohen, 1997).

Conclusion

A clinician's treatment plan can only be effective if the patient follows instructions. When a patient has been prescribed medication(s) that impairs sexual function, the likelihood of non-compliance with that aspect of treatment increases dramatically. Therapists working with these individuals have a valuable opportunity to offer hope to their patients as they recognize this action, and collaborate with the patient and their prescriber to discover alternative approaches to the problem. This may involve minimizing medication and maximizing other resources by improving diet and fitness, promoting exercise, reducing or eliminating caffeine, alcohol, and nicotine, and practicing stress reduction behaviors. It can also involve a medication adjustment, substitution, or augmentation. Reinforce patient hope and treatment compliance by asserting that, sometimes, a small change can reap big rewards in improved sexual functioning.

An understanding of what is happening to the patient physically and pharmacologically will allow the therapist to better address the psychological, spiritual, emotional, and relational concerns presented in treatment. Successful resolution of the psychotherapeutic issues may well involve a more complete awareness of their medical condition. This type of integrative approach becomes increasingly important as research findings and high-level practice further blur the distinction between medical and psychological conditions.

James K. Childerston, Ph.D., FICPP, MP *is a licensed psychologist in private practice, and is Board Certified in Psychopharmacology and in Medical Psychology. He teaches with The Psychopharmacological Institute and with the Institute for Sexual Wholeness. He can be reached by e-mail at: jkc@nfis.com.*

References

Aizenberg, D., Sigler, M., Zemishlany, Z, & Weisman, A. (1996). Lithium and male sexual function. *Clinical Neuropharmacology*, 19(6), 515-519.

Boyarsky, B.K., & Hirschfeld, R.M. (2000). The management of medication-induced sexual dysfunction. *Essential Psychopharmacology*, 3(2), 39-58.

Boyce, E.G. & Umland, E.M (2001). Sildenafil citrate: A therapeutic update. *Clinical Therapy*, 23(1), 2-23.

Cohen, A.J. (1997). *Ginkgo Biloba for Drug-induced Sexual Dysfunction.* 1997 American Psychiatric Association meetings, San Diego, CA.

Cooper, A.J. (1988). Medroxyprogesterone acetate as a treatment for sexual acting out in organic brain syndrome [letter to the editor]. *American Journal of Psychiatry*, 145, 1179-1180.

Crenshaw, T.L., & Goldberg, J.P. (1996). Sexual Pharmacology: *Drugs That Affect Sexual Functioning.* New York: W.W. Norton & Co.

DeVeaugh-Geiss, J., Landau, P., & Katz, R. (1989). Preliminary results from a

multi-center trial of clomipramine in obsessive-compulsive disorder. *Psychopharmacology Bulletin*, 25, 36-40.

Elmore, J.L. & Quattlebaum, J.T. (1997). Female sexual stimulation during antidepressant treatment. *Pharmacotherapy*, 17, 612-616.

Fisher, H.E., (1993). *Anatomy of Love: The Mysteries of Mating, Marriage, and Why We Stray*. New York: Random House.

Gottesman, H.G., & Schubert, D.S. (1993). Low-dose oral medroxyprogesterone acetate in the management of the paraphilias. *Journal of Clinical Psychiatry*, 54, 12-188.

Greenblatt, R.B. (1987). The use of androgens in the menopause and other gynecic disorders. *Obstetrics and Gynecology Clinics of North America*, 14, 251-268.

Halikas, J., Weller, R., & Morse, C. (1982). Effects of regular marijuana use on sexual performance. *Journal of Psychoactive Drugs*, 14, 59-70.

Harrison, W.M., Rabkin, J.G., Ehrhardt, A.A., Stewart, J.W., McGrath, P.J., Ross, D., & Quitkin, F.M. (1986). Effects of antidepressant medication on sexual function: A controlled study. *Journal of Clinical Psychopharmacology*, 6, 144-149.

Harvey, K.V., Balon, R. (1995). Clinical implications of antidepressant drug effects on sexual function. *Annals of Clinical Psychiatry*, 7, 189-201.

Jeffries, J.J., Vanderhaeghe, L., Remington, G.J., & Al-Jeshi, A. (1996). A clozapine-associated retrograde ejaculation. *Canadian Journal of Psychiatry*, 41(1), 62-63.

Karaki, H., Ahn, H.Y., & Urakawa, N. (1987). Caffeine-induced contraction in vascular smooth muscle. *Archives of Internationales de Pharmacodyam et de Therapie*, 285, 60-71.

Keverne, E.B. (1979). Sexual and aggressive behavior in social groups of talapoin monkeys. *In Ciba Foundation Symposium. Vol. 62. Symposium on sex, hormones, and behavior, London* (pp. 291-297. Amsterdam: Excerpta Medica.

Kiel, D.P., Baron, J.A., Anderson, J.J., Hannan, M.T., & Feston, D.T. (1992). Smoking eliminates the protective effect of oral estrogens on the risk for hip fracture among women. *Annals of Internal Medicine*, 116, 716-721.

King, V.L., Jr., & Horowitz, I.R. (1993). Vaginal anesthesia associated with fluoxetine use [Letter to the editor]. *American Journal of Psychiatry*, 150, 984-985.

Kolodny, R.C., Masters, W.H., & Johnson, V.E. (1979). *Textbook of Sexual Medicine.* Boston: Little Brown & Co.

Kuhn, C., Swartzwelder, S., & Wilson, W. (1998). *Buzzed: The Straight Facts about the Most Used and Abused Drugs from Alcohol to Ecstasy*. New York: W.W. Norton & Co.

Lyles, M.R., (2001). Viagra and women. *Christian Counseling Today,* 9(4), 42-44.

MacDonald, P.C., Dombroski, R.A., & Casey, M.L. (1991). Recurrent secretion of progesterone in large amounts: An endocrine/metabolic disorder unique to young women? *Endocrine Reviews*, 12, 372-394.

MacPhee, G.J.A., Larkin, J.G., Butler, E., Beastall, G.H., & Brodie, M.J. (1988). Circulating hormones and pituitary responsiveness in young epileptic men receiving long-term epileptic medication. *Epilepsia*, 29, 468-475.

Melis, M.R., Argiolas, A. (1995). *Dopamine and sexual behavior. Neuroscience Biobehavioral Review*, 19, 19-38.

Mendelson, J.H., Kuehnle, J., Ellingboe, J., & Babor, T.F. (1974). Plasma testosterone levels before, during, and after chronic marijuana smoking. *New England Journal of Medicine*, 291, 1051-1055.

Meston, C.M. & Frohlich, P.F. (2000). The neurobiology of sexual function. *Archives of General Psychiatry*, 57, 1012-1030.

Noyes, R., Garvey, M.J., Cook, B.L., Samuelson, L. (1989). Problems with tricyclic antidepressant use in patients with panic disorder or agoraphobia: Results of a naturalistic follow-up study. *Journal of Clinical Psychiatry*, 50, 163-169.

O'Carroll, R., Shapiro, C., & Bancroft, J. (1985). Androgens, behavior, and nocturnal erection in hypogonadal men: The effects of varying the replacement dose. *Clinical Endocrinology*, 23, 527-538.

Owen, A.M. (1986). Venlafaxine-induced increased libido and spontaneous erections. *British Journal of Psychiatry*, 170, 193.

Persky, H., Charney, N., Lief, H.I., O'Brien, C.P., Miller, W.R., & Strauss, D. (1978). The relationship of plasma estradiol level to sexual behavior in young women. *Psychological Medicine*, 40, 523-535.

Physicians Desk Reference. (1999). *Physicians Desk Reference: 53rd edition.* Montvale, NJ: Medical Economics Data.

Racke, K., Haas, U., Sperb, S., Fischbach, A., Hof, H., Sirrenberg, S., & Wammack, R. (1991). Opioid inhibition of oxytocin release, but not autoinhibition of dopamine release, may involve activation of potassium [K+] channels. *Advances in the Biosciences*, 82, 265-267.

Riley, A.J., Peet, M., Wilson (eds). (1993). *Sexual Pharmacology.* New York: Oxford University Press.

Sarrel, P.M. (1988). Sexuality. In J.W. Studd & I.M. Whitehead (eds.), *Menopause* (p.65-75). London: Blackwell Scientific.

Schiavi, R.C., & Seagraves, R.T. (1995). The biology of sexual function. *Psychiatry Clinics of North America*, 18, 7-23.

Shiwach, R.S., & Carmody, T.J. (1998). Prolactogenic effects of risperidone in male patients: a preliminary study. *ACTA Psychiatry Scandinavia*, 98(1), 81-83.

Stahl, S.M. (1996). *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* New York: Cambridge University Press, 152-157.

Sullivan, G., & Lukoff, D. (1990). Sexual side effects of antipsychotic medication: evaluation and interventions. *Hospital Community Psychiatry*, 41, 1238-1241.

Virag, R., Bouilly, P., & Frydman, D. (1985). Is impotence an arterial disorder? *Lancet*, 1, 181.

Waddinger, M.D. (1997). Treatment of primary premature ejaculation: A model for investigation of SSRI-induced sexual side effects. Presented at the New Research, American Psychiatric Association 150th Annual Meeting, San Diego, May 17-22.

Walker, P.W., Cole, J.O., Gardner, E.A., Hughes, A.R., Johnston, J.A., Batey, S.R., & Lineberry, C.G. (1993). Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. *Journal of Clinical Psychiatry*, 54, 459-465.

Zajecka, J., Mitchell, S., & Fawcett, J. (1997). Treatment-emergent changes in sexual function with selective serotonin reuptake inhibitors as measured with the Rush Sexual Inventory. *Psychopharmacology Bulletin*, 33, 755-760.