

Psychoactive Drugs and Human Sexual Behavior: The Role of Serotonergic Activity[†]

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Abstract — A wide range of both prescription and nonprescription drugs has been reported to affect human sexual functioning. While the sexual side effects resulting from drug use have often been attributed to adrenergic, anticholinergic or dopaminergic activity, the present review considers the potential role of serotonin. Based on animal studies, serotonin has been shown to either facilitate or inhibit sexual activity depending on which serotonin receptor subtype is activated. However, few studies have been done in the human that assess the effects of drugs that bind selectively to serotonin receptors. Consequently, little is known about the role of serotonin in human sexual functioning. In this review, a wide range of drugs that affect both brain serotonergic systems and human sexual behavior is examined in an effort to determine the possible role of serotonin in human sexual behavior. A review of the literature is consistent with the hypothesis that the 5-HT_{1A} and the 5-HT₂ receptor subtypes play a facilitatory role in human sexual behavior. The evidence suggests that drugs that act as agonists on these receptor sites enhance sexual functioning in the human, while those that act as antagonists inhibit sexual functioning.

Keywords — human sexual behavior, human sexual function, psychoactive drugs, serotonin

Serotonin has been implicated as a transmitter substance involved in several behavioral functions. In addition to playing a generally inhibitory role in the regulation of mood, pain, eating, sleep and arousal, serotonin has more recently been associated with the control of sexual behavior.

In 1979, Peroutka and Snyder described the presence of two serotonin receptor subtypes in the brain, the 5-HT₁ and 5-HT₂ receptors. Since this time, at least seven receptor subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT₂, 5-HT₃, 5-HT₄) have been identified (Fuller 1991). The 5-HT_{1B} receptor is not found in humans.

Based on research in the rat, serotonin has been shown to either facilitate or inhibit sexual behavior depending on which of these serotonin receptor subtypes are activated (Gorzalka, Mendelson & Watson 1990). In the female rat, the 5-HT_{1A} (Mendelson & Gorzalka 1986a,b) receptor ap-

pears to inhibit sexual behavior. In contrast, the 5-HT₂ receptor may mediate the facilitating effects of serotonin on sexual receptivity (Gorzalka, Mendelson & Watson 1990). In the male rat, the 5-HT_{1A} receptor appears to play a facilitatory role. The role of the 5-HT₂ receptor in male sexual behavior is less clear, as some evidence indicates that 5-HT₂ activation is facilitatory (Mendelson & Gorzalka 1985) and more recent evidence suggests it is inhibitory (Watson & Gorzalka In press, 1991, 1990). There is also evidence consistent with the hypothesis that 5-HT_{1C} activity inhibits male sexual behavior but facilitates female sexual behavior (Mendelson & Gorzalka 1990).

Most of the literature associated with the relationship between sexual behavior and serotonergic activity is based on animal studies. Classic antagonists (such as methysergide and cyproheptadine) and agonists (such as quipazine) are used in animal research to assess the relationship between serotonin and sexual behavior. These drugs provide an easy and effective means to determine the relationship because they are relatively selective or specific to serotonergic systems.

In contrast to animal research, most information relating serotonin to human sexuality is complicated by the fact that few studies use drugs that bind selectively to serotonin

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receptors. As a result, most drugs administered produce a variety of sometimes interrelated symptoms and involve many different systems.

There are three possible levels at which many of the drugs may affect sexual functioning: the peripheral, the hormonal, and the central (Nurnberg & Levine 1987). At the peripheral level, adrenergic blockade or anticholinergic activity may produce adverse effects on erection and/or orgasm (Shen & Sata 1983; Buffum 1982; Kulik & Wilbur 1982; Blackwell 1981; Horowitz & Goble 1979; Ellinwood & Rockwell 1975; Karczmar 1975). At the hormonal level, elevated prolactin levels (Mitchell & Popkin 1983) and β -endorphins (Pfaus & Gorzalka 1987) have been implicated in sexual dysfunction, and at the central level, changes in neurotransmitters, such as dopamine and/or serotonin, have been shown to inhibit sexual functioning (Nurnberg & Levine 1987; Barnes, Bamber & Watson 1979; Hollister 1975; Karczmar 1975). Therefore, it is through a process of elimination that the factors responsible for the changes in sexual functioning may be determined. Furthermore, while many authors have postulated that peripheral or hormonal levels are responsible for the changes in sexual functioning, these changes may in fact be a result of central serotonergic activity.

The evaluation of serotonergic effects on human sexual behavior is also made difficult by the fact that the available information on human sexual behavior is based mainly on case reports of individuals or small groups of patients. Such reports generally lack sufficient information to determine the precise role of serotonin in sexual functioning. Authors frequently mention one particular problem and ignore changes in other sexual functions, the previous sexual history, and the contribution of other drugs. Furthermore, such studies often suffer from methodological flaws. A control group is seldom used, patients are not randomly assigned, and patients with previous sexual disturbances are not eliminated from the studies. Another complicating variable is that, unlike animal experiments where actions can be directly observed, researchers must rely solely on what the patient reports. This self-reported information is confined to the experience of the patient and is dependent on the patient's willingness to volunteer relevant information.

In an effort to attain a more integrated picture of how serotonin affects sexual functioning, this article reviews a wide range of literature on drugs that affect both brain serotonergic systems and human sexual behavior. A brief description of the various stages of the human sexual response and difficulties associated with each of these stages is presented first. Available information regarding changes in sexual functioning associated with the use of various drugs that affect central serotonergic systems is then reviewed. Five drug categories are discussed: antidepressants, lithium, antipsychotics, stimulants, and

miscellaneous drugs and treatments. In each of these sections, a brief description of the use and neurochemical effects of the drug is provided and is followed by a review of the drug effects on both male and female sexual behavior. The areas of sexual function examined in the male include changes in sexual desire, erectile capacity, and ejaculation. In the female, changes in sexual desire and orgasm are discussed. Following this review of the literature, the possible mechanism of action of drugs in each category is discussed and an attempt is made to link the behavioral effect to a specific serotonergic system.

SEXUAL BEHAVIOR: DEFINITIONS AND DYSFUNCTIONS

Sexual Behavior

For the purpose of this review, sexual behavior is defined as manifest sexual activity and includes both sexual intercourse and masturbation.

Sexual Desire

Sexual desire defines a person's interest in initiating or having sexual intimacies. The psychosexual dysfunction *inhibited sexual desire* reflects a subjective opinion and perception that interest in sexual behavior is abnormally low (Davison & Neale 1974).

Sexual Excitement

In both sexes, sexual excitement refers to the body's response to sexual stimulation. The two basic responses are myotonia (increased muscle tension) and vasocongestion (filling of the blood vessels with fluid) primarily in the genital organs (Belliveau & Richter 1970). According to *DSM-III-R* (American Psychiatric Association 1987), inhibited sexual excitement is defined in males as "persistent or recurrent partial or complete failure to attain or maintain erection until completion of the sexual activity," and in females as "persistent or recurrent partial or complete failure to attain or maintain the lubrication-swelling response of sexual excitement until completion of the sexual activity." Dysfunctions at this stage also include functional dyspareunia, which refers to pain during intercourse in either the male or female. According to *DSM-III-R*, this dysfunction is not diagnosed when it is caused exclusively by a physical disorder or by lack of lubrication or functional vaginismus in the female.

Orgasm

The orgasm, or climactic phase, is an involuntary response that occurs when "body changes resulting from stimulation reach their maximum intensity" (Belliveau & Richter 1970). In the female, it is expressed by the rhythmic contractions of vaginal muscles. An inhibition of orgasm in females is generally referred to as anorgasmia.

In the male, orgasm is almost always accompanied by ejaculation. The *DSM-III-R* diagnosis *inhibited male orgasm* is applied to problems associated with ejaculation. An additional ejaculatory problem is premature ejaculation, which according to *DSM-III-R* is defined as "persistent or recurrent ejaculation with minimal sexual stimulation or before, upon, or shortly after penetration and before the person wishes it."

THE EFFECTS OF ANTIDEPRESSANT DRUGS ON MALE SEXUAL BEHAVIOR

Tricyclic Antidepressants

Tricyclic antidepressants are used in the treatment of depressive affective disorders, primarily major depression. The drugs are used to treat depressive stages of bipolar disorder and to alleviate anxiety and phobias, such as simple phobia and agoraphobia (McEvoy 1990).

The mechanism of action by which the tricyclics exert their effects is still unclear. However, the drugs have been shown to block the reuptake of various neurotransmitters and to exhibit anticholinergic activity. Any or all of these effects may account for the behavioral effects resulting from treatment with these drugs; however, alterations in norepinephrine and serotonin activity are generally considered to be the most important (McEvoy 1990).

Sexual Desire. Changes in sexual desire have been reported in association with antidepressant treatment. It is difficult, however, to interpret these changes as directly resulting from the drug treatment. First, a decrease in sexual desire is a common symptom of depression (Mathew, Weiman & Claghorn 1980; Beaumont 1973), and second, it is possible that the change in sexual desire is secondary to other sexual disorders that have developed as a result of drug administration. Nevertheless, a decrease in sexual desire has been reported in association with amitriptyline (Hekimian, Friedhoff & Deever 1978; Couper-Smartt & Rodham 1973), clomipramine (Monteiro et al. 1987; Yassa 1982; Couper-Smartt & Rodham 1973), and imipramine (Kafka 1991a; Harrison et al. 1985; Couper-Smartt & Rodham 1973). In a double-blind study conducted by Harrison and colleagues, three of 14 patients on 200-300 mg/day of imipramine reported a decrease in sexual desire. In comparison, only one of 12 in the placebo condition reported a similar decrease. Yassa reported a case in which, one week after the start of 300 mg/day of clomipramine, the patient experienced a lack of sexual drive and desire. This effect was eliminated within one week after the cessation of medication.

In several cases, the decrease in tricyclic-induced sexual desire is reported in conjunction with other sexual dysfunctions (Monteiro et al. 1987; Harrison et al. 1985; Couper-Smartt & Rodham 1973). In a study by Monteiro

and colleagues, all six of the patients who reported a decrease in sexual desire attributed it to the difficulty they experienced in achieving orgasm. However, it should not be concluded that antidepressant-induced sexual dysfunctions, such as impotence or erectile difficulties, necessarily lead to a decrease in desire. Many cases have been reported where changes in sexual desire are denied despite other antidepressant-induced difficulties (Yeragani 1988; McLean, Forsythe & Kapkin 1983; Kulik & Wilbur 1982; Yassa 1982; Couper-Smartt & Rodham 1973; Eaton 1973).

In a study by Couper-Smartt and Rodham, one patient reported an increase in sexual desire as a result of 75 mg/day of imipramine. Although there have been few similar reports, it is likely that more people would be concerned with, and thus voluntarily report, a decrease, as opposed to an increase, in sexual desire resulting from drug treatment. It is difficult to interpret such findings because information on sexual history is frequently omitted. Although the increase in sexual desire may be a direct result of the antidepressant treatment, it may also be a result of the amelioration of depression.

Erectile Capacity. Although the incidence of tricyclic-induced erectile dysfunction appears to be relatively low (Petrie 1980), cases have been reported following treatment with a variety of tricyclics. Amitriptyline has been associated with this effect (Hekimian, Friedhoff & Deever 1978; Couper-Smartt & Rodham 1973) at doses as low as 90 mg/day (Hekimian, Friedhoff & Deever 1978). In addition, desipramine (Simpson, Blair & Amuso 1965), clomipramine (Price & Grunhaus 1990; Yassa 1982), and imipramine (Shader 1983; Couper-Smartt & Rodham 1973; Greenberg 1965; Simpson, Blair & Amuso 1965) have been noted to produce difficulty in achieving erection. Yassa reported three cases in which patients experienced impotence after only four days of clomipramine treatment and at doses as low as 50 mg/day. Although two of the patients were on other medication during tricyclic treatment, no sexual difficulties were present prior to the addition of clomipramine. In all three cases, when medication was discontinued, sexual activity returned to normal within one week. Similarly, Price and Grunhaus reported a case of erectile difficulty at 200 mg/day of clomipramine. Erectile difficulty was not a problem at 150 mg/day. In a double-blind study conducted by Hekimian, Friedhoff and Deever, eight of 19 males treated with 176 mg/day of amoxapine reported impotence or reduced sexual interest. In comparison, only three of 16 males reported similar effects with the administration of 90 mg/day of amitriptyline. The higher incidence of sexual side effects reported with amoxapine treatment is possibly a reflection of the higher drug dosage administered.

Ejaculation. Delayed or complete abolition of ejaculation appears to be the principal complaint of patients taking tricyclic antidepressants. Delayed ejaculation has

been reported with amitriptyline (Couper-Smartt & Rodham 1973), amoxapine (American Journal of Nursing 1982; Kulik & Wilbur 1982; Schwarcz 1982), clomipramine (Price & Grunhaus 1990; Couper-Smartt & Rodham 1973), and imipramine (Harrison et al. 1985; Couper-Smartt & Rodham 1973). Couper-Smartt and Rodham noted one case of delayed ejaculation with the administration of clomipramine and three cases with the administration of imipramine at individual doses as low as 75 mg/day. Price and Grunhaus reported inhibited orgasmic ability with the administration of 150 mg/day of clomipramine. Two cases of ejaculatory delay have been described in patients receiving a minimum of 75 mg/day of amoxapine (American Journal of Nursing 1982). This problem was noted after only three days of treatment and eliminated within four days of discontinuation. In addition, both patients experienced pain on ejaculation. Pain on ejaculation has also been noted with desipramine therapy (Sorvino 1986) at a dosage of 150 mg/day, and clomipramine therapy at a dosage of 140 mg/day (Monteiro et al. 1987).

The ability of the tricyclics to inhibit ejaculation has been used to advantage in the treatment of premature ejaculation. Several cases have been reported in which clomipramine has successfully controlled the disorder (Klug 1984; Goodman 1980; Eaton 1973). In a study by Eaton, 13 patients with a long history of premature ejaculation were placed on doses of 25-75 mg/day of clomipramine. With the exception of one patient, all noticed an improvement within two weeks to two months of treatment. In a double-blind study conducted by Goodman, the effects of 10-40 mg/day of clomipramine on premature ejaculation were assessed. Although there appeared to be no difference between the clomipramine and placebo groups in the first four weeks of treatment, by the end of the five-month study, nine of 16 patients found clomipramine beneficial in treating premature ejaculation.

While delayed ejaculation occurs with tricyclic treatment in doses of approximately 75 mg/day, higher doses appear to cause a complete abolition of ejaculation (Monteiro et al. 1987; American Journal of Nursing 1982; Glass 1981; Nininger 1978; Couper-Smartt & Rodham 1973; Eaton 1973). Monteiro and colleagues reported 13 of 17 previously orgasmic patients were unable to attain orgasm while on clomipramine treatment. Three of the remaining four reported delayed ejaculation. A delay in ejaculation was noted within a few days at doses of 25-50 mg/day and complete abolition noted at doses of 100-150 mg/day. Return to normal sexual functioning occurred within three days of discontinuing clomipramine use. An inhibition of ejaculation has also been described with amitriptyline treatment at doses of 100 mg/day (Nininger 1978), 150 mg/day of amoxapine (American Journal of

Nursing 1982), and 125-150 mg/day of imipramine (Glass 1981; Couper-Smartt & Rodham 1973).

In contrast to the seemingly inhibitory effect of clomipramine on ejaculation, McLean, Forsythe and Kapkin (1983) described a case in which treatment of 75 mg/day of clomipramine led to spontaneous orgasms with ejaculation. Without a reported increase in sexual desire, the patient experienced frequent intense urges to yawn accompanied by orgasm. Discontinuation of the drug led to remission of these symptoms.

Monoamine Oxidase Inhibitors

The monoamine oxidase inhibitors (MAOIs) are mainly used in the treatment of neurotic or atypical depression. These drugs exert their primary effects by inhibiting the enzyme monoamine oxidase. As a result of this inhibition, the levels of epinephrine, norepinephrine, dopamine, and serotonin are increased. The behavioral effects of MAOIs are thought to be related to these increases, but the exact mechanisms are not known (McEvoy 1990).

Sexual Desire. Relatively few cases of changes in sexual desire are reported as a result of MAOI treatment (Harrison et al. 1985; Fraser 1984). In a controlled study conducted by Harrison and colleagues, three of ten males on a dosage of 60-90 mg/day of phenelzine complained of a decrease in sexual desire. It should be noted, however, that one of 12 males in the placebo condition also reported a similar decrease.

Contrary to this finding, Nurnberg and Levine (1987) described a patient who reported an increase in sexual desire as a result of 75 mg/day of phenelzine. The increase in desire was reported concurrently with the remittance of depression and thus it is possible that the sexual effect was secondary to an overall increase in well-being.

Erectile Capacity. As in the case of tricyclic antidepressants, the incidence of MAOI-induced erectile dysfunction appears to be relatively low. One case of failure of erection has been reported by Evans, Davidson and Raft (1982). The problem was reported after two to three months of treatment with 77 mg/day of phenelzine. In addition, one case of impotence has been reported in association with 50 mg/day of tranylcypromine (Rabkin et al. 1984).

Ejaculation. Impaired ejaculation is apparently the most common sexual side effect of treatment with MAOIs. Reports of delayed ejaculation have been made by patients treated with phenelzine (Harrison et al. 1985; Rapp 1979), at doses of 60-90 mg/day. Inhibited ejaculation has been reported in association with 50 mg/day of pargyline (Kohn 1964), phenelzine (Nurnberg & Levine 1987; Decastro 1985; Harrison et al. 1985; Fraser 1984; Glass 1981; Rapp 1979) at doses as low as 60 mg/day (Fraser 1984), and 30 mg/day of tranylcypromine (Decastro 1985). Fraser reported a case in which the patient experienced an inability

to ejaculate while receiving treatment of 60 mg/day of phenelzine. When the dose was reduced to 45 mg/day his sexual function returned to normal.

In addition, MAOIs have been used successfully in the control of premature ejaculation (Bennett 1961). Bennett reported three cases of successful treatment with 10 mg/day of isocarboxazid. In all three cases, an improvement in premature ejaculation was noted in three weeks, and the problem was fully controlled in six weeks. When treatment was discontinued the problem reappeared in less than two weeks.

Atypical Antidepressants

Cyproheptadine. Cyproheptadine is used primarily in the treatment of allergic conditions. In addition, it has been used in the treatment of Cushing's syndrome secondary to pituitary disorders, and in the management of anorexia nervosa. Cyproheptadine has potent antihistaminergic and serotonergic properties, as well as anticholinergic and sedative effects (McEvoy 1990).

Ejaculation. Cyproheptadine has been used successfully in the treatment of drug-induced failure to ejaculate (Zajacka et al. 1991; Jeffries & Walker 1987; Decastro 1985). Jeffries and Walker reported a case in which the patient suffered a long history of inhibition of ejaculation as the direct result of neuroleptic drug treatment. Within a few days of beginning treatment of 8 mg/day of cyproheptadine, the patient was able to have normal ejaculatory responses. Similarly, Decastro described a patient with no history of ejaculatory dysfunction suffering from MAOI-induced inhibition of ejaculation. The disorder remitted when 12 mg/day of cyproheptadine was taken one hour prior to intercourse.

Fluoxetine. Fluoxetine is used primarily in the treatment of major depression. Less commonly, fluoxetine has been used in the management of bipolar disorder, and in the control of obsessive compulsive disorder. In addition, fluoxetine has been effective as a treatment for eating disorders, such as anorexia nervosa, bulimia nervosa, and the short-term management of obesity.

Fluoxetine is a highly selective inhibitor of serotonin reuptake. Unlike most other antidepressant drugs, fluoxetine appears to have little or no effect on the reuptake of other neurotransmitters, such as norepinephrine and dopamine, and does not exhibit significant anticholinergic, α -adrenergic, or antihistaminergic effects (McEvoy 1990).

Sexual Desire. Kafka (1991) reported a loss of sexual interest and a decrease in atypical sexual behavior with the treatment of fluoxetine. The seven patients who experienced this effect were suffering from paraphilias and/or nonparaphilic addictions.

Ejaculation. Two cases of orgasmic difficulty have been reported with fluoxetine therapy (Zajacka et al. 1991; Kline 1989) at a minimum daily dose of 40 mg. In one case

(Kline 1989), the patient was taking no other medication and denied previous sexual dysfunction. The problem subsided over a three-week period when the dose of fluoxetine was reduced to 20 mg and 40 mg on alternate days.

Sertraline. Sertraline is a relatively new antidepressant drug. In comparison to other antidepressants, it is the most potent and specific inhibitor of serotonin uptake (Doogan & Caillard 1988). In addition, it has been shown to weakly inhibit the uptake of norepinephrine. Sertraline lacks stimulant and anticholinergic effects (Koe et al. 1983).

Ejaculation. In a double-blind placebo-controlled study by Doogan and Caillard (1988), the side effects of sertraline were compared to those of amitriptyline. Results showed that 17% of patients treated with sertraline reported experiencing sexual dysfunction, primarily ejaculatory delay. In comparison, only 8% of patients treated with amitriptyline, and one percent of the placebo control group reported similar side effects.

Trazodone. Trazodone is used in the treatment of major depression. The precise mechanisms of action of trazodone are unclear, but the drug has been shown to act as both a serotonin agonist and antagonist (Maj, Palider & Rowlow 1979). Trazodone does not appear to influence the reuptake of dopamine or norepinephrine within the central nervous system (CNS), but has been shown to enhance the release of norepinephrine from neuronal tissue. Unlike several other antidepressant drugs, trazodone exhibits very little anticholinergic activity. Long-term treatment with trazodone has been shown to decrease the number of postsynaptic serotonergic and β -adrenergic binding sites. It has been suggested that this postsynaptic receptor modification is largely responsible for the antidepressant action of trazodone (McEvoy 1990).

Erectile Capacity/Ejaculation. Two cases of sexual dysfunction have been described in association with trazodone treatment (Patt 1985; Jones 1984). Jones reported a case of inhibition of ejaculation in a patient receiving 100 mg/day and Patt described a case of prolonged painful erection in a patient receiving 200 mg/day.

THE EFFECTS OF ANTIDEPRESSANT DRUGS ON FEMALE SEXUAL BEHAVIOR

Tricyclic Antidepressants

Sexual Desire. Three cases of decreased sexual desire have been reported in association with tricyclic treatment (Monteiro et al. 1987; Harrison et al. 1985). Harrison and colleagues noted that two of 11 patients receiving 200-300 mg/day of imipramine reported a decrease in sexual desire. However, this effect was likely not attributable to the drug because two of 18 patients in the placebo-control group also experienced a similar decrease.

TABLE I
THE EFFECTS OF ANTIDEPRESSANT DRUGS ON MALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT PRIOR TO DRUG ADMINISTRATION	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Tricyclics Amitriptyline	75 mg, 2-6 wks.	—	decrease in sexual desire	1	Couper-Smartt & Rodham 1973
	75 mg, 2 wks.	no history of sexual dysfunction	decreased penile circumference and duration of nocturnal erections	6	Kowalski et al. 1985
	90 mg, 4 wks.	depression	decrease in sexual desire, impotence	3/16	Hekimian, Friedhoff & Deever 1978
	150 mg, 2-6 wks.	—	decrease in sexual desire, erectile difficulty, delayed ejaculation	1	Couper-Smartt & Rodham 1973
Amoxapine	100-200 mg, 4 days	depression	inhibition of ejaculation	1	Nininger 1978
	75 mg, 3 days	panic disorder	inhibition of ejaculation, painful ejaculation	1	Kulik & Wilbur 1982
	75-150 mg, 3 days	anxiety, depression	delayed, painful ejaculation, inhibition of ejaculation	2	Am. J. Nursing 1982
	150 mg, 1 day	depression	painful ejaculation	1	Schwartz 1982
Clomipramine	176 mg, 4 wks.	depression	decrease in sexual desire, impotence	8/19	Hekimian, Friedhoff & Deever 1978
	10-40 mg, —	premature ejaculation	control of premature ejaculation	9/16	Goodman 1980
	25-75 mg, —	premature ejaculation	control of premature ejaculation	12/13	Eaton 1973
	25-150 mg, 2 days	obsessive compulsive disorder	decrease in sexual desire	6/17	Monteiro et al. 1987
	25-150 mg, —	obsessive compulsive disorder	organic difficulty (25-50 mg), inhibition of ejaculation (100-150 mg)	16/17	Monteiro et al. 1987
	25-150 mg, —	obsessive compulsive disorder	pain on ejaculation	4/17	Monteiro et al. 1987
	50 mg, 4 days	paranoid schizophrenia	impotence	1	Yassa 1982
	75 mg, —	phobia	inhibition of ejaculation	1	Eaton 1973
	75 mg, 4 days	manic depression	impotence	1	Yassa 1982
	75 mg, —	depression	yawning and spontaneous ejaculations	1	McLean, Forsythe & Kapkin 1983
	75 mg, 2-6 wks.	—	delayed ejaculation	1	Couper-Smartt & Rodham 1973
	100 mg, 5 wks.	obsessive compulsive disorder, premature ejaculation	control of premature ejaculation	1	Klug 1984
	100 mg, 2-6 wks.	—	decrease in sexual desire	1	Couper-Smartt & Rodham 1973
	150 mg, 2 days	depression, obsessive compulsive disorder	inhibition of ejaculation	1	Price & Grunhaus 1990
Desipramine	200 mg, —	depression, obsessive compulsive disorder	impotence	1	Price & Grunhaus 1990
	300 mg, 1 wk.	obsessive compulsive disorder	decrease in sexual desire, impotence	1	Yassa 1982
	150 mg, 2 wks.	major depression	pain on ejaculation	1	Sorvino 1986
	150 mg, —	depression	impotence	1	Simpson, Blair & Arnuso 1965
Doxepin	50 mg, 3 days	trazodone-induced ejaculatory inhibition	ability to ejaculate	1	Jones 1984
Imipramine	75 mg, 2-3 wks.	depression, no history of erectile difficulty	impotence	1	Greenberg 1965
	75 mg, —	retrograde ejaculation	retrograde ejaculation successfully treated	1	Brooks & Sidi 1981
	75 mg, 2-6 wks.	—	increase in sexual desire, delayed ejaculation	1	Couper-Smartt & Rodham 1973
	125 mg, 1 wk.	mild depression	inhibition of ejaculation	1	Glass 1981
	125-225 mg, —	depression, atypical sexual behavior	decrease in atypical sexual behavior	2	Kafka 1991a
	150 mg, 2-6 wks.	—	decrease in sexual desire, impotence	1	Couper-Smartt & Rodham 1973
	150 mg, 2-6 wks.	—	delayed ejaculation	1	Couper-Smartt & Rodham 1973
	175 mg, —	major depression	erectile difficulty, decreased frequency of nocturnal erections	1	Shader 1983
MAO Inhibitors Isocarboxazid Pargyline	200-300 mg, 2 wks.	mild-moderate depression	decrease in sexual desire	3/14	Harrison et al. 1985
	200-300 mg, 2 wks.	mild-moderate depression	delayed ejaculation	4/14	Harrison et al. 1985
	20-40 mg, 3-6 wks.	premature ejaculation	control of premature ejaculation	3	Bennett 1961
	20 mg, 2 wks.	compulsive masturbation	decreased frequency of masturbation	—	Buffum 1982
	50 mg, 2 mos.	apprehension	inhibition of ejaculation	1	Kohn 1964
	60 mg, 2 wks.	dysthymia, anxiety	inhibition of ejaculation	1	Decastro 1985
	60 mg, 6 wks.	depression	decrease in sexual desire, inhibition of ejaculation	1	Fraser 1984
	75 mg, 6 wks.	dysthymic disorder	inhibition of ejaculation	1	Glass 1981
	75 mg, 5 days	bipolar affective disorder	delayed ejaculation	1	Rapp 1979
	75 mg, 2 wks.	major depression, no history of sexual dysfunction	increase in sexual desire, inhibition of ejaculation	1	Nurnberg & Levine 1987
Phenelzine	60-90 mg, 2 wks.	mild-moderate depression	delayed ejaculation	6/10	Harrison et al. 1985
	75 mg, 3 wks.	anxiety	inhibition of ejaculation	1	Rapp 1979
	77 mg, 2-3 mos.	depression, anxiety	erectile difficulty	1/2	Evans, Davidson & Raft 1982
	60-90 mg, 2 wks.	mild-moderate depression	decrease in sexual desire	3/10	Harrison et al. 1985
	30 mg, —	dysthymia, anxiety	inhibition of ejaculation	—	Decastro 1985
	50 mg, —	depression	impotence	1	Rabkin et al. 1984

(continued on next page)

TABLE I (continued)
THE EFFECTS OF ANTIDEPRESSANT DRUGS ON MALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT PRIOR TO DRUG ADMINISTRATION	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Atypical Antidepressants Cyproheptadine	4 mg, 2 wks.	clomipramine-induced ejaculatory inhibition	no effect	1	Price & Grunhaus 1990
	4-12 mg, 1-2 hr. prior to intercourse	fluoxetine-induced ejaculatory inhibition	ability to ejaculate	1	Zajack et al. 1991
	8 mg, 2 days	schizophrenia, inability to ejaculate	ability to ejaculate	1	Jeffries & Walker 1987
	12 mg, 1 hr. prior to intercourse	MAOI-induced ejaculatory inhibition	ability to ejaculate	1	Decastro 1985
Fluoxetine	10-60 mg, -	depression, atypical sexual behavior	decrease in atypical sexual behavior	7	Kafka 1991a, b
	20-80 mg, 3 wks.	major depression, no sexual dysfunction	inhibition of orgasm	3	Kline 1989
Sertraline	150 mg, 8 wks.	depression	sexual dysfunction, inhibition of ejaculation		Doogan & Caillard 1988
Trazodone	100 mg, 1 wk.	major depression, no sexual dysfunction	inhibition of ejaculation	1	Jones 1984
	150 mg, -	depression, atypical sexual behavior	decrease in atypical sexual behavior	1	Kafka 1991a
	200 mg, 2 mos.	severe depression	priapism	1	Patt 1985

Contrary to these reports, Sovner (1983) reported a case in which the patient experienced increased interest in sex as a result of 125 mg/day of desipramine. The patient claimed that, even when compared to her predepression level, her sexual desire increased significantly. Couper-Smartt and Rodham (1973) reported a case of an increase in sexual desire resulting from 75 mg/day of amitriptyline, and McLean, Forsythe and Kapkin (1983) described a patient who experienced "yawning spells [and] unresistable sexual urges," while receiving 100 mg/day of clomipramine. Symptoms abated on discontinuation of the drug.

Orgasm. Anorgasmia appears to be the most commonly reported sexual side effect of tricyclic treatment. Orgasmic difficulty has been noted during treatment with 25-50 mg/day of clomipramine (Monteiro et al. 1987), 60 mg/day of nortriptyline (Sovner 1984), and 100-200 mg/day of imipramine (Harrison et al. 1985; Couper-Smartt & Rodham 1973). Total inhibition of orgasm has been noted with 150 mg/day of amoxapine (Shen 1982), 75-150 mg/day of clomipramine (Monteiro et al. 1987; Riley & Riley 1986), 150-200 mg/day of desipramine (Pontius 1988; Yeragani 1988), and 75-200 mg/day of imipramine (Riley & Riley 1986; Steel & Howell 1986; Sovner 1983). Sovner reported a case in which the patient was unable to achieve orgasm while receiving 150-200 mg/day of imipramine. Six days after the drug was replaced by 200 mg/day of desipramine, the symptom remitted and normal orgasmic functioning returned. A similar finding was reported in association with amoxapine treatment (Shen 1982). One patient reported orgasmic inhibition during treatment with 150 mg/day of amoxapine.

When the drug was substituted for 150 mg/day of imipramine, she regained sexual functioning in two days. Four weeks later, amoxapine treatment was reinstated and again inhibited an ability to experience orgasm. Normal sexual functioning was regained within two days of cessation of the drug. In a controlled study by Monteiro and colleagues, orgasmic difficulty was noted at a dosage of 25-50 mg/day of clomipramine and total anorgasmia at doses of 100-150 mg/day. Five of seven previously orgasmic women reported an inability to attain orgasm even after prolonged effort.

Monoamine Oxidase Inhibitors

Sexual Desire. Friedman and colleagues (1978) reported decreased libido in five patients receiving phenelzine at dosages of 75 mg/day. All subjects were previously sexually functional. Similarly, Harrison and colleagues (1986) reported decreased sexual interest and desire among 15 females treated with phenelzine (mean dose=66 mg).

Orgasm. Cases of lack of orgasm during treatment with MAOIs are fairly numerous (Jacobson 1987; Harrison et al. 1986; Fraser 1984; Christenson 1983; Moss 1983; Pohl 1983; Barton 1979; Friedman et al. 1978; Lesko, Stotland & Segraves 1982). Lesko, Stotland and Segraves reported a case in which the patient experienced difficulty achieving orgasm while on a dose of 30 mg/day of isocarboxazid. Anorgasmia persisted at 20 mg/day and did not abate until one month after the dose was reduced to 10 mg/day. Ten cases of anorgasmia have been reported in association with phenelzine treatment (Jacobson 1987; Fraser 1984; Christenson 1983; Moss 1983; Pohl 1983;

Lesko, Stotland & Segraves 1982; Barton 1979) at doses of approximately 60 mg/day. The symptoms remitted in all cases where doses were lowered to 15-45 mg/day (Jacobson 1987; Moss 1983; Lesko, Stotland & Segraves 1982; Barton 1979) or when the drug was discontinued (Christenson 1983; Pohl 1983).

Atypical Antidepressants: Cyproheptadine, Fluoxetine, and Trazodone

Several cases have been reported on the effectiveness of cyproheptadine in alleviating antidepressant-induced orgasmic inhibition (Pontius 1988; Riley & Riley 1986; Steel & Howell 1986; Sovner 1984; Tolis, Bertrand & Pinter 1979). Pontius described a case in which cyproheptadine was used to treat desipramine-induced anorgasmia. The patient reported complete relief of her symptoms after a single dose of 4 mg, taken one hour prior to intercourse. Similarly, Riley and Riley reported that after only a single treatment of 8 mg of cyproheptadine taken 90 minutes before sexual activity, the patient's clomipramine-induced anorgasmia remitted. Sovner also reported a case in which cyproheptadine relieved anorgasmia (induced by nortriptyline) at a dose of 4 mg/day. When the drug was stopped, orgasmic inhibition recurred and again remitted when cyproheptadine was reinstated. In a double-blind, placebo-controlled study of a patient suffering from imipramine-induced anorgasmia, Steel and Howell demonstrated that cyproheptadine alleviated anorgasmia in four of ten trials. In comparison, the placebo alleviated anorgasmia in only two of eight trials. There are no reports in the literature that indicate undesirable sexual side effects of cyproheptadine treatment.

A case of orgasmic difficulty has been reported in a patient treated with fluoxetine at a dosage of 20 mg/day (Kline 1989). A reduction of her dose to 20 mg every other day resulted in partial alleviation of the disorder. However, complete sexual functioning was not restored. In a study by Zajecka and colleagues (1991), five women complained of orgasmic dysfunction resulting from fluoxetine treatment. Doses ranged from 20-80 mg/day and the dysfunction was reported spontaneously within six weeks of beginning treatment. None of the patients experienced orgasmic dysfunction prior to fluoxetine treatment. In a carefully detailed report, Modell (1989) described a patient who experienced clitoral engorgement and multiple spontaneous orgasms with the administration of fluoxetine. The patient began on 20 mg/day, which after one week, was increased to 40 mg/day. While no side effects were reported at the lower dosage, within two days of treatment at 40 mg/day, the patient experienced yawning sensations accompanied by spontaneous orgasms. A causal relationship between the medication and side effects was determined; dosage was lowered to 20 mg/day and increased to 40 mg/day on four separate occasions, each time causing

an alleviation and return of the symptoms.

Gartrell (1986) reported three cases in which 150 mg/day of trazodone led to an increase in sexual desire. Patients claimed that their "sex drive was greater than it had ever been." A diminution of desire was reported within one to two weeks after the cessation of treatment. In another case study, trazodone was reported to cause anorgasmia at 50-100 mg/day (Jani et al. 1988). This effect was apparent despite active sexual desire. A return to normal sexual functioning was noted four days after medication was discontinued.

SUMMARY OF THE EFFECTS OF ANTIDEPRESSANT DRUGS ON MALE AND FEMALE SEXUAL BEHAVIOR

The preceding review of the literature suggests a possible causal relationship between antidepressant drug treatment and changes in sexual functioning (see Tables I and II). While a decrease in sexual desire and impotence are often mentioned as side effects of several antidepressant drugs, the dysfunction most commonly reported in the male is a delay or inhibition of ejaculation and in the female, anorgasmia. The tricyclics that cause these disorders most frequently include clomipramine, imipramine, amitriptyline, and less frequently desipramine, amoxapine, and nortriptyline. Of the MAOIs, phenelzine appears most often in association with these dysfunctions, while pargyline, isocarboxazid, and tranlycypromine seem less likely to disturb sexual functioning. Of the atypical antidepressants, trazodone is described in association with both inhibited ejaculation and anorgasmia, sertraline has been reported to cause a delay in ejaculation, and fluoxetine is reported to cause both orgasmic difficulty and spontaneous orgasms. In contrast to all other antidepressant drugs reviewed, cyproheptadine causes a consistent increase in ejaculatory/orgasmic functioning. Its ability to reverse antidepressant-induced ejaculatory/orgasmic dysfunction is described in many case studies.

The severity of reported disorders appears to be a function of the dosage administered and individual sensitivity. Orgasmic difficulty is caused by 25 mg/day of clomipramine, while 100 mg/day is sufficient to cause anorgasmia.

No significant difference in side effects is apparent between males and females. Orgasm in the female and ejaculation in the male are considered analogous (Segraves 1977) and difficulty with these functions appears to be the primary sexual side effect of antidepressant drugs. However, in terms of the frequency of these side effects, a disproportionately high incidence of reported effects among males is apparent. Hekimian, Friedhoff & Deever (1978) noted that eight of nine males receiving amoxapine

TABLE II
THE EFFECTS OF ANTIDEPRESSANT DRUGS ON FEMALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT PRIOR TO DRUG ADMINISTRATION	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Tricyclics					
Amitriptyline	75 mg, 2-6 wks.	—	increased sexual desire	1	Couper-Smartt & Rodham 1973
Amoxapine	150 mg, 2 mos.	depression	anorgasmia	1/5	Shen 1982
Clomipramine	25-150 mg, 2 days	obsessive compulsive disorder	decreased sexual desire	3/7	Monteiro et al. 1987
	25-50 mg, 2 days	obsessive compulsive disorder	orgasmic difficulty	6/7	Monteiro et al. 1987
	75 mg, 2 wks.	depression	anorgasmia	1	Riley & Riley 1986
	100-150 mg, 2 days	obsessive compulsive disorder	anorgasmia	5/7	Monteiro et al. 1987
	100 mg, 2 wks.	depression, obsessive compulsive disorder	yawning with sexual urges	1	McLean, Forsythe & Kapkin 1983
Desipramine	150 mg, 5 wks.	depression, no history of sexual dysfunction	anorgasmia	1	Yeragani 1988
	200 mg, 6 days	imipramine-induced anorgasmia	normal orgasmic response		Sovner 1983
Imipramine	75-150 mg, 1 wk.	depression	anorgasmia	2	Riley & Riley 1986
	100 mg, 2-6 wks.	—	delayed orgasm	1	Couper-Smartt & Rodham 1973
	150 mg, 2 days	depression, amoxapine-induced anorgasmia	normal orgasmic response	1	Shen 1982
	200 mg, 17 days	major depression	anorgasmia	1	Sovner 1983
	200-300 mg, 2 wks.	mild-moderate depression	decreased sexual desire	2/11	Harrison et al. 1985
	200-300 mg, 2 wks.	mild-moderate depression	delayed orgasm	3/11	Harrison et al. 1985
Nortriptyline	60 mg, —	depression	anorgasmia		Sovner 1984
MAO Inhibitors					
Isocarboxazid	20-30 mg, —	depression	anorgasmia	1	Lesko, Stotland & Segraves 1982
Phenelzine	45-60 mg, 3-6 wks.	agoraphobia, panic attacks	orgasmic difficulty, anorgasmia	2	Moss 1983; Pohl 1983
	45 mg, 3 wks.	depression	anorgasmia	3	Fraser 1984; Lesko, Stotland & Segraves 1982
	60 mg, 5.5 wks.	obsessive compulsive disorder	anorgasmia		Jacobson 1987
	60 mg, 2 mos.	panic disorder, no history of sexual dysfunction	anorgasmia	1	Moss 1983
	66 mg, —	—	decreased sexual desire, anorgasmia	15/15	Harrison et al. 1986
	75 mg, —	neurodermatitis, no history of sexual dysfunction	decreased sexual desire, anorgasmia	5/5	Friedman et al. 1978
	75 mg	depression, borderline personality disorder, no history of sexual dysfunction	anorgasmia	1	Christenson 1983
	90 mg, 2 wks.	atypical depression, no history of sexual dysfunction	anorgasmia	1	Moss 1983
Atypical Antidepressants					
Cyproheptadine	4-12 mg, 1-2 hrs. prior to intercourse	antidepressant-induced anorgasmia (desipramine, imipramine, clomipramine, fluoxetine, nortriptyline)	normal orgasmic response		Sovner 1984; Steel & Howell 1986; Zajacka et al. 1991
	8 mg, prior to intercourse	imipramine-induced anorgasmia	no effect	1	Riley & Riley 1986
Fluoxetine	20 mg, 5 wks.	obsessive compulsive disorder, major depression	orgasmic difficulty	1	Kline 1989
	20-80 mg, 6 wks.	depression	anorgasmia	5	Zajacka et al. 1991
	40 mg, 2 days	depression, no history of sexual dysfunction	increased sexual excitement, spontaneous orgasms	1	Modell 1989
Trazodone	50-100 mg, —	dysthymia	anorgasmia	1	Jani et al. 1988
	150 mg, 1 wk.	dysthymia, depression	increased sexual desire	6/13	Gartrell 1986

treatment and three of 16 males receiving amitriptyline treatment reported sexual side effects. In contrast, of 11 and 25 females receiving amoxapine and amitriptyline treatment, respectively, none reported experiencing sexual side effects. A similar finding was reported by Harrison and colleagues (1985). A decrease in sexual functioning was found in 80% of males and 57% of females receiving phenelzine treatment, and in 50% of males and 27% of females receiving imipramine treatment. In addition, Rabkin and colleagues (1985, 1984) reported that 70% of the patients studied who experienced sexual side effects resulting

from phenelzine treatment were male. While it is possible that this effect is a result of a higher susceptibility among males to the placebo effect, in the study by Harrison and colleagues, 16% of the females and only 8% of the males treated with a placebo reported a decrease in sexual functioning. Thus, in this particular study, the higher incidence of sexual side effects seen in males cannot be attributed to the placebo effect. Additionally, Rabkin and colleagues (1984) noted that there were no significant differences between males and females when comparing the overall number of reported side effects resulting from MAOI treat-

ment. Thus, if the sex differences were solely attributable to the placebo effect, one would expect such variations between the sexes also to be apparent when assessing other antidepressant-induced side effects. While it is tempting to speculate that more sexual side effects are seen in males receiving specific types of antidepressant treatment, the possibility exists that this trend is a result of males being more willing to report the dysfunction in comparison to females.

It may also be cautiously added that the sexual dysfunctions described in association with the reviewed antidepressants appear relatively benign. In virtually all cases, when drug treatment was discontinued the symptoms disappeared within approximately one week.

DISCUSSION

The pharmacology and physiology of sexual functioning are highly complex. Drug-induced sexual disorders present many perplexing questions. Although a wide range of literature has attempted to explain such phenomena, the possible mechanisms of antidepressant-induced sexual dysfunctions are still poorly understood.

Many authors have reasoned that the changes in sexual functioning resulting from antidepressant treatment are attributable to peripheral events, such as adrenergic blockade, anticholinergic activity or to changes in central dopamine activity. However, in light of the following studies, it is evident that these events cannot totally account for the side effects resulting from all antidepressant drugs.

In a study conducted by Snyder and Yamamura (1977), the anticholinergic properties of tricyclic antidepressants and MAOIs were tested using the receptor binding technique with radioactive [^3H]-quinuclidinyl benzilate (QNB), a potent muscarinic cholinergic antagonist. While many of the tricyclics possess considerable anticholinergic activity, MAOIs failed to show significant potency. Phenelzine, isocarboxazid, and pargyline all failed to inhibit QNB binding by more than 25%. Similarly, trazodone and mianserin have little anticholinergic activity (Kowalski et al. 1985; Jones 1984; Taylor, Hyslop & Riblet 1980), and yet trazodone has been shown to inhibit ejaculation and orgasm, and mianserin has been shown to decrease the duration of nocturnal penile tumescence.

In addition to these studies, other evidence exists that suggests the decrease in sexual functioning attributed to antidepressant therapy cannot be considered a purely anticholinergic event. In a study conducted by Wagner and Brindley (1980), large doses of atropine did not prevent penile erection in the human male. Also, no cases of ejaculatory impairment associated with atropine or scopolamine treatment have been reported despite the potent anticholinergic properties of these drugs. Similarly, the administration of anticholinergic drugs to women prior

to sexual activity has not been shown to inhibit orgasm (Shen & Mallya 1983a; Levin 1980).

Perhaps the mechanism most often cited as responsible for ejaculatory impairment is peripheral adrenergic blockade. Although erectile failure has been noted among patients receiving β -adrenergic blockers (Shen & Sata 1983), it is unlikely that antidepressant-induced anorgasmia and inhibited ejaculation can be solely attributed to adrenergic events. Charney, Heninger and Sternberg (1983) studied the effects of antidepressant drugs on α_2 -adrenergic receptor sensitivity. Although the authors found that long-term amitriptyline treatment decreased the sensitivity of the α_2 -adrenergic autoreceptors, they noted that this effect was not common to all antidepressant drugs. Clomipramine does not share this ability (Svensson 1980) and yet it is the tricyclic most commonly reported in association with both antidepressant-induced anorgasmia and inhibition of ejaculation. Thus, this lack of a uniform α_2 -adrenergic autoreceptor effect cannot account for the clinical activity of all antidepressant drugs. Moreover, this suggests that α_2 -adrenergic activity does not account for the effects of these drugs on sexual function.

Further evidence exists against an adrenergic explanation of antidepressant-induced sexual dysfunction. U'Price and Green (1978) studied the potency of tricyclic antidepressants in competitive binding for [^3H] WB-4104, a potent α -adrenergic antagonist. It was shown that doxepin and amitriptyline are approximately two and one-half times more potent than clomipramine and imipramine in their binding affinity. Recent evidence indicates that doxepin and amitriptyline have higher binding affinities for both the α_1 and α_2 receptor than either clomipramine or imipramine (Richelson 1991). Although doxepin is not frequently used in major depression, it is nevertheless interesting to note that few cases of inhibition of ejaculation or anorgasmia have been reported in association with doxepin or amitriptyline, whereas many cases have been described with clomipramine and imipramine treatment. It is therefore unlikely that adrenergic activity is solely responsible for the sexual side effects resulting from antidepressant treatment. If this were the case, one would expect a high incidence of side effects to be reported in association with those antidepressants, such as doxepin and amitriptyline, which are more potent in their α -adrenergic binding ability. In addition, Jones (1984) described a case in which 50 mg/day of doxepin eliminated the inhibition of ejaculation induced by 100 mg of trazodone. It is unlikely that this dysfunction can be attributed to adrenergic activity, as doxepin possesses a significantly higher affinity for alpha receptors in comparison to other antidepressants. Jones (1984) does not rule out the possibility that a higher dose of doxepin might have had a different effect. Similarly, Kulik and Wilbur (1982) described a case in which the patient experienced pain and inhibition

of ejaculation with 75 mg/day of amoxapine. This effect was eliminated when treatment was substituted with 75 mg/day of maprotiline. Maprotiline is a potent norepinephrine reuptake inhibitor. Although amoxapine is somewhat more potent than maprotiline as an α_1 -blocker, this does not appear to account for the magnitude of the effect.

Furthermore, in a study assessing the effects of chlorimipramine on sexual behavior in the male rat (Ahlenius, Heimann & Larsson 1979), it was shown that while chlorimipramine caused a marked delay in ejaculation, neither phenoxybenzamine, a central norepinephrine receptor blocking agent, nor phentolamine, a peripheral norepinephrine receptor blocking agent that has been used to treat human premature ejaculation, caused a delay in ejaculation. The authors concluded that the delay in ejaculation reported in association with chlorimipramine use is not due to central or peripheral adrenergic blockade.

Several studies have suggested that antidepressant-induced sexual dysfunction is a result of reduced dopaminergic activity. Frequently these implications are based on the fact that many patients suffering from hyperprolactinaemia, a possible manifestation of reduced dopamine levels, also experience a decrease in sexual functioning (Matsuoka et al. 1986; Bancroft et al. 1984; Bommer et al. 1979; Tolis, Bertrand & Pinter 1979; Ambrosi et al. 1977). While elevated prolactin levels interfere with sexual functioning by causing a decrease in sexual desire or erectile difficulty, there are no reports that describe an inhibition of ejaculation or anorgasmia resulting from increased prolactin levels. This evidence tends to argue against a dopaminergic explanation of antidepressant-induced sexual side effects, as the side effects most commonly reported in association with antidepressant treatment are an inhibition of ejaculation and anorgasmia. In addition, there is considerable evidence indicating that most patients on antidepressants do not have elevated prolactin levels (Mitchell & Popkin 1983; Meltzer 1980). More importantly, trazodone and several of the classic tricyclics do not elevate serum prolactin levels (Jones 1984; Meltzer, Piyakalmala & Schyve 1977) and MAOIs may even suppress prolactin (Mitchell & Popkin 1983). However, it should be noted that depressed patients have blunted prolactin responses.

A potential consideration for the mechanism involved in antidepressant-induced sexual dysfunction is that of serotonergic systems. Although the available data are somewhat conflicting as to whether the role of serotonin is primarily inhibitory or excitatory, this contradiction can be explained, at least in part, in terms of the receptor subtype stimulated (Modell 1989).

In a study by Luine and Paden (1982), the effects of MAOIs on serotonin levels and sexual behavior in the female rat were studied. The results showed an inverse re-

lationship between the MAOIs' effect on serotonin and sexual response. The MAOIs that were most potent in increasing serotonin levels were also most effective in inhibiting the sexual response (measured by the lordosis quotient).

Further evidence for a possible role of serotonin in antidepressant-induced sexual dysfunction, particularly inhibition of ejaculation and anorgasmia, is provided by receptor binding studies. Repeated administration of most MAOIs and tricyclics does not alter the density of α_1 -adrenergic receptors (Peroutka & Snyder 1980a; Bergstrom & Kellar 1979), muscarinic cholinergic receptors (Maggi, U'Prichard & Enna 1980; Peroutka & Snyder 1980a), or dopamine receptors in rat brain (Peroutka & Snyder 1980a). However, there is considerable evidence showing an alteration in serotonin binding sites as a result of antidepressant treatment (Kellar et al. 1981; Peroutka & Snyder 1980a,b).

While findings obtained in laboratory animals often differ from those in humans, many human studies also implicate serotonin in antidepressant-induced sexual dysfunctions. As discussed previously, the tricyclics and MAOIs often produce a decrease in ejaculatory/orgasmic functioning. In contrast, the antidepressant cyproheptadine has been reported to occasionally increase ejaculatory/orgasmic ability. Its consistency in this regard is highly relevant. Unlike the tricyclics and MAOIs, which act as serotonin agonists, cyproheptadine is a serotonin antagonist (Pontius 1988; Riley & Riley 1986; Steel & Howell 1986). This provides evidence for a role of serotonin in antidepressant-induced sexual difficulties.

The ability of cyproheptadine to enhance sexual functioning in humans is consistent with animal research, which has shown that cyproheptadine facilitates sexual behavior in the male rat (Gorzalka, Mendelson & Watson 1990). However, this effect is not seen in the female rat. Administration of cyproheptadine in the female rat has been shown to inhibit lordosis behavior (Gorzalka, Mendelson & Watson 1990).

Further human evidence supporting an inhibitory role of serotonin in antidepressant-induced ejaculatory/orgasmic dysfunctions was shown in a double-blind placebo-controlled clinical study conducted by Steel and Howell (1986). The effectiveness of cyproheptadine in treating imipramine-induced anorgasmia was studied using diphenhydramine as an active placebo. The study showed that cyproheptadine was significantly more effective than diphenhydramine. Both cyproheptadine and diphenhydramine have antihistaminergic, anticholinergic, and sedating properties (although the equivalence of these effects at the doses used is uncertain), but only cyproheptadine is a potent serotonin antagonist (Pontius 1988; Steel & Howell 1986).

Two cases of anorgasmia have been reported in asso-

ciation with imipramine but not desipramine (Steel & Howell 1986; Sovner 1983). In both patients, when 200 mg/day of imipramine was replaced with 200 mg/day of desipramine, the anorgasmia was eliminated. This provides further evidence for an inhibitory role of serotonin in tricyclic-induced sexual dysfunctions; the tertiary tricyclics (i.e., imipramine) are much more potent in their ability to increase serotonin in comparison to the secondary tricyclics (i.e., desipramine) (Willner 1985; Montigny & Aghajanian 1978). Anorgasmia and inhibition of ejaculation induced by trazodone treatment may also be explained in terms of serotonergic activity. While the possibility of adrenergic blockade exists, trazodone has little anticholinergic activity (Gershon & Newton 1980; Taylor, Hyslop & Riblet 1980), no significant ability to increase prolactin (Rolandi et al. 1981; Roccatagliata et al. 1979), and in comparison to its dopamine-blocking activity is 370 times more potent in inhibiting serotonin uptake into brain synaptosomes (Stefanini et al. 1976a,b).

Similarly, in a study by Doogan and Caillard (1988), sertraline was reported to cause male sexual dysfunction, primarily ejaculatory delay, more than twice as frequently as amitriptyline. In comparison to the tricyclic antidepressants, sertraline is 10 to 50 times more potent in potentiating the behavioral effects of serotonin (Doogan & Caillard 1988). Furthermore, sertraline has minimal binding affinity to muscarinic, dopaminergic, or adrenergic receptors (Doogan & Caillard 1988). It is therefore likely that the higher incidence of sexual dysfunction reported in association with sertraline treatment is attributable to serotonergic activity.

In addition to these studies, Modell (1989) has explained the yawning and spontaneous orgasms resulting from fluoxetine and clomipramine treatment in terms of the drugs' serotonergic activity. He noted that inhibition of serotonin reuptake is a factor common to the pharmacology of fluoxetine and clomipramine, as are the side effects of yawning and sexual arousal. He also noted that yawning has been induced in animals by administering serotonergic agonists. Harrison and colleagues (1986) have provided a further explanation for this phenomenon. They suggested that the increase in serotonin stimulates the hypothalamic release of corticotropin-releasing factor, which in turn activates neural circuits responsible for the yawning and spontaneous sexual response. As mentioned by the authors, this hypothesis is based on animal studies showing that the injection of ACTH-like peptides into cerebrospinal fluid results in spontaneous penile erection and ejaculation.

While it clearly cannot be concluded that serotonergic activity is the sole mediator of antidepressant-induced sexual dysfunctions, evidence suggests a significant serotonergic contribution. In all likelihood, a complex interplay of peripheral, hormonal, and central mechanisms is in-

volved. It is important to note that the side effects of the various antidepressant drugs do not necessarily involve a common mechanism of drug action. Perhaps changes in sexual desire are the result of an increase in prolactin levels or the amelioration of depressive symptoms. Moreover, erectile difficulty and impotence may result from anticholinergic activity or adrenergic blockade, whereas anorgasmia and inhibition of ejaculation are the results of an increase in central serotonin.

THE SEROTONERGIC ACTIVITY OF ANTIDEPRESSANT DRUGS

The tricyclic antidepressants and MAOIs have actions as serotonin agonists. The tricyclics inhibit the reuptake of serotonin, thereby prolonging neurotransmitter contact with the postsynaptic receptors (Carlson 1986). MAOIs increase serotonin levels by inhibiting monoamine oxidase, which destroys excess serotonin inside the terminal buttons (Carlson 1986). Many studies, perhaps based on the original monoamine deficiency hypothesis of depression (Carlson 1986), have attributed the mechanism of action of antidepressant treatment to these presynaptic events. There is considerable evidence, however, that other events in addition to a blockade of reuptake and an inhibition of amine catabolism are responsible for the side effects resulting from antidepressant treatment.

A decrease in turnover rate often reflects an increase in serotonin levels. While the tricyclics cause a consistent decrease in turnover rate (Marco & Meek 1979; Svensson 1978; Van Wijk, Meisch & Korf 1977; Leonard & Kafoe 1976; Meek & Werdinius 1970), MAOIs produce an increase (Robinson et al. 1979). This can perhaps be explained by the fact that although MAOIs act as agonists, most of the serotonin increase is in a cytoplasmic pool (Willner 1985). Thus, although the level of serotonin is increased in the cytoplasm, it is likely unavailable for release. In addition, Robinson and colleagues studied the effects of MAOI treatment on amine metabolism and showed that although high daily doses of either phenelzine or clorgyline initially increased serotonin levels, a decline back to control levels occurred within a two-week period despite sustained MAO inhibition. This finding was duplicated by Campbell and colleagues (1979) and, together with the previous study, provides evidence that presynaptic events cannot fully explain the decline in sexual functioning that results from antidepressant treatment. Both MAOIs and tricyclics cause a consistent decline in sexual functioning, yet while the tricyclics elevate serotonin levels, the brief increase resulting from MAOI treatment appears insignificant.

Furthermore, the blockade of reuptake resulting from tricyclic treatment and the MAO inhibition of amine catabolism occur within minutes or hours of drug admin-

istration (Charney, Menkes & Heninger 1981). In contrast, the side effects resulting from treatment with antidepressant drugs do not become apparent until approximately two to seven days after commencement of the drug treatment. Thus, events other than presynaptic increases in serotonin must be considered (see Table III).

Changes in receptor sensitivity also vary between MAOI and tricyclic treatment; tricyclics increase the sensitivity (Meijer & Groos 1988; Menkes, Aghajanian & McCall 1980; Gallager & Bunney 1979; Montigny & Aghajanian 1978), while MAOIs decrease it (Olpe, Schellenberg & Jones 1984; Olpe & Schellenberg 1981). This can perhaps be explained by presynaptic events. The decrease in turnover rate resulting from tricyclic treatment leads to an increase in receptor sensitivity, and conversely, an increase in turnover rate resulting from MAOI treatment leads to a decrease in sensitivity. This lack of consistency between classes of antidepressant drugs cannot account for the similar decline in sexual functioning resulting from treatment with both MAOIs and tricyclics (see Table IV).

The possibility exists that changes in serotonin receptor systems may explain the sexual side effects of antidepressant treatment (see Table V). Biochemical studies of antidepressant drugs have focused on two binding sites for serotonin: the 5-HT₁ binding site, which has a high affinity for radiolabeled serotonin (Nelson 1988), and the 5-HT₂ binding site, which has a high affinity for ³H-spiroperidol (Lyon & Titeler 1988). Both the 5-HT₁ and 5-HT₂ binding sites appear to be located postsynaptically (Willner 1985).

Studies that have focused on the 5-HT₁ binding site indicate that this site is probably unaffected by long-term tricyclic treatment. Only two (Maggi, U'Prichard & Enna 1980; Segawa, Mizuta & Nomura 1979) of 19 experiments that have looked at the effect of long-term tricyclic treatment on 5-HT₁ binding sites (Kellar & Bergstrom 1983; Stolz, Marsden & Middlemiss 1983; Lucki & Fraser 1982; Koide & Matsushita 1981; Olpe 1981; Olpe & Schellenberg 1981; Maggi, U'Prichard & Enna 1980; Bergstrom & Kellar 1979; Savage, Fraser & Mendels 1979; Segawa, Mizuta & Nomura 1979; Wirz-Justice et al. 1978) revealed a decrease in receptor number. One of these studies (Maggi, U'Prichard & Enna 1980) revealed a decrease in receptor number with imipramine treatment but either a decrease or no effect with desipramine treatment depending on the brain region involved. Conversely, long-term MAO inhibitor treatment seems to result in a diminished number of 5-HT₁ receptors. Lucki and Fraser (1982) and Savage, Mendels and Fraser (1980) reported a decrease in the number of 5-HT₁ receptor sites labeled after treatment with either clorgyline, pargyline or phenelzine. Thus, it appears that while tricyclics do not affect 5-HT₁ receptors, the MAOIs have an effect by caus-

ing a decrease in receptor number. Welner and colleagues (1989) studied the effects of long-term antidepressant treatment on the more specific 5-HT_{1A} receptor subtype. While amitriptyline increased the number of receptor sites labeled, fluoxetine decreased the number. The finding that fluoxetine decreased the density of 5-HT_{1A} receptor sites is consistent with the finding by Fuxe and colleagues (1983) who reported a decrease in 5-HT₁ binding sites after treatment with fluoxetine. However, this finding is in contrast to studies conducted by Stolz, Marsden and Middlemiss (1983), Maggi, U'Prichard and Enna (1980), and Savage, Fraser and Mendels (1979) who reported no effect on 5-HT₁ binding sites after treatment with fluoxetine. Thus, although the 5-HT₁ receptor may be implicated in the mechanism of action of MAOIs, it cannot account for the decrease in sexual functioning resulting from treatment with many other antidepressant drugs. Tricyclics and fluoxetine fail to show a consistent effect on 5-HT₁ receptors, suggesting that other systems are likely involved.

In contrast to the different effects noted with various antidepressant drugs on 5-HT₁ binding sites, many studies report that long-term treatment with MAOIs and tricyclics consistently reduces the density of 5-HT₂ receptors. All but two (Green et al. 1983; Stolz, Marsden & Middlemiss 1983) of 14 experiments (Fuxe et al. 1983; Green et al. 1983; Kellar & Bergstrom 1983; Stolz, Marsden & Middlemiss 1983; Dumbrille-Ross, Tang & Coscina 1982; Kellar et al. 1981; Peroutka & Snyder 1980a,b; Tang, Seeman & Kwan 1980) that have looked at the effects of long-term tricyclic treatment on 5-HT₂ binding sites, showed a decrease in receptor density. Of the two studies that did not show a decrease in receptor density, one study showed no effect (Stolz, Marsden & Middlemiss 1983) with amitriptyline or imipramine treatment but did show a decrease with clomipramine treatment. The second study found a significant increase in 5-HT₂ binding sites with desmethylinipramine relative to saline treatment (Green et al. 1983). However, it should be noted that statistical significance appeared to reflect unusually low levels of 5-HT₂ binding in the control group. Similarly, in all of the studies reviewed that looked at the effects of long-term MAOI treatment on 5-HT₂ receptor binding sites (Kellar & Bergstrom 1983; Kellar et al. 1981; Peroutka & Snyder 1980b), diminished receptor numbers were reported. Consistent with these findings, both fluoxetine (Stolz, Marsden & Middlemiss 1983) and trazodone (Georgotas et al. 1982) seem to cause a decrease in 5-HT₂ receptor binding sites.

The effects of cyproheptadine on serotonin binding sites are somewhat less clear. Decreases in both 5-HT₁ and 5-HT₂ receptor binding sites have been reported (Peroutka 1986; Peroutka & Snyder 1979). One would expect the difference between the sexual side effects of cyprohep-

TABLE III
THE EFFECTS OF ANTIDEPRESSANT TREATMENT ON PRESYNAPTIC AND
POSTSYNAPTIC RESPONSES TO SEROTONIN: EFFECT ON TURNOVER

DRUG	ACUTE	CHRONIC
Tricyclics		
Tertiary Amines		
Amitriptyline	0 Marco & Meek 1979 [A,B]	0 Marco & Meek 1979 [A,B]
Clomipramine	↓ Meek & Werdinius 1970 [A]; Marco & Meek 1979 [A,B]; VanWijk, Meisch & Korf 1977 [A]	0 Marco & Meek 1979 [A,B]; Sugrue 1980 [A]; Van Wijk, Meisch & Korf 1977 [A]
Imipramine	↓ Svensson 1978 [B]; Leonard & Kafoe 1976 [C]; VanWijk, Meisch & Korf 1977 [A]	0 Svensson 1978 [B] ↓ Alpers & Himwich 1972 [A]; Leonard & Kafoe 1976 [C]; Van Wijk, Meisch & Korf 1977 [A]
Secondary Amines		
Desipramine	0 Marco & Meek 1979 [A,B]	0 Sugrue 1980 [A]; ↓ Leonard & Kafoe 1976 [C]
MAO Inhibitors		
Clorgyline		
Clorgyline	0 Campbell et al. 1979 [A]	0 Campbell et al. 1979 [A]
Pargyline		
Pargyline	0 Campbell et al. 1979 [A]	0 Campbell et al. 1979 [A]
Phenelzine		
Phenelzine	0 Robinson et al. 1979 [B]	0 Robinson et al. 1979 [B]
Tranlycypromine		
Tranlycypromine	0 Robinson et al. 1979 [B]	↑ Robinson et al. 1979 [B]
Atypical Drugs		
Fluoxetine		
Fluoxetine	↓ Marco & Meek 1979 [A,B]	↓ Marco & Meek 1979 [A,B]
Trazodone		
Trazodone	↓ Stefanini et al. 1976b [D]	
0 = no effect; ↑ = increase; ↓ = decrease [A] measured by brain accumulation of 5-HIAA; [B] measured by 5-HTP after decarboxylase inhibition; [C] measured by incorporation of tritiated tryptophan; [D] measured by uptake into synaptosomes		

tadine and other antidepressants (cyproheptadine enhances ejaculatory/orgasmic ability, while other antidepressants inhibit it) to also be reflected in biochemical studies. It is difficult however, to assess the serotonergic effects of cyproheptadine, as studies are few and they are complicated by the fact that cyproheptadine, generally considered a serotonin antagonist, may have partial agonist activity (Mendelson & Gorzalka 1986c). Moreover, cyproheptadine is nonselective with respect to the serotonin receptor subtype activated.

In summary, studies reveal a consistent decrease in 5-HT₂ receptor density resulting from long-term treatment with MAOIs, tricyclics, fluoxetine, and trazodone. It is tempting to speculate that this effect is responsible for the consistent decline in ejaculatory/orgasmic ability that also results from treatment with these drugs. This finding would be in agreement with studies in the female rat that suggest 5-HT₂ binding sites mediate the excitatory action of serotonin (Mendelson & Gorzalka 1986c), but contrasts with recent evidence in the male rat that indicates inhibitory 5-HT₂ receptor activity (Watson & Gorzalka In press, 1991, 1990).

THE EFFECTS OF LITHIUM ON MALE SEXUAL BEHAVIOR

Lithium

Lithium is used in the treatment of affective disorders, primarily bipolar disorder. The mechanisms of action of lithium have not been fully elucidated; however, the drug has been shown to interfere with the synthesis, storage, release, and reuptake of central monoamine neurotransmitters including serotonin and the catecholamines. In addition, lithium interacts with several secondary messenger processes (McEvoy 1990).

Sexual Desire. Disinterest in sex has been reported in association with lithium treatment (Kafka 1991a; Jefferson et al. 1985; Kristensen & Jorgensen 1987; Simhandl et al. 1987; Blay, Ferraz & Calil 1982; Vestergaard, Amdisen & Schou 1980) at serum lithium levels of .5mEq/L (Blay, Ferraz & Calil 1982) (see Table VI). However, whether these effects can be directly attributed to drug treatment is questionable. In virtually all cases reviewed (Kristensen & Jorgensen 1987; Blay, Ferraz & Calil 1982; Jefferson et al. 1985), other sexual disorders, such as erectile dif-

TABLE IV
THE EFFECTS OF ANTIDEPRESSANT TREATMENT ON PRESYNAPTIC AND POSTSYNAPTIC
RESPONSES TO SEROTONIN: CHANGES IN RECEPTOR SENSITIVITY

DRUG	ACUTE	CHRONIC
Tricyclics		
Tertiary Amines		
Amitriptyline	0 Menkes, Aghajanian, & McCall 1980; Montigny & Aghajanian 1978	↑ Menkes, Aghajanian, & McCall 1980; Montigny & Aghajanian 1978
Clomipramine	0 Montigny & Aghajanian 1978	0 Olpe, Schellenberg, & Jones 1984; Olpe & Schellenberg, 1981 ↑ Gallager & Bunney 1979; Montigny & Aghajanian 1978
Imipramine	0 Menkes, Aghajanian, & McCall 1980; Montigny & Aghajanian 1978	0 Blier & deMontigny 1980 ↑ Menkes, Aghajanian, & McCall 1980; Montigny & Aghajanian, 1978; Meijer & Groos 1988; Gallager & Bunney 1979
Secondary Amines		
Desipramine	0 Menkes, Aghajanian, & McCall 1980; Montigny & Aghajanian 1978	0 Blier & deMontigny 1980; Olpe & Schellenberg 1981 ↑ Menkes, Aghajanian, & McCall 1980; Montigny & Aghajanian 1978
MAO Inhibitors		
Clorgyline		↓ Olpe & Schellenberg 1981; Olpe, Schellenberg & Jones, 1984
Atypical Drugs		
Fluoxetine		0 Menkes, Aghajanian, & McCall 1980; Montigny & Aghajanian 1978
0 = no effect; ↑ = increase; ↓ = decrease		

ficulty and premature ejaculation were reported in conjunction with a decreased interest in sex. It is therefore likely that this side effect is secondary to other lithium-induced sexual difficulties. In a controlled study by Kristensen and Jorgensen, the sexual functioning of 14 male patients on lithium treatment was compared to that of a control group. While two patients reported a disinterest in sex as a result of drug treatment, two of 17 control patients also reported a similar decreased interest. Additionally, in a survey by Vestergaard, Amdisen and Schou, only one of 125 men on long-term lithium treatment complained of a disinterest in sex. This one complaint was reported concurrently with erectile difficulty.

Erectile Capacity. Reports of erectile difficulties resulting from lithium treatment have been reported (Kristensen & Jorgensen 1987; Jefferson et al. 1985; Blay, Ferraz & Calil 1982) at serum lithium levels of .5 mEq/L. Blay, Ferraz and Calil reported two cases in which impaired erection was experienced after one month of drug treatment. In one case, the symptom remitted spontaneously after two months of treatment. In the second case, a program was initiated in which two weeks of lithium treatment was alternated with a two-week drug-free period. During the two weeks of drug treatment, the patient experienced sexual impairment that then abated during

the two weeks off medication. Similarly, Weddige (1980) reported a case of lithium-related impotence in which the symptom remitted on each of the several occasions when lithium was discontinued. In a controlled study by Kristensen and Jorgensen, one of 14 patients reported erectile dysfunction resulting from long-term lithium treatment. It should be noted, however, that two of 17 control patients also reported a similar dysfunction.

Ejaculation. Two cases have been reported of premature ejaculation resulting from lithium treatment (Kristensen & Jorgensen 1987). However, in comparison to a control group, there were 50% fewer cases reported among patients receiving lithium treatment. Apparently, there are no cases of an inhibition of ejaculation reported in association with lithium treatment.

THE EFFECTS OF LITHIUM ON FEMALE SEXUAL BEHAVIOR

There are no conclusive reports of sexual dysfunction in women resulting from lithium treatment. In a controlled study by Kristensen and Jorgensen (1987), a decrease in sexual desire was described by one of ten patients receiving lithium treatment and also by three of 25 control patients (see Table VII). Similarly, orgasmic dysfunction was

TABLE V
THE EFFECTS OF ANTIDEPRESSANT TREATMENT ON PRESYNAPTIC AND POSTSYNAPTIC
RESPONSES TO SEROTONIN: RECEPTOR SITES LABELED

DRUG	5-HT ₁ *		5-HT ₂ **	
	ACUTE	CHRONIC	ACUTE	CHRONIC
Tricyclics				
Tertiary Amines				
Amiripryline	↓ Stolz, Marsden & Middlemiss 1983	0 Stolz, Marsden & Middlemiss 1983; Lucki & Fraser, 1982; Savage, Fraser & Mendels, 1979 ↓ Segawa, Mizuta & Nomura 1979 ↑ [5-HT _{1A}] Welner et al. 1989	0 Peroutka & Snyder 1980a ↓ Stolz, Marsden & Middlemiss 1983	0 Stolz, Marsden & Middlemiss 1983 ↓ Dumbrille-Ross, Tang & Coscina 1982; Keller & Bergstrom 1983; Kellar et al. 1981; Tang, Seeman, & Kwan 1980; Peroutka & Snyder 1980a,b
Clomipramine	0 Savage, Fraser & Mendels 1979 ↓ Stolz, Marsden & Middlemiss 1983	0 Wirz-Justice et al. 1978; Stolz, Marsden & Middlemiss 1983; Keller & Bergstrom 1983; Savage, Fraser & Mendels 1979; Lucki & Fraser 1982		↓ Stolz, Marsden & Middlemiss 1983
Imipramine	0 Koide & Matsushita 1981 ↓ Stolz, Marsden & Middlemiss 1983	0 Stolz, Marsden & Middlemiss 1983; Koide & Matsushita 1981; Lucki & Fraser 1982 ↓ Segawa, Mizuta & Nomura 1979; Maggi, U'Prichard & Enna 1980	↓ Peroutka & Snyder 1980b; Stolz, Marsden & Middlemiss 1983	0 Stolz, Marsden & Middlemiss 1983 ↓ Peroutka & Snyder 1980b ↓ Fuxe et al. 1983
Secondary Amines				
Desipramine	0 Segawa, Mizuta & Nomura 1979; Koide & Matsushita 1981	0 Bergstrom & Kellar 1979; Kellar & Bergstrom 1983; Koide & Matsushita 1981; Lucki & Fraser 1982; Maggi, U'Prichard & Enna 1980		↓ Dumbrille-Ross, Tang & Coscina 1982; Tang, Seeman & Kwan 1980; Fuxe et al. 1983 ↑ Green et al. 1983a
MAO Inhibitors				
Clorgyline	↓ Savage, Fraser & Mendels 1979	↓ Savage, Mendels & Fraser 1980		
Pargyline	0 Lucki & Fraser 1982	↓ Lucki & Fraser 1982		↓ Peroutka & Snyder 1980b
Phenelzine	0 Lucki & Fraser 1982	↓ Lucki & Fraser 1982		
Tranylcypromine				↓ Keller et al. 1981; Kellar & Bergstrom 1983
Atypical Drugs				
Cyproheptadine	↓ Peroutka 1986		↓ Peroutka & Snyder 1979	
Fluoxetine	0 Stolz, Marsden & Middlemiss 1983; Savage, Fraser & Mendels 1979	0 Stolz, Marsden & Middlemiss 1983; Savage, Fraser & Mendels 1979; Maggi, U'Prichard & Enna 1980 ↓ Fuxe et al. 1983 ↓ [5-HT _{1A}] Welner et al. 1989	0 Stolz, Marsden & Middlemiss 1983	↓ Stolz, Marsden & Middlemiss 1983 0 Fuxe et al. 1983
Trazodone				↓ Georgotas et al. 1982
* 5-HT ₁ sites labelled with [³ H] 5-HT ** 5-HT ₂ sites labelled with [³ H] spiperone 0 = no effect; ↑ = increase; ↓ = decrease				

TABLE VI
THE EFFECTS OF LITHIUM ON MALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT PRIOR TO DRUG ADMINISTRATION	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Lithium	serum level 5-9 mEq/l, 1 mo.	bipolar depression	decrease in sexual desire, erectile difficulty	2	Blay, Ferraz & Calil 1982
	5-1.0 mEq/l, -	bipolar/unipolar depression	decrease in sexual desire, erectile difficulty, premature ejaculation	5/14	Kristensen & Jorgensen 1987
	—	bipolar depression	decrease in sexual desire	1/125	Vestergaard, Amdisen & Schou 1980
	5-1.0 mEq/l	bipolar depression	impotence	2	Weddige 1980
	1.28 mEq/l	depression, atypical sexual behavior	decrease in atypical sexual behavior	2	Kafka 1991a

TABLE VII
THE EFFECTS OF LITHIUM ON FEMALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT PRIOR TO DRUG ADMINISTRATION	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Lithium	serum level .5-1.0 mEq/L, - serum level .5-1.0 mEq/L, - —	major affective disorder bipolar/unipolar depression	decrease in sexual desire decrease in orgasmic ability no effect	1/10 2/10 112	Kristensen & Jorgensen 1987 Kristensen & Jorgensen 1987 Vestergaard, Amdisen & Schou 1980

described by two of ten patients and also by two of 25 control patients. Clearly, the reported difficulties cannot be attributed to lithium treatment. Vestergaard, Amdisen and Schou (1980) surveyed 112 women on long-term lithium treatment and were unable to conclude that any sexual difficulties were attributable to the drug.

SUMMARY OF THE EFFECTS OF LITHIUM ON MALE AND FEMALE SEXUAL BEHAVIOR

There are few reports concerning sexual difficulties as a side effect of lithium treatment. The available reports predominantly concern male dysfunctions, namely a decrease in sexual desire and erectile dysfunction. While it is likely that a decrease in desire is secondary to either the patient's overall life situation or to other side effects resulting from drug treatment, the possibility exists that erectile difficulty is a direct result of lithium treatment. This possibility is supported by the two studies (Blay, Ferraz & Calil 1982; Weddige 1980) in which a cessation and re-institution of medication led to an alleviation and recurrence of symptoms, respectively.

DISCUSSION

The inhibition of phosphoinositide turnover by lithium has been used frequently to account for some effects resulting from lithium treatment. It has been suggested (Casebolt & Jope 1989; Godfrey et al. 1989; Elphick et al. 1988) that an increase in phosphoinositide turnover, due to overactive neurotransmitter function, exists in patients with untreated bipolar affective disorder. An inhibition of this turnover by lithium would reduce brain inositol levels, thus normalizing the neurotransmitter activity transduced by this secondary messenger system. Lithium has been shown to reduce inositol phosphate formation by various neurotransmitters including acetylcholine, norepinephrine, and serotonin. It is difficult to ascertain which of these three possible transmitters may be responsible for the sexual side effects resulting from lithium treatment.

Casebolt and Jope (1989) showed that long-term lithium treatment significantly reduced the inositol phos-

pholipid response to norepinephrine in the cerebral cortex, hippocampus, and striatum. By comparison, the response to serotonin was reduced in the hippocampus and striatum only, and the response to carbachol, a cholinergic agonist, was reduced in the striatum only. When lithium was administered for a shorter time interval, the inositol response to all three neurotransmitters was reduced in the cerebral cortex (Godfrey et al. 1989; Kendall & Nahorski 1987). Although all three neurotransmitters are affected by lithium, it is interesting to note that the lithium-induced reduction in response to serotonin was proportionately greater than in response to either carbachol or norepinephrine (Godfrey et al. 1989).

If changes in sexual functioning resulting from lithium treatment are attributable to serotonergic changes in phosphoinositide turnover, important considerations should be made. First, one would expect that if an overactivity of neurotransmitters exists in untreated bipolar depressed patients, then changes in sexual functioning between the period of illness and patients' premorbid states would also be apparent. However, it is impossible to determine whether a difference in sexual functioning exists between the premorbid and untreated states of patients with bipolar affective disorder, as previous sexual history is frequently not mentioned, and when it is it refers to the state prior to the administration of medication, not to the state prior to the onset of illness. Second, if lithium normalizes this increase in neurotransmitter function, then changes in sexual functioning should also be normalized once the drug has been administered. This is consistent with the finding that lithium-induced sexual difficulties are infrequent. In addition, Kristensen and Jorgensen (1987) reported that there was no difference in the number of sexual dysfunctions between lithium-treated and control patients. Perhaps an increase in serotonin during the period of untreated illness caused a decrease in sexual functioning that abated when lithium normalized serotonin levels.

Unfortunately, information on previous sexual history was not provided in most of the studies reviewed. It is tempting to speculate that either an excitatory serotonergic effect or a normalization in serotonin levels is responsible for the unusually high incidence of sexually well-adapted patients on lithium treatment.

THE SEROTONERGIC ACTIVITY OF LITHIUM

Various pharmacological agents have been used in biochemical studies in an effort to determine the precise serotonin receptor subtype that may be altered as a result of lithium treatment. Treiser and Kellar (1980) reported a 33% reduction in [^3H]5-HT binding as a result of long-term lithium treatment. Although this radioligand has been shown to label 5-HT $_1$ receptors (Nathan 1988), the specific subtype cannot be determined as [^3H]5-HT labels, among others, 5-HT $_{1A}$, and 5-HT $_{1C}$ receptors indiscriminately (Peroutka et al. 1986). The reduction in binding does, however, indicate that the density of 5-HT $_1$ receptors is reduced as a result of lithium treatment.

Studies using 8-hydroxy-N, N-dipropyl-2-amino-tetralin (8-OH-DPAT) focus on the more specific 5-HT $_{1A}$ receptor subtype (Peroutka et al. 1986). Using this radioligand, Blier, de Montigny and Tardif (1987) reported that lithium caused significant enhancement of the sensitivity of 5-HT $_{1A}$ postsynaptic receptors. Similarly, Goodwin and colleagues (1986a,b) found that both short-term and long-term lithium treatment enhanced the behavioral effects mediated by postsynaptic 5-HT $_{1A}$ receptors. In addition, studies that have focused on alterations in adenylate cyclase activity resulting from lithium treatment provide further evidence for the involvement of 5-HT $_{1A}$ receptors. Hotta and Yamawaki (1986) reported that lithium potentiated serotonin-stimulated adenylate cyclase activity. Adenylate cyclase stimulation has been linked to the 5-HT $_{1A}$ receptor (Peroutka et al. 1986) and thus it is apparent that this receptor subtype may be involved in the behavioral effects resulting from lithium treatment. This finding is consistent with the fact that no cases of an inhibition of ejaculation have been reported in association with lithium treatment; however, two cases of premature ejaculation have been described (Kristensen & Jorgensen 1987). It is interesting to note that, in animal studies, the 5-HT $_{1A}$ receptor has been implicated in the facilitation of ejaculation and/or seminal emission (Mendelson & Gorzalka 1986a; Peroutka et al. 1986).

As previously discussed, lithium appears to cause a marked reduction in the inositol phospholipid response to serotonin. Phosphoinositol turnover has been linked to the 5-HT $_{1C}$ receptor (Peroutka et al. 1986) and thus it appears that lithium reduces the density of this serotonin receptor subtype. While there are few studies assessing the effects of 5-HT $_{1C}$ receptors on sexual behavior, it has been noted (Gorzalka, Mendelson & Watson 1990) that this receptor subtype may play a facilitatory role in female rat sexual receptivity.

Studies using [^3H] ketanserin (a 5-HT $_2$ antagonist) have failed to show consistent alterations in 5-HT $_2$ receptors resulting from lithium treatment (Godfrey et al. 1989;

Goodwin et al. 1986a; Treiser & Cascio 1981). Godfrey and colleagues (1989) reported that short-term lithium treatment had no effect on 5-HT $_2$ receptors, and Treiser and Cascio (1981) reported that long-term lithium treatment reduced [^3H] spiperone binding in the hippocampus but had no effect on these binding sites in the cortex. As noted by Treiser and Cascio, it is still tentative whether [^3H] spiperone binding sites in the hippocampus are necessarily 5-HT $_2$ receptors. Furthermore, a role of 5-HT $_{1C}$ receptors in effects attributable to 5-HT $_2$ activity cannot be ruled out as all 5-HT $_2$ selective drugs developed thus far also show moderate to high 5-HT $_{1C}$ activity (Hoyer 1988).

In summary, it appears that lithium may exert some of its effects on serotonin by means of the 5-HT $_{1A}$ and 5-HT $_{1C}$ receptors. The studies reviewed indicate that while lithium does not appear to exert an effect on 5-HT $_2$ receptors, an increase in 5-HT $_{1A}$ receptors and a decrease in 5-HT $_{1C}$ receptors are seen as a result of lithium treatment.

THE EFFECTS OF ANTIPSYCHOTIC DRUGS ON MALE SEXUAL BEHAVIOR

Major Tranquilizers

The major tranquilizers are primarily used for the management of psychotic symptoms, especially those associated with schizophrenia and mania. Less commonly, these drugs have been used to treat severe behavioral problems in children.

The precise mechanism of action by which the major tranquilizers exert their effects has not been determined but is considered to be principally related to antidopaminergic action. However, these drugs are also antagonists peripherally and/or centrally at α -adrenergic, serotonergic, histaminergic, and muscarinic receptors. The behavioral effects of the major tranquilizers may be related to any or all of these effects.

Sexual Desire. There are relatively few reported cases of changes in sexual desire resulting from phenothiazine treatment (Mitchell & Popkin 1982; Tennent, Bancroft & Cass 1974; Greenberg 1971; Freyhan 1961) (see Table VIII). Freyhan reported a case in which the patient, a repeated sex offender, experienced a decrease in sexual desire at a dosage of 300 mg/day of thioridazine. Similarly, in a double-blind controlled study conducted by Tennent, Bancroft and Cass, 12 sex offenders, receiving 125 mg/day of chlorpromazine, reported a decrease in sexual interest. There were, however, no significant differences between the chlorpromazine group and placebo-control group. Greenberg reported a case in which the patient experienced a decreased interest in sex at a dosage of 1000 mg/day of chlorpromazine. Sexual desire was restored, inhibited, and again restored at dosages of 400, 1200, and 600 mg/day,

TABLE VIII
THE EFFECTS OF ANTIPSYCHOTIC DRUGS ON MALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT PRIOR TO DRUG ADMINISTRATION	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Phenothiazines Chlorpromazine	100 mg	—	priapism	6	Bastecky & Gregova 1974; Dawson-Butterworth 1969; Dawson-Butterworth 1970; Meiraz & Fishelovitch 1969
	125 mg, 2-6 wks.	sex offender	decrease in sexual desire and activity, increase in erections to erotic films	12	Tennent, Bancroft & Cass 1974
	200-400 mg	atypical sexual behavior	partial control of atypical sexual behavior	23/36	Flach & Regan 1959
	1000-1250 mg	psychotic episodes, decrease in sexual desire	inhibition of ejaculation, erectile difficulty	1	Greenberg 1965
	1000-2750 mg	psychotic episodes	decrease in sexual desire, erectile difficulty, inhibition of ejaculation	—	Mitchell & Popkin 1982; Nestoros, Lehmann & Ban 1980
Thioridazine	30-300 mg, 3 days	schizophrenia	inhibition of ejaculation	3	Clein 1962; Heller 1961
	50-600 mg, 1 wk.	paranoid schizophrenia	inhibition of ejaculation	2	Shader 1964
	50-100 mg, 1 wk.	mild depression/ personality disorder	inhibition of ejaculation	2	Freyhan 1961
	50-400 mg, 1 wk.	anxiety, paranoia	delayed ejaculation, inhibition of ejaculation	2	Shader 1964; Singh 1963
	75 mg, 2 wks.	premature ejaculation, anxiety, depression	control of premature ejaculation	1	Singh 1963
	100 mg	—	priapism	6	Dorman & Schmidt 1976; Mitchell & Popkin 1982
	100-600 mg, 2 wks.	schizophrenia	retrograde ejaculation	—	Kotin et al. 1976
	100-600 mg, 2 wks.	schizophrenia	erectile difficulty	10/23	Kotin et al. 1976
	100-600 mg, 2 wks.	schizophrenia	changes in ejaculation	28/57	Kotin et al. 1976
	100 mg, 1 mo.	grief reaction and nocturnal emissions	decrease in the frequency of nocturnal emissions	1	Clein 1962
	100-600 mg, 2 wks.	—	erectile difficulty	3	Haider 1966; Yassa 1982; Witton 1962
	200 mg, 1 wk.	schizophrenia	inhibition of ejaculation	1	Greenberg & Carrillo 1968
	300 mg, 1 wk.	acute anxiety	inhibition of ejaculation	1	Singh 1961
Trifluoperazine	300 mg, 1 wk.	sex offender	decrease in sexual desire, inhibition of ejaculation	1	Freyhan 1961
	400 mg	manic psychosis	inhibition of ejaculation	1	Taubel 1962
	5 mg, 9 days	psychotic symptoms, no history of sexual dysfunction	spontaneous orgasms and ejaculation	1	Keitner & Selub 1983
Thioxanthenes Chlorprothixene	300 mg, 2 mos.	anxiety, alcoholism	inhibition of ejaculation	1	Ditman 1964
	400-600 mg	chlorpromazine-induced inhibition of ejaculation	normal ejaculatory response	1	Greenberg 1971

respectively. It should be noted that alterations in sexual desire were reported concurrently with alterations in erectile ability.

Erectile Capacity. Erectile dysfunction has been reported in association with several phenothiazine tranquilizers (Mitchell & Popkin 1982; Kotin et al. 1976; Greenberg 1971; Goldstein, Weiner & Banas 1969; Haider 1966; Witton 1962). In a survey by Kotin and colleagues, 10 of the 23 patients taking thioridazine experienced erectile dysfunction. Also, Witton and Haider each described a case of erectile dysfunction associated with thioridazine. The lowest daily dose linked to this disorder is 150 mg. Chlorpromazine has been reported to cause erectile failure at a dosage of 1000 mg/day (Greenberg 1971).

In a study by Nestoros, Lehman and Ban (1980), the sexual function of 50 schizophrenic patients on long-term neuroleptic treatment was assessed. Although a decrease in the frequency of erections of schizophrenic patients in comparison to their premorbid state appeared to be statistically significant, it was noted that schizophrenic patients showed a significantly lower frequency of erections,

in comparison to a normal population, both in the past and present. The percent of patients experiencing an inability to ejaculate was highest in the high-dosage group (1500-2750 mg/day chlorpromazine). Among the other two dosage groups (low dosage: 327-600 mg/day, and moderate dosage: 700-1267 mg/day), the percentages were similar.

Priapism (prolonged, painful erection) has been described in association with chlorpromazine (Bastecky & Gregova 1974; Dawson-Butterworth 1970, 1969; Meiraz & Fishelovitch 1969) at a minimum daily dose of 100 mg. This disorder has also been linked to thioridazine therapy (Dorman & Schmidt 1976) at a minimum daily dose of 100 mg.

Ejaculation. Impaired ejaculation appears to be the most common sexual side effect of major tranquilizer treatment. Reports of total inhibition of ejaculation have been made in association with thioridazine (Kotin et al. 1976; Greenberg & Carrillo 1968; Shader 1964; Singh 1963, 1961; Clein 1962; Taubel 1962; Freyhan 1961; Heller 1961), chlorpromazine (Nestoros, Lehman & Ban 1980;

Greenberg 1971), and chlorprothixene (Ditman 1964). Kotin and colleagues reported that 10 of the 23 patients surveyed experienced difficulties in ejaculation, including retrograde ejaculation, as a result of thioridazine treatment. In sharp contrast, none of the 30 patients taking other major tranquilizers reported a similar difficulty. In agreement with this study, Shader (1964) described two cases in which an inhibition of ejaculation was experienced with thioridazine treatment. In both cases the symptom was not present with chlorpromazine or trifluoperazine treatment. The lowest daily dosage of thioridazine described in association with this disorder is 30 mg (Heller 1961). Greenberg (1971) described a case in which a patient experienced an inability to ejaculate while receiving 400 mg/day of chlorpromazine. The disorder remitted when the medication was replaced by 600 mg/day of chlorprothixene. Similarly, Ditman (1964) described a case in which the patient received increasing doses of chlorprothixene. While no side effects were noted at 100-200 mg/day, when the dosage was increased to 300 mg/day, the patient complained of inhibited ejaculation. The problem was alleviated one week after chlorprothixene was discontinued.

One case was described (Singh 1963) in which 75 mg/day of thioridazine was successfully used to treat premature ejaculation. It should be noted however, that the patient was also receiving antidepressant medication and the control of premature ejaculation was possibly secondary to the alleviation of anxiety and depression.

Keitner and Selub (1983) described a patient who experienced spontaneous orgasms accompanied by ejaculation while receiving 5 mg/day of trifluoperazine. The patient did not experience any sexual difficulties when receiving thioridazine or tricyclic antidepressant medication. He also denied any sexual dysfunctions prior to trifluoperazine administration.

THE EFFECTS OF ANTIPSYCHOTIC DRUGS ON FEMALE SEXUAL BEHAVIOR

Antipsychotic Drugs

Sexual Desire. In a study by Kotin and colleagues (1976), one of four women on 200 mg/day of thioridazine experienced a decrease in sexual desire. One case of decreased sexual arousal has been noted at 200 mg/day of thioridazine (Degen 1982)(see Table IX).

Orgasm. Two cases of delayed orgasm have been reported in association with major tranquilizer therapy (Degan 1982). One patient was receiving 15 mg/day of trifluoperazine and the other 200 mg/day of thioridazine. In the second case, when thioridazine treatment was replaced with 200 mg/day of chlorpromazine, the patient experienced functional dyspareunia. All sexual difficulties

were resolved when the drug was withdrawn.

SUMMARY OF THE EFFECTS OF ANTIPSYCHOTIC DRUGS ON MALE AND FEMALE SEXUAL BEHAVIOR

The frequency of sexual dysfunction, secondary to antipsychotic drug therapy, is difficult to assess. The majority of people receiving such treatment have considerable psychopathology and thus several factors must be considered. First, the alleviation of psychotic symptoms by antipsychotic drug treatment likely leads to the facilitation of sexual functioning, and it is possible that an increase in overall functioning at a global level masks some of the more specific, sexual effects of antipsychotic medication. Second, as noted by Nestoros, Lehmann and Ban (1980), schizophrenic patients, in comparison to normal control patients, show a considerably lower level of sexual functioning prior to the onset of mental illness. Thus, it is difficult to ascertain the extent to which antipsychotic medication contributes to sexual dysfunction. Furthermore, the drugs' sedative effects and the decrease in mobility associated with the extrapyramidal side effects further confound interpretation of the sexual difficulties associated with major tranquilizer treatment.

Based on the preceding review of literature, an inhibition of ejaculation is apparently the most common sexual difficulty reported by men who take these medications. Thioridazine and chlorpromazine appear to be the worst offenders, while chlorprothixene and trifluoperazine seem less likely to inhibit ejaculation. The fact that these drugs vary in the degree to which they inhibit ejaculation is evidenced in the findings that chlorpromazine eliminated thioridazine-induced ejaculatory difficulty, chlorprothixene eliminated difficulties resulting from chlorpromazine treatment and, in one isolated case, trifluoperazine led to spontaneous ejaculation. It is tempting to conclude that these side effects are not directly related to the dosage administered. One might expect a delay in ejaculation to occur at lower drug doses. However, complete inhibition of ejaculation is seen in doses ranging from 25-600 mg/day of thioridazine.

While many studies have looked at male sexual dysfunction, secondary to antipsychotic drug use, there is a paucity of information concerning the sexual effects of these drugs on females. Most reports have focused on reproductive function and make only incidental comments on sexual function. In addition, the difficulty some females have in articulating sexual problems cannot be discounted. In consideration of these factors, it is impossible to conjecture the frequency of antipsychotic-induced sexual difficulties. The two studies of females reveal that a delay in orgasm is the most frequent complaint made concerning

TABLE IX
THE EFFECTS OF ANTIPSYCHOTIC DRUGS ON FEMALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT PRIOR TO DRUG ADMINISTRATION	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Phenothiazines					
Chlorpromazine	200 mg, -	ameliorated psychotic symptoms	functional dyspareunia	1	Degen 1982
Thioridazine	200 mg, -	—	decrease in sexual excitement	1/4	Kotin et al. 1976
	200 mg, -	ameliorated psychotic symptoms	delayed orgasm	1	Degen 1982
Trifluoperazine	15 mg, 2 wks. -	schizophrenia	delayed orgasm	1	Degen 1982

antipsychotic drug therapy. This disorder is analogous to an inhibitor of ejaculation and thus there appears to be a similarity between male and female sexual side effects resulting from antipsychotic medication.

Most reviewed cases indicate the appearance of sexual difficulties approximately one to two weeks after the initiation of drug treatment; however, it may be a reflection of a time lapse when the patient was questioned by the physician. In virtually all of the cases in which medication was discontinued, normal sexual functioning was restored within approximately three days.

DISCUSSION

An explanation of the mechanisms by which antipsychotic drugs interfere with sexual functioning can be found at both the peripheral and central levels. At the peripheral level, anticholinergic and antiadrenergic properties of the drugs may affect sexual functioning; at the central level, changes in dopamine and serotonin activity may be implicated. While many studies have solely attributed antipsychotic-induced sexual dysfunction to peripheral or dopaminergic mechanisms, it is likely that, in addition to these effects, other factors play a role.

Shader and Elkins (1980) suggested that, in theory, the anticholinergic properties of antipsychotic drugs may promote erectile dysfunction by blocking parasympathetic functions. Similarly, the sexual excitement phase in the female sexual response is partially under parasympathetic control (Shader & Elkins 1980) and thus may be influenced by the anticholinergic effects of antipsychotic drugs. While a decrease in sexual arousal and erectile difficulty have been mentioned in association with the major tranquilizers, inhibition of ejaculation and orgasm are the most frequently reported side effects of treatment with these drugs and cannot be explained entirely by peripheral cholinergic activity.

Antiadrenergic properties may effect ejaculation by means of sympathetic intervention (Shader & Elkins 1980; Horowitz & Goble 1979). Orgasm in the female is considered analogous to male ejaculation (Shader & Elkins 1980); however, there is no emission phase in women and thus while peripheral mechanisms may play a role in the male experience, orgasm in the female is a cortical sensory

experience (Kedia & Markland 1975) and is not influenced by antiadrenergic events (Shader & Elkins 1980).

Further evidence suggests that the decrease in sexual functioning, attributed to antipsychotic drug treatment, cannot be considered a purely adrenergic event. Two cases were reported (Shader 1964) in which patients experienced ejaculatory failure while receiving thioridazine but did not experience this effect with chlorpromazine treatment. Interestingly, these drugs have equal antiadrenergic potencies (Anden et al. 1970). In addition, an overwhelmingly large number of cases of inhibited ejaculation have been described in association with thioridazine. In comparison, very few other antipsychotic drugs, which have similar antiadrenergic properties as thioridazine, have been implicated to such an extent (Anden et al. 1970). Perphenazine (a phenothiazine) and clothiapine (a dibenzazepine) have been shown to block adrenergic activity in rats at doses as low as 1 mg/kg (Anden et al. 1970). However, these drugs have not been reported to cause sexual side effects. Furthermore, in a study assessing the effects of thioridazine on sexual behavior in the male rat (Ahlenius, Heimann & Larsson 1979), it was shown that, as in the human male, thioridazine prolonged time to ejaculation. In contrast, phenoxylbenzamine, a central norepinephrine blocking agent, and phentolamine, a peripheral norepinephrine blocking agent, did not cause a delay in ejaculation. The authors concluded that the prolonged time to ejaculation noted with thioridazine treatment is not due to the blockade of central or peripheral adrenergic receptors.

The dopaminergic effects of antipsychotic drugs have been well documented (Carlson 1986). Central dopamine has been shown to have an inhibitory effect on receptivity behavior in the female rat and that this effect appears to be exerted through D₂ dopamine receptors (Grierson et al. 1988). However, evidence indicates that dopamine mechanisms cannot fully account for the decline in sexual functioning resulting from treatment with antipsychotic drugs. In a receptor-binding study conducted by van der Heyden (1989), the ability of neuroleptics to block D₂ receptors was examined. In comparison to chlorprothixene and haloperidol, thioridazine and chlorpromazine were shown to be less potent in their ability to block D₂ receptors. As mentioned previously, thioridazine and chlorpromazine are the antipsychotic drugs that most often cause

a decrease in sexual functioning. This finding by van der Heyden was duplicated by Creese, Schneider and Snyder (1977) and Anden and colleagues (1970). Creese, Schneider and Snyder studied the potencies of 25 antipsychotic drugs in competing for [3 H] dopamine and [3 H] haloperidol binding. In comparison to thioridazine, haloperidol was shown to be approximately three times more potent in its ability to inhibit [3 H] dopamine binding, and approximately ten times more potent in its ability to inhibit [3 H] haloperidol binding. While cases of thioridazine-induced ejaculatory dysfunction are in abundance, cases of haloperidol-induced ejaculatory dysfunction in men are apparently nonexistent. As [3 H] dopamine and [3 H] haloperidol label distinct agonist and antagonist states of dopamine receptors respectively, it is unlikely that either of these properties of dopamine can fully account for the decline in sexual functioning reported in association with antipsychotic medication.

Thioridazine and chlorpromazine are potent α -adrenergic receptor blockers at the peripheral and central level. The possibility that this contributes to their ability to impair sexual functioning has not been ruled out. Furthermore, both of these antipsychotics stimulate norepinephrine synthesis. It is unlikely, however, that increased synthesis of norepinephrine contributes to the observed sexual dysfunctions.

In addition to their effects on neurotransmitter activity, antipsychotics are known to increase prolactin levels. Because elevated prolactin levels have been associated with decreased sexual desire and erectile problems in males, this effect may be an additional mechanism by which antipsychotics contribute to sexual dysfunction.

Evidence for the role of serotonin in antipsychotic-induced sexual dysfunctions is provided in a study by van der Heyden (1989). The affinity of several neuroleptic drugs for 5-HT₂ receptors was studied and it was shown that thioridazine and chlorpromazine are more potent in their ability to block 5-HT₂ receptors in comparison to haloperidol and trifluoperazine. This finding correlates with the higher incidence of sexual dysfunction associated with thioridazine and chlorpromazine. It is interesting to note that no correlation between clinical dose and affinity for 5-HT₂ receptors was found; higher doses of neuroleptic drugs did not increase binding affinity. Perhaps this explains why a complete inhibition of ejaculation is reported at doses ranging from 30-2750 mg/day.

In summary, the antipsychotic drugs reviewed share several common properties. All have adrenergic and cholinergic blocking abilities as well as dopaminergic and serotonergic effects. Each of these properties has the ability to influence sexual functioning. While it is impossible to speculate on the precise mechanism of action involved in antipsychotic-induced sexual difficulty, the role of serotonin cannot be discounted. Based on the preceding studies, the

anticholinergic, antiadrenergic blocking and dopaminergic properties of the various antipsychotic drugs do not show a significant correlation with the reported sexual side effects. In contrast, the potent ability of thioridazine and chlorpromazine to block 5-HT₂ receptors is consonant with the unusually high incidence of sexual side effects resulting from treatment with these major tranquilizers.

THE SEROTONERGIC ACTIVITY OF ANTIPSYCHOTIC DRUGS

Menkes, Aghajanian and McCall (1980) and Montigny and Aghajanian (1978) studied the effects of chlorpromazine on serotonin receptor sensitivity. Both studies showed that long-term treatment with chlorpromazine did not alter the sensitivity of serotonin receptors.

While it is possible that an increase in serotonin synthesis may account for some of the serotonergic effects of antipsychotic drugs, most studies of serotonin synthesis show conflicting results. Bender (1976) showed that chlorpromazine increased brain serotonin level. However, in a study conducted by Green (1977), chlorpromazine was shown to cause only very slight increases in serotonin levels. This study also indicated that chlorpromazine enhanced the serotonin-mediated hyperactivity syndrome. However, as there were no statistically significant differences in serotonin synthesis between the chlorpromazine- and saline-treated groups, it is reasonable to speculate that the behavioral changes were a result of postsynaptic receptor blocking (Green 1977).

Green's hypothesis is consistent with a study conducted by Andorn (1986) in which chlorpromazine selectively caused a down regulation of [3 H] spiperone binding sites in human prefrontal cortex. In addition, several other studies have shown that antipsychotic drugs potently block 5-HT₂ receptor sites (van der Heyden 1989; Lyon & Titeler 1988). As mentioned previously, thioridazine and chlorpromazine are most influential, while haloperidol, trifluoperazine, and several other neuroleptics are less potent in this regard (van der Heyden 1989). The 5-HT₂ receptor has been linked to a facilitatory role in lordosis behavior (Gorzalka, Mendelson & Watson 1990) and thus a decrease in these receptors is consistent with the decline in sexual functioning noted with major tranquilizer treatment.

The ability of antipsychotic drugs to cause a decrease in 5-HT₂ receptor density is reminiscent of the serotonergic activity of antidepressant drugs at this receptor site. It is tempting to assume that this common site of action of serotonin, in these two biochemically different drug groups, may account for the similar decline in sexual functioning associated with treatment of drugs from these two categories.

TABLE X
THE EFFECTS OF STIMULANTS ON MALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Amphetamine	150-250 mg, —	chronic drug use	increase in atypical sexual behavior	20+	Bell & Trethowan 1961; Ellinwood & Rockwell 1975; Ellinwood 1967; Gossop, Stern & Connell 1974; Greaves 1972; Knapp 1952; Gay & Sheppard 1973; Ellinwood 1967
	—	chronic drug use	spontaneous erection	—	
	>30 mg, 3 mos.	chronic drug use, psychotic symptoms	increase in sexual desire, increase in atypical sexual behavior	10	
	>30 mg, 3 mos.	chronic drug use, no psychotic symptoms	decrease in sexual desire, no effect	8	Ellinwood 1967
	60 mg, —	chronic drug use	impotence	1	Bell & Trethowan 1961
	1000 mg, —	chronic drug use	increase in sexual desire	10	Angrist & Gershon 1976; Bell & Trethowan 1961
	—	chronic drug use	delayed ejaculation	8	Angrist & Gershon 1976; Bell & Trethowan 1961; Smith, Buxton & Dammann 1979
	—	chronic drug use	increase in sexual desire, delayed ejaculation	20+	Buffum 1982; Cocores et al. 1988; Grinspoon & Bakalar 1976; Smith, Wesson & Apter-Marsh 1984; Wesson 1982; Siegel 1977
Cocaine	—	chronic cocaine use	erectile difficulty, situational impotence	40+	Cocores et al. 1988; Ellinwood & Rockwell 1975; Siegel 1982a,b; Smith, Wesson & Apter-Marsh 1984; Wesson 1982
	—	chronic cocaine use	increase in atypical sexual behavior	—	Smith, Wesson & Apter-Marsh 1984
	—	chronic cocaine use	spontaneous erection	—	Gay & Sheppard 1973
	—, 3 mos.	chronic cocaine use	decrease in sexual desire	31/50	Cocores et al. 1988
	—, 3 mos.	cocaine & alcohol abuse	premature ejaculation	4/50	Cocores et al. 1988
	—, 3 mos.	cocaine & alcohol abuse			

THE EFFECTS OF STIMULANTS ON MALE SEXUAL BEHAVIOR

Amphetamine

Amphetamine is used in the treatment of narcolepsy and in the treatment of attention-deficit disorder with hyperactivity in children. Additionally, amphetamine is used in the short-term treatment of obesity and as a recreational drug to combat fatigue, or to "replace sleep" (McEvoy 1990).

Amphetamine is a CNS stimulant. Peripherally, it has both α - and β -adrenergic activity; centrally it inhibits monoamine oxidase and blocks the uptake of catecholamines and serotonin. In addition, amphetamine may have a direct effect on norepinephrine receptors and may cause a decrease in dopamine synthesis. It is generally believed that the primary effect of amphetamine involves a release of dopamine (McEvoy 1990).

Sexual Desire. Changes in sexual desire have been reported in association with amphetamine use (Smith, Buxton & Dammann 1979; Ellinwood & Rockwell 1975; Greaves 1972; Ellinwood 1967; Bell & Trethowan 1961; Waud 1938) (see Table X). In a study conducted by Ellinwood and Rockwell, six of 12 patients (gender and dosage not indicated) using amphetamine experienced an increase in sexual desire, four experienced a decrease, and two exhibited no apparent change. Similarly, Angrist and Gershon (1970) stated that in a study of 43 male amphetamine users, nine reported an increase in sexual desire, two reported a decrease, and two reported no change. It should be noted that in a large portion of reported cases,

increases in sexual desire were reported concurrently with increases in promiscuity, compulsive masturbation, sado-masochistic fantasies, pedophilia, prostitution, and genital mutilation (Ellinwood & Rockwell 1975; Gossop, Stern & Connell 1974; Greaves 1972; Ellinwood 1967; Bell & Trethowan 1961; Knapp 1952). In one reported case (Ellinwood 1967), patients without psychotic symptoms experienced a decrease in sexual desire, while those with psychotic symptoms experienced an increase in both desire and atypical sexual behavior.

Erectile Capacity. Of the cases reviewed, only one case of erectile difficulty was reported in association with amphetamine use (Bell & Trethowan 1961). The patient, who became impotent when taking amphetamine, had a history of repressed homosexuality. In addition, one report has been made of spontaneous erections following an intravenous injection of amphetamine (Gay & Sheppard 1973).

Ejaculation. Cases of delayed ejaculation have been reported in association with amphetamine use (Smith, Buxton & Dammann 1979; Angrist & Gershon 1976; Bell & Trethowan 1961). In a study by Angrist and Gershon, seven of 43 male amphetamine users experienced this side effect. Ellinwood (1967) mentioned that patients using amphetamine described increases in sexual desire "... as a driven state, in which orgasm was either absent or prolonged for hours."

Cocaine

Cocaine is used topically to produce local anesthesia. In addition, because of the euphoric effects associated with cocaine use, it is often used as a recreational drug. Cocaine

TABLE XI
THE EFFECTS OF STIMULANTS ON FEMALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Amphetamine	—	chronic drug use	delayed orgasm	1	Bell & Trethowan 1961
	150-350 mg, —	chronic drug use	increase in sexual desire, increase in atypical sexual behavior, decrease in sexual satisfaction	10+	Bell & Trethowan 1961; Ellinwood & Rockwell 1975; Ellinwood 1967; Greaves 1972
	—	chronic drug use	increase in sexual desire & activity	8/17	Angrist & Gershon 1976
	100-700 mg, 6 mos.	chronic drug use	decrease in sexual desire, increase in atypical sexual behavior	2	Knapp 1952
Cocaine	compulsive use, 6 mos.	chronic drug use	anorgasmia	1	Siegel 1982a
	—	chronic drug use	increase in orgasmic ability	20%	Smith, Wesson & Apter-Marsh 1984
	—	chronic drug use	increase in sexual desire, increase in atypical sexual behavior, decrease in sexual satisfaction		Siegel 1982a,b; Smith, Wesson & Apter-Marsh 1984

blocks the uptake of monoamine neurotransmitters and has CNS-stimulating effects (McEvoy 1990).

Sexual Desire. Both increases (Buffum 1982; Wesson 1982; Grinspoon & Bakalar 1976) and decreases (Cocores et al. 1988) in sexual desire resulting from cocaine use have been reported (see Table X). In a study by Siegel (1977), 11% of the 85 social users of cocaine surveyed experienced increases in sexual desire and stimulation as a result of the drug. Some males reported having used the drug for specific purposes; of these, 42% stated that they used it to enhance sexual performance. In his study of cocaine use in prostitution parlors, Wesson reported that clients experienced an increase in sexual desire and sensations as a result of cocaine use.

Contrary to these findings, in a study conducted by Cocores and colleagues (1988), 62% of the 50 cocaine users surveyed reported a decrease in sexual desire in comparison to their predrug state. It should be noted, however, that the population studied was dually-addicted to both cocaine and alcohol. Consistent with the results of this study, Siegel (1982b) reported that when the sexual partners of 23 cocaine smokers were interviewed, all reported that their partners had experienced episodes of sexual disinterest.

Erectile Capacity. Several cases of erectile difficulty have been described in association with cocaine use (Cocores et al. 1988; Smith, Wesson & Apter-Marsh 1984; Siegel 1982a,b; Wesson 1982; Ellinwood & Rockwell 1975). Wesson (1982) reported that despite reports of heightened sexual desire, cocaine increased the difficulty of achieving an erection. Similarly, 52% of the 50 abusers of cocaine and alcohol surveyed by Cocores and colleagues reported erectile difficulty and/or impotence. In contrast to these findings, Gay and Sheppard (1973) reported cases of spontaneous erections following intravenous cocaine injection.

Ejaculation. Delayed ejaculation appears to be the most common sexual side effect of cocaine use (Cocores

et al. 1988; Smith, Wesson & Apter-Marsh 1984; Buffum 1982; Siegel 1982a; Wesson 1982). There are several reported cases of "pleasurable delay in orgasm" (Grinspoon & Bakalar 1976) resulting from cocaine use. Wesson found that clients of the prostitution parlors studied used cocaine to specifically inhibit ejaculation in an effort to prolong the period of sexual excitation. Smith, Wesson & Apter-Marsh reported that 65% of the cocaine users surveyed indicated that the drug facilitated orgasm, while the remaining 35% reported that cocaine impaired ejaculatory ability. Similarly, Cocores and colleagues noted that 30% of 50 cocaine and alcohol abusers experienced inhibition of ejaculation and 8% experienced premature ejaculation.

THE EFFECTS OF STIMULANTS ON FEMALE SEXUAL BEHAVIOR

Amphetamine

Sexual Desire. Both increases (Buffum 1982; Ellinwood & Rockwell 1975; Greaves 1972; Ellinwood 1967; Bell & Trethowan 1961) and decreases (Knapp 1952) in sexual desire have been reported as resulting from amphetamine use (see Table XI). Angrist and Gershon (1976) reported that eight of 17 females studied experienced increased sexual desire and activity. One patient reported decreased sexual feelings and activity resulting from amphetamine use. In a study by Bell and Trethowan, three sexually inhibited patients noted that their sexual desire was enhanced under the influence of amphetamine. Ellinwood reported that increases in sexual desire and atypical sexual activities, such as extreme masochism, were most prevalent in female amphetamine users who, when abstaining from the drug, were sexually inhibited. Several other cases of increased sexual behavior as well as increased promiscuity, compulsive masturbation, prostitution, and sadomasochism resulting from amphetamine use have been reported (Ellinwood & Rockwell 1975;

Gossop, Stern & Connell 1974; Greaves 1972; Bell & Trethowan 1961). Despite many reports of increases in sexual desire and activity, there seems to be a "general disenchantment" with sex among female amphetamine users (Greaves 1972). It is possible that this attitude toward sex preceded their amphetamine use.

Orgasm. Changes in orgasm resulting from amphetamine use appear relatively infrequently (Buffum 1982; Bell & Trethowan 1961). Bell and Trethowan reported a case in which the patient experienced "delayed orgasm sometimes for as long as nine hours."

Cocaine

Sexual Desire. Changes in sexual desire resulting from cocaine use have been reported (Smith, Wesson & Apter-Marsh 1984; Siegel 1982a,b) (see Table XI). In a study by Smith, Wesson and Apter-Marsh, 20% of the female cocaine and alcohol users surveyed reported that the drug enhanced sexual desire, while 80% felt that cocaine decreased desire. Changes in desire have been reported concurrently with atypical sexual behavior and a decrease in sexual satisfaction.

Orgasm. Smith, Wesson and Apter-Marsh (1984) reported that 20% of the female cocaine and alcohol users surveyed felt that cocaine enhanced orgasmic ability. In contrast, one case of total anorgasmia (Siegel 1982a) has been clearly associated with cocaine use (see Table XI).

SUMMARY OF THE EFFECTS OF STIMULANTS ON MALE AND FEMALE SEXUAL BEHAVIOR

Several considerations must be taken into account when assessing stimulant-induced sexual functioning. First, amphetamine addicts differ from the normal population in that they have a higher incidence of antisocial, schizoid, and paranoid personalities (Ellinwood 1967). In addition, amphetamine-dependent persons tend to have a higher incidence of sexual identity problems (Mott 1972). Second, it should be noted that changes in sexual desire resulting from amphetamine use appear to bear a close relationship to the patient's preexisting sexual adjustment. Patients who are sexually inhibited prior to amphetamine use experience a lessening in inhibition, and patients involved in atypical sexual practices, such as extreme sadomasochism and incest, seem to experience an exaggeration of the behavior. No studies have examined amphetamine-induced sexual side effects in a population free of psychological and sexual disturbances. Given these factors, it is difficult to assess adequately the effects of amphetamine on sexual functioning.

From a review of the preceding literature, sexual side effects resulting from amphetamine and cocaine use ap-

parently are highly variable and somewhat contradictory. Increases and decreases in desire, spontaneous erections, and impotence have all been reported in association with stimulant use. This diversity of sexual effects may be a function of drug dose. Although few studies report the dosage or duration of drug use, it has been noted (Piemme 1976; Ellinwood & Rockwell 1975) that both the dose and chronicity of use are important considerations of the drug response. One report (Ellinwood & Rockwell 1975) suggested that the drug facilitates sexual behavior at low doses and inhibits sexual behavior at high doses. This pattern of dose response is seen with many drugs that influence sexual behavior.

In addition to drug dose and duration, other factors must be considered. For example, a sexually inhibited individual may find a lowering of inhibitions as a result of drug use; consequently, sexual desire or enjoyment may be enhanced through this mechanism alone. Similarly, the euphoria and floating sensation associated with use of stimulant drugs (Siegel 1982a; Hollister 1975) may heighten or imitate the experience of orgasm. The mode in which the person uses the drug, the individual's sexual history, the social setting, and even the user's expectations can influence the drug's effect on sexual performance (Piemme 1976). These variables complicate the assessment of stimulant-induced alterations in sexual behavior. As no controlled studies have been conducted using these drugs, interpretations must be made on highly speculative findings.

Based on the studies reviewed, three consistent findings appear with respect to stimulant drugs. First, relative to various control groups, both male and female stimulant users participate in atypical sexual practices with much higher frequency. It appears that certain behaviors, such as exhibitionism, promiscuity, sadomasochism, and incest become amplified with stimulant use. Second, the most common sexual side effect resulting from stimulant use is a delay or inhibition of ejaculation. However, this sexual response to amphetamine may be a direct consequence of the dose, rate of administration and/or duration of use (Smith, Buxton & Dammann 1979). Finally, there is a pronounced difference in sexual attitudes between male and female users. While male stimulant users seem to hold a positive view toward sex, female users express negative views and a general dissatisfaction with their sexual situation (Ellinwood & Rockwell 1975; Gossop, Stern & Connell 1974; Greaves 1972; Knapp 1952).

DISCUSSION

Little consideration has been given to the possible neurochemical changes related to the sexual behavior of amphetamine and cocaine users. An understanding of the stimulant-induced neurotransmitter alterations may contribute to an understanding of how these drugs influence

sexual functioning.

Several studies have associated the catecholamines, dopamine and norepinephrine, with the behavioral effects of amphetamine (Buffum 1982; Scheel-Kruger 1972; Fuxe & Ungerstedt 1970; Welch & Welch 1970). Studies have shown that amphetamine releases these transmitters (Carr & Moore 1970; Glowinski 1970; Besson, Cheramy & Glowinski 1969; Carlsson et al. 1969; Fuxe & Ungerstedt 1968) and produces an inhibition of reuptake (Glowinski 1970; Carlsson et al. 1969; Fuxe & Ungerstedt 1968). These and other effects of amphetamine, such as dopamine receptor upregulation, may contribute to sexual dysfunction. Amphetamine has also been reported to influence serotonergic activity. Some reports have found amphetamines to elevate brain serotonin (Welch & Welch 1970), while others have reported a decrease in serotonin levels resulting from amphetamine use (Laverty & Sharman 1965; Pletscher et al. 1964). Welch and Welch reported that within five minutes of the administration of amphetamine, norepinephrine, dopamine, and serotonin levels were all significantly elevated. Measures taken 45 minutes later provided different results; norepinephrine and dopamine were lowered significantly and only serotonin remained elevated. The authors concluded that the serotonergic response to amphetamine is biphasic; at moderate doses amphetamine increases serotonin levels and at large doses it decreases serotonin levels.

The hypothesis that the serotonergic response to amphetamine is biphasic has been strongly supported by a number of studies (Jacobs & Trulson 1973; Fuxe & Ungerstedt 1970). Jacobs and Trulson repeatedly administered high doses of amphetamine to cats and observed a number of unique behaviors. Two of these behaviors, limb flicking and abortive grooming, are specifically dependent on a depression of central serotonergic neurotransmission. This finding was confirmed by a neurochemical analysis that showed serotonin levels decreased by 37%. It is interesting to note that single injections, regardless of the dosage, did not produce these behavioral effects. Similar behavioral findings, which reflect a decrease in serotonin levels, have been reported by Ellinwood and Kilbey (1977) and Sloviter, Drust and Connor (1978).

Based on the preceding studies, it appears that both dosage and chronicity play a role in the serotonergic effects of amphetamine; low doses increase serotonin, high doses decrease it and, while acute doses appear to have no effect, chronic administration lowers the level of serotonin. It is interesting to note that, in animal studies, a biphasic sexual effect has also been shown in response to amphetamine treatment. Low doses of amphetamine have been shown to facilitate sexual behavior and high doses have been shown to inhibit it.

With respect to cocaine, many studies have characterized the drug as a potent monoamine uptake blocker

(Hanson et al. 1989; Reith et al. 1985; Reith et al. 1983). In a study assessing [^3H] cocaine binding, Reith and colleagues (1983) reported that there was no correlation between the inhibition of cocaine binding and the uptake of dopamine or norepinephrine. However, the study showed a significant correlation between the inhibition of cocaine binding and the inhibition of serotonin uptake. In addition, this study suggested an association between cocaine binding and serotonergic nerve terminals. The authors hypothesized that serotonergic neurons may mediate some of the behavioral effects resulting from cocaine use.

THE SEROTONERGIC ACTIVITY OF STIMULANTS

There are few studies that assess the specific serotonergic binding sites that may be altered as a result of cocaine and amphetamine use. Although cocaine is known to be a relatively weak antagonist of 5-HT₃ receptors (Watling 1989), most research on the serotonergic effects of these drugs has emphasized overall measures of serotonin levels and blockade of reuptake. As previously discussed, amphetamine appears to increase and decrease serotonin at low and high doses respectively and to produce little effect with single administrations. It is difficult to link this finding to changes in sexual functioning that result from use of these drugs, as much of the published literature fails to reveal both the dosage and duration of drug use. It is interesting to note, however, that depending on the dosage administered these drugs have been shown to have opposite effects: they facilitate sexual functioning at low doses and inhibit sexual functioning at high doses. It is possible that these differential effects reflect changes in serotonin levels. It is also possible that low doses of these drugs facilitate sexual behavior by means of their disinhibiting and euphoric effects and that at higher doses, central serotonergic mechanisms mask these effects and cause a decline in sexual functioning.

THE EFFECTS OF MISCELLANEOUS DRUGS ON MALE SEXUAL BEHAVIOR

Buspirone

Buspirone is used in the treatment of anxiety and phobic neurosis and for the short-term relief of anxiety symptoms. Buspirone affects several central neurotransmitter systems, including serotonergic, dopaminergic, and noradrenergic systems (McEvoy 1990).

Sexual Desire. In a small uncontrolled study, Othmer and Othmer (1987) assessed the effects of buspirone on nine patients (three males, six females) with generalized anxiety disorder and impaired sexual function (see Table XII). The patients received increasing doses of buspirone up to a max-

TABLE XII
THE EFFECTS OF MISCELLANEOUS DRUGS ON MALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT PRIOR TO DRUG ADMINISTRATION	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Buspirone	60 mg, 4 wks.	generalized anxiety disorder and sexual dysfunction	increase in sexual functioning	3	Othmer & Othmer 1987
Danitracen	3 mg, 4 wks.	impotence	no effect	20	Benkert 1980
Fenfluramine	120 mg, 3 mos. 240 mg, 12-20 wks.	anxiety obesity	decrease in sexual desire decrease in sexual desire	14 3	Hughes 1971 Sproule 1971
Lisuride	.075 mg, 4 wks.	chronic renal failure, hyperprolactinemic	increase in sexual desire, increase in sexual activity	8/10	Ruilope et al. 1985
	.075 mg, 4 wks.	chronic renal failure, normoprolactinemic	increase in sexual desire, increase in sexual activity	6/10	Ruilope et al. 1985
Methysergide	6 mg, 4 wks.	impotence	no effect	10	Benkert 1980
PCPA	.5 g + testosterone, 4 wks.	impotence	no effect	5	Benkert 1980
	500-3000 mg, 5 days	prison inmate volunteers	no effect	9	Cremata & Koe 1966
	—	cancer	no effect	—	Sjoerdama et al. 1970
	1 g, 4 wks.	impotence	no effect	20	Benkert 1980
	1 g + placebo or 25 mg of testosterone, 20 days	migraine headache, decrease in sexual desire and activity	increase in sexual functioning	20	Sicuteri 1974
	PCPA + testosterone, 10 days	impotence	erectile ability	2	Sicuteri 1974
	chronic administration	migraine headache	increase in sexual desire, erectile ability	3/32	Sicuteri 1974
Tryptophan	100 mg/kg	normal	no effect	2	Hyypya 1976
	1.5-2.0 g, 1 mos.	multiple sclerosis	no effect	—	Hyypya 1976
	3 g, —	schizophrenia, paranoid psychosis	sexual disinhibition	4	Egan & Hammad 1976
	—	normal	sexual disinhibition	2	Oswald 1976
	3 g, 2 wks.	headache, compulsive sexual behavior	decrease in sexual compulsion	1	Sicuteri 1974
	3 g, 1 mos.	headache	decrease in sexual desire, inhibition of ejaculation	1	Sicuteri 1974
	—	psychosis, depression	sexual disinhibition	5+	Hyypya 1976; Kent 1981

imum of 60 mg/day. After four weeks of treatment, eight of the nine dysfunctional patients reported a restoration of sexual function. The degree of improvement was independent of, and more pronounced than, the drug's anxiolytic effect. Thus, it is unlikely that the normalization of sexual function was secondary to this effect. Unfortunately, the study did not specify the type of sexual dysfunction experienced by the patients. Sexual function was assessed according to the Sexual Evaluation Scales (SES).

Danitracen

Danitracen has both peripheral and central serotonin-inhibiting effects (Benkert 1980).

Erectile Capacity. In a double-blind cross-over study conducted by Benkert (1980), the effects of danitracen on 20 patients with sexual impotence were assessed. During an eight-week period, subjects received 3 mg/day of danitracen for four weeks, followed by four weeks of a placebo. Results failed to reveal a difference in sexual functioning between the placebo and danitracen administration periods.

Fenfluramine

Fenfluramine is used in the short-term treatment of obesity. It is an anorectic agent that—unlike amphetamine

— produces CNS depression rather than stimulation. In addition, fenfluramine increases serotonin release and blocks its reuptake (McEvoy 1990).

Sexual Desire. A decrease in sexual desire has been reported in association with fenfluramine treatment. Hughes (1971) reported that several of 14 patients experienced a loss of sexual desire at a dosage of 120 mg/day. Similarly, Sproule (1971) reported a loss of sexual desire in patients at a higher dosage of 240 mg/day. It should be noted, however, that the decrease in sexual desire may be secondary to other side effects of fenfluramine, such as dysphoria, abdominal distension and cramps, constipation, and anxiety (O'Keane & Dinan 1991).

Erectile Capacity. Hollingsworth and Amatruda (1969) reported that two of 33 patients studied experienced impotence as a result of fenfluramine treatment.

Lisuride

Lisuride has been used in the treatment of hyperprolactinemia. It is a dopaminergic agonist and a potent stimulator of serotonin-sensitive adenylate cyclase activity. Lisuride acts as both a serotonin agonist and antagonist (Rosenfeld & Makman 1981).

Sexual Desire. Ruilope and colleagues (1985) studied the effects of lisuride on the sexual functioning of 20 pa-

tients with chronic renal failure. Ten of these patients had elevated prolactin levels. The patients received 0.075 mg/day of lisuride for a period of four weeks. Of the hyperprolactinemic patients, 80% experienced an increase in sexual desire and 60% reported an increase in sexual activity as a result of lisuride treatment. Of the patients with normal prolactin levels, 40% reported an increase in sexual desire and 20% reported an increase in sexual activity resulting from the drug treatment.

Methysergide

Methysergide is used in the management of vascular headaches, including migraine and cluster headaches. In addition, methysergide has been used to control diarrhea in patients with carcinoid disease (McEvoy 1990). Moreover, it is a potent serotonin antagonist at 5-HT₁ and 5-HT₂ receptors.

Sexual Desire and Erectile Capacity. In an uncontrolled study conducted by Benkert (1980), the effects of methysergide on ten sexually impotent patients were assessed. The patients received 6 mg/day of methysergide over a four-week period. Two patients showed an increase in sexual desire, and two others showed an increase in erectile ability. As noted by the author, however, these results do not exceed those expected from a placebo.

Parachlorophenylalanine

Parachlorophenylalanine (PCPA) is an inhibitor of serotonin synthesis and has been used in the treatment of migraine headaches.

Sexual Desire. One study reported an increased interest in sex as a result of PCPA treatment (Sicuteri 1974). The drug was administered to a group of 32 migraine headache sufferers. Three patients (two male, one female) reported an increase in sexual desire and excitement as a result of PCPA treatment. Low doses of PCPA have been administered to carcinoid patients (Sjoerdsma et al. 1970) and to prison inmate volunteers (Cremata & Koe 1966) with no reported changes in sexual interest. As mentioned by Gessa and Tagliamonte (1974), the possibility exists that dosages were insufficient to cause changes in sexual functioning or the social conditions were unfavorable for assessing sexual behavior.

Erectile Capacity. The effects of PCPA on sexual functioning were assessed in a study conducted by Sicuteri (1974). Twenty (20) patients suffering from migraine headaches and decreased interest in sexual desire and activity were treated with PCPA. The drug was administered alone or combined with either a placebo or testosterone. Ten patients received one gram of PCPA and a placebo for ten days followed by ten days of treatment with one gram of PCPA and 25 mg of testosterone. The remaining ten patients received a placebo for ten days followed by ten days of treatment with 25 mg/day of testosterone and a placebo.

Results indicated that the placebo alone had little effect on the frequency of daily erections. Testosterone increased the number of erections, recorded over the ten-day period, from a baseline of five to 15. However, testosterone in combination with PCPA showed the most dramatic increase; the frequency of daily erections increased from a baseline of six to 36.

Two other cases report an increase in erectile ability resulting from PCPA administration (Sicuteri 1974). One patient suffering from migraine headache and a two-year history of complete impotence was put on PCPA treatment. During the first ten days of drug therapy the patient reported an increase in sexual desire and ability to maintain an erection. When PCPA was supplemented with testosterone the patient's sexual motivation was amplified.

The effectiveness of PCPA in the treatment of impotence has not been confirmed in controlled studies. In a double-blind study conducted by Benkert (1980), the effects of PCPA on sexual function were assessed in ten patients with sexual impotence. All patients received a placebo for the first two weeks, after which five patients received one gram/day of *l*-PCPA for an additional four weeks, and five patients continued on the placebo. All ten patients then received a placebo for a final two-week period. Results indicated that PCPA was no more effective than the placebo in alleviating sexual impotence. In a similar study, Benkert (1980) showed that PCPA, in combination with testosterone, was no more effective than placebo plus testosterone.

Tryptophan

L-tryptophan has been used as a hypnotic agent to reduce sleep latency, increase sleep time, and to decrease the number of awakenings. Less commonly, it has been used as an antidepressant (Kastrup 1989). *L*-tryptophan is a serotonin precursor.

Sexual Desire. Changes in sexual desire and activity resulting from *l*-tryptophan treatment have been reported in several cases (Kent 1981; Egan & Hammad 1976; Hyypä 1976; Oswald 1976). Egan and Hammad reported that four patients (three with schizophrenia, one with paranoid psychosis) became sexually disinhibited while receiving 3 g/day of *l*-tryptophan. Sexual behavior was controlled in all four cases when the dosage was lowered to 1.5 g/day. Similarly, both Hyypä and Kent reported that *l*-tryptophan caused sexual disinhibition among both psychiatric and depressed patients. In addition, Oswald reported patients' "lewd and libidinous behavior" after oral administration of *l*-tryptophan. Contrary to these findings, Hyypä reported no change in sexual desire among multiple sclerosis patients receiving 1.5-2.0 g/day of *l*-tryptophan. Likewise, Hyypä did not experience a change in sexual desire after having ingested 100 mg/kg of *l*-tryptophan. Discordant with the above studies, Sicuteri (1974)

TABLE XIII
THE EFFECTS OF MISCELLANEOUS DRUGS AND TREATMENTS ON FEMALE SEXUAL BEHAVIOR

DRUG	DOSE AND DURATION PRIOR TO REPORTED EFFECT	STATE OF SUBJECT PRIOR TO DRUG ADMINISTRATION	REPORTED EFFECTS	NUMBER OF PATIENTS	REFERENCES
Buspirone	60 mg, 4 wks.	generalized anxiety disorder, sexual dysfunction	increase in sexual functioning	5	Othmer & Othmer 1987
ECT	5 treatments	depression	increase in sexual desire and activity	1	Hullin & Jerram 1976
Fenfluramine 1990	60-120 mg, 4 days	bulimia	increase in sexual desire and activity	2	Stevenson & Solym
	240 mg, 12-20 wks.	obesity	decrease in sexual desire	17	Sproule 1971
LSD	25-100 ug/wk., 3 wks.	sexual inhibition	increase in sexual functioning	5	MacCallum 1968
PCPA	chronic administration	migraine headache	increase in sexual excitement	1	Sicuteri 1974
Tryptophan	6 g, 1 wk.	psychotic depression	no effect	1	Hullin & Jerram 1976
	15 g, 3 wks.	schizophrenia (also receiving MAOI's)	increase in sexual desire, increase in atypical sexual behavior	5/7	Lovett Doust & Huszka 1972

described a patient, suffering from migraine headaches, who experienced a decrease in sexual desire and activity after one to two months of 3 g/day of tryptophan. Sexual activity returned to normal after tryptophan treatment was discontinued.

Ejaculation. One case of inhibited ejaculation has been reported in association with 3 g/day of tryptophan (Sicuteri 1974). The patient denied experiencing sexual dysfunctions prior to the drug administration. Discontinuation of tryptophan led to an alleviation of the symptoms.

THE EFFECTS OF MISCELLANEOUS DRUGS AND TREATMENTS ON FEMALE SEXUAL BEHAVIOR

Buspirone

Buspirone has been reported to improve sexual functioning in patients suffering from a history of sexual dysfunction and generalized anxiety disorder (Othmer & Othmer 1987) (see Table XIII). The dosage administered was 60 mg/day for a period of four weeks.

Electroconvulsive Therapy

An increase in sexual desire and activity has been reported in association with electroconvulsive therapy (ECT) (Hullin & Jerram 1976). The patient received 6 g/day of *l*-tryptophan, which was later followed by five ECT treatments. While the *l*-tryptophan therapy had no effect on sexual behavior, ECT led to a dramatic change. The patient experienced an increase in sexual desire and activity, which subsided over a three-week period. Later treatment with *l*-tryptophan failed to have an effect on sexual behavior, and thus the reported change cannot be attributed to the administration of *l*-tryptophan. However, it is possible that this effect was secondary to the alleviation of depression.

Fenfluramine

A loss of sexual desire resulting from 240 mg/day of

fenfluramine has been reported (Sproule 1971). Sproule suggested that approximately 85% of women receiving fenfluramine experience this difficulty as a direct result of the treatment. In contrast to the above report, Stevenson and Solym (1990) reported two cases of increased sexual desire resulting from fenfluramine treatment. One patient reported frequent sexual arousal at 60 mg/day and at 120 mg/day she reported a total preoccupation with sex. When treatment was discontinued, she was still more frequently aroused for the first five days, but by the seventh day she returned to her accustomed level of sexual arousal. Reinstatement of the drug treatment led to the same increase in libido and sexual response within four days.

Lysergic Acid Diethylamide

Lysergic acid diethylamide (LSD) is a hallucinogenic drug used for the recreational purpose of enhancing sensations and reducing inhibitions. It is both a serotonin agonist and antagonist depending on which serotonin receptor is activated and its location in the CNS. In addition, it has been shown to depress the activity of nor-epinephrine-containing neurons and to act as a dopamine agonist (Jacobs & Trulson 1973).

Sexual Desire. In a study conducted by MacCallum (1968), LSD was shown to enhance sexual functioning among five patients with psychosexual disorders. Prior to LSD treatment, all patients experienced an aversion to sex and consequently, although married, had abstained from sexual intercourse for several years. After approximately two months of treatment with 25-100 ug of LSD/week, the reported sexual inhibition was reduced and normal sexual relations resumed in all patients.

Parachlorophenylalanine

In a study of 32 patients with untractable essential headache, three patients (one female, two male) reported an increase in sexual excitement as a result of parachlorophenylalanine (PCPA) treatment (Sicuteri 1974). It is possible that this effect was secondary to a re-

duction in the number of headaches experienced.

Tryptophan

Aphrodisiac effects have been reported in association with *l*-tryptophan therapy at a dosage of 15 g/day (Lovett Doust & Huszka 1972). Five of seven schizophrenic patients showed an increase in sexual desire and atypical sexual behavior as a result of *l*-tryptophan treatment. It should be noted, however, that the patients were also receiving treatment with MAOIs. Hullin and Jerram (1976) reported a case in which a schizophrenic patient received 6 g/day of *l*-tryptophan with no change in sexual desire or behavior.

SUMMARY OF THE EFFECTS OF MISCELLANEOUS DRUGS AND TREATMENTS ON MALE AND FEMALE SEXUAL BEHAVIOR

Of the drugs reviewed, it appears that buspirone and lisuride facilitate sexual behavior, fenfluramine facilitates or inhibits it, and while the reports are very limited, methysergide shows a modest facilitation of sexual behavior and danitracen shows no effect. It also appears that ECT can enhance sexual desire, although this finding has been reported in only one case.

An increase in sexual desire and activity and a disinhibition of sexual behavior are seen with tryptophan, serotonin, and LSD treatment. However, there are factors that should be considered when interpreting these results. First, LSD causes CNS stimulation and euphoric effects that may alter sexual functioning. Second, as noted by Benkert (1980), while short-term LSD use may facilitate sexual behavior, chronic use of this drug commonly results in a decline in sexual functioning. It should also be noted that most reports of increased sexual desire and behavior following *l*-tryptophan treatment are among schizophrenic and psychiatric patients. Although several studies have examined the sexual side effects in multiple sclerosis and normal patients, none have found similar effects.

Studies concerning PCPA reveal a facilitatory effect of the drug on sexual behavior in both male and female essential headache sufferers. Interestingly, the drug does not appear to affect sexual behavior in carcinoid or normal persons. As noted by Buffum (1982), migraine sufferers have both a decrease in sexual desire and an increase in serotonin levels. Perhaps then, PCPA has a facilitatory effect only when serotonin levels are initially abnormally high.

DISCUSSION WITH REFERENCE TO THE SEROTONERGIC ACTIVITY OF MISCELLANEOUS DRUGS

Many of the drugs previously reviewed exert their primary effects by means of serotonergic systems. Methysergide (Klawans, D'Amiga & Patel 1975) and dan-

itracen (Benkert 1980) are serotonin antagonists, while fenfluramine releases serotonin and blocks serotonin reuptake, thus acting as an agonist (Pinder et al. 1975). PCPA is a relatively selective depletor of brain serotonin (Koe & Weissman 1966) and tryptophan is a serotonin precursor (Carlson 1986). In the case of LSD, depending on the serotonin receptor subtype activated, it may act as either a serotonin agonist or antagonist (Gorzalka, Mendelson & Watson 1990).

The agonistic and antagonistic effects of these drugs correlate, to some degree, with the sexual side effects that result from their usage (see Table XIV). Methysergide and PCPA are antagonists and facilitate sexual behavior, fenfluramine is an agonist and inhibits it, and LSD is both an agonist and antagonist and has been shown to both enhance and cause a decline in sexual functioning. While one might expect the agonist *l*-tryptophan to decrease sexual functioning, results are conflicting; some studies report an increase while others report no effect. This may be attributable in part to the fact that, in addition to being a 5-hydroxytryptophan and serotonin precursor, *l*-tryptophan is a precursor to *l*-kynurenine and kynuramine. While serotonin has been shown to inhibit sexual behavior in the female rat, *l*-kynurenine and kynuramine have been shown to facilitate lordosis behavior (Mendelson, Lee & Gorzalka 1987).

Information on the specific receptor subtype activated by these drugs would better elucidate the role each plays in human sexual behavior. However, methysergide and LSD are relatively nonselective in binding to the various serotonin receptor subtypes (Gorzalka, Mendelson & Watson 1990), and PCPA inhibits serotonin synthesis without necessarily having an effect on serotonin binding sites (Cremata & Koe 1966).

Animal studies that have examined the effects of these drugs on sexual behavior have shown that, in the male rat, methysergide either facilitates sexual behavior or has no effect; in the female rat, methysergide is mainly inhibitory, although it may also facilitate or have no effect on lordosis behavior depending on the interval between administration and testing (Mendelson & Gorzalka 1986d). Studies that have assessed the effects of PCPA on rat sexual behavior have shown that the drug enhances sexual behavior in males with a low but not high baseline level of sexual activity (Gessa & Tagliamonte 1974). LSD has been shown to facilitate or inhibit lordosis behavior in the female rat depending on the dose (Sietnieks & Meyerson 1983). Similarly, in the male rat, LSD has been reported to inhibit sexual behavior at higher doses and to cause a modest facilitation at low doses (Gorzalka, Mendelson & Watson 1990). The differential effects of low versus high doses of LSD on sexual behavior in the rat may perhaps be analogous to the differential effects of acute versus chronic effects seen in human sexual behavior.

Unlike the previously mentioned drugs, buspirone and lisuride influence several monoaminergic systems, and

TABLE XIV
DRUG EFFECTS ON SEROTONIN AND HUMAN SEXUAL BEHAVIOR

DRUG	EFFECT ON MALE SEXUAL BEHAVIOR			EFFECT ON FEMALE SEXUAL BEHAVIOR		EFFECT ON SEROTONERGIC ACTIVITY
	SEXUAL DESIRE	ERECTILE CAPACITY	EJACULATION	SEXUAL DESIRE	ORGASM	
Antidepressants						
Tricyclics						
Amiripityline	↓	↓	↓	—	↓	↑
Amoxapine	↓	↓	↓	—	↓	↑
Cloimipramine	↓	↓	↓	↓	↓	↑
Desipramine	—	↓	—	↑	↓	↑
Imipramine	↓	↓	↓	↓	↓	↑
MAO Inhibitors						
Isocarboxazid	—	—	↓	—	↓	↑
Pargyline	—	—	↓	—	—	↑
Phenelzine	↓	↓	↓	—	↓	↑
Tranylcypromine	—	↓	↓	—	—	↑
Atypical Antidepressants						
Cyproheptadine	—	—	↑	—	↑	↓(↑?)
Fluoxetine	—	—	↓	—	↓	↑
Sertraline	—	—	↓	—	—	↑
Trazodone	—	—	↓	↑	↓	↓
Drugs Used In Bipolar Depression						
Lithium	0	↓	↑	0	0	↓
Major Tranquillizers						
Phenothiazines						
Chlorpromazine	↓	↓	↓	—	↓	↓
Thioridazine	↓	↓	↓	↓	↓	↓
Trifluoperazine	—	—	0/↑	—	↓	↓
Thioxanthenes						
Chlorprothixene	—	—	0/↓	—	—	↓
Stimulants						
Amphetamine	↓	↓	↓	↓	↓	↑
Cocaine	↓	↓	↓	↓	↓	↑
Miscellaneous Drugs and Treatments						
Bupirone	↑	—	—	↑	—	—
Danitracen	—	0	—	—	—	↓
ECT	—	—	—	↑	—	—
Fenfluramine	↓	↓	—	↓	—	↑
Lisuride	↑	—	—	—	—	↓
LSD	—	—	—	↓	—	↓
Methysergide	(↑?)	(↑?)	—	—	—	↓
PCPA	0/↑	0/↑	—	↑	—	↓
Tryptophan	0/↓	—	↓	0/↑	—	↑
EFFECT ON SEXUAL BEHAVIOR						
↑ = facilitates						
↓ = inhibits						
0 = no effect						
EFFECT ON SEROTONERGIC ACTIVITY						
↑ = agonist						
↓ = antagonist						

thus the precise mechanism by which they influence sexual behavior is difficult to assess. Lisuride acts as a serotonin agonist at 5-HT_{1A} and 5-HT₂ receptor sites. In addition, it acts as a serotonin antagonist, has dopaminergic agonist action, and is highly potent in its ability to lower prolactin levels (Rosenfeld & Makman 1981). Any one of these effects could enhance sexual functioning. Lisuride also increases testosterone levels but not to an extent that would influence sexual activity. Bupirone enhances both dopaminergic and noradrenergic activities and inhibits serotonergic activity (Fuller & Perry 1989; Eison & Temple 1986; Lucki 1986). In addition, several studies (Reynolds, Seymour & Heym 1986; Peroutka 1985; Glasser & Traber 1983) have shown that bupirone acts as an agonist at the 5-HT_{1A} receptor subtype. As the 5-HT_{1A} receptor has been linked in the male rat to a fa-

cilitatory role in sexual behavior (Mendelson & Gorzalka 1986a), this finding is consistent with the enhanced sexual functioning noted among patients receiving bupirone treatment.

It has been well documented that an increase in prolactin levels is associated with decreased sexual interest (Cleaves & Findley 1987; Matsuoka et al. 1986; Bancroft et al. 1984; Oseko et al. 1983; Tolis, Bertrand & Pinter 1979; Ambrosi et al. 1977). Lisuride effectively inhibits prolactin secretion and, in several cases, has been shown to be effective in the restoration of sexual functioning. Thus, in many studies it has been hypothesized that the increase in sexual functioning resulting from lisuride treatment is a direct consequence of the reduction of prolactin levels. However, lisuride has been shown to increase sexual desire and activity among both hyperprolactinemic pa-

tients and patients with normal prolactin levels. While it is possible that a normalization of prolactin levels enhances sexual functioning among hyperprolactinemic patients, this cannot account for the enhanced sexual functioning reported among patients with normal prolactin levels. Therefore, other contributing factors are likely. The serotonergic activity of lisuride provides a possible explanation. Rosenfeld and Makman (1981) demonstrated an agonist interaction of lisuride at both the 5-HT_{1A} and 5-HT₂ receptor binding sites. Consistent with this, lisuride stimulates adenylate cyclase activity, thus implicating an enhancement of the 5-HT_{1A} receptor subtype. In the male rat, the 5-HT_{1A} and in the female rat the 5-HT₂ receptors have been linked to a facilitatory role in sexual behavior (Gorzalka, Mendelson & Watson 1990; Mendelson & Gorzalka 1986a,c). These receptor subtypes may account for the enhanced sexual functioning that results from lisuride treatment.

Animal studies that have examined the effects of lisuride or buspirone on sexual behavior have shown that lisuride facilitates sexual behavior in the male rat (Gorzalka, Mendelson & Watson 1990). In contrast, small doses of lisuride have been shown to inhibit lordosis in estrogen- and progesterone-primed female rats (Gorzalka, Mendelson & Watson 1990). Buspirone has been shown to inhibit lordosis behavior in rats treated with estrogen or estrogen and progesterone (Mendelson & Gorzalka 1986b).

Finally, it should be noted that although there is a paucity of information on sexual side effects resulting from ECT treatment, the one study cited indicates an enhancement of sexual functioning. This study is consistent with the finding that ECT causes an up-regulation of 5-HT_{1A} receptors (Hayakawa, Yokota & Yamawaka 1990). The 5-HT_{1A} receptor in the male rat has been linked to a facilitatory role in sexual behavior (Mendelson & Gorzalka 1986a). However, other evidence has shown that ECT increases the density of 5-HT₂ receptors (Green, Johnson & Nimgaonkar 1983; Kellar et al. 1981; Vetulani, Lebrecht & Pilc 1981). The 5-HT₂ receptor has been shown to play an inhibitory role in male rat sexual behavior (Watson & Gorzalka In press, 1991). On the basis of the present review, it is reasonable to speculate that the function of the 5-HT₂ receptor in the human and in the male rat are not analogous.

CONCLUSION

This review of the literature has provided a detailed examination of the sexual side effects resulting from treatment by drugs that affect brain serotonergic systems. The focus has been to discern whether a correlation exists between the drugs' specific serotonergic activity and the facilitatory or inhibitory effect they exert on human sexual

behavior. The findings suggest several interesting trends that warrant consideration.

Authors have attributed the sexual side effects resulting from treatment with many of the drugs reviewed to specific factors, such as adrenergic, cholinergic, and dopaminergic activity, and have made only incidental reference to the involvement of serotonergic systems. Based on the original understanding that serotonin plays an inhibitory role in sexual behavior, many authors have discounted the role of serotonin. In doing so, they have failed to consider the fact that more recent evidence indicates that serotonin can either facilitate or inhibit sexual behavior depending on which serotonin receptor subtype is activated. Furthermore, an examination of the many studies presented reveals that no simple, direct relationship exists between the peripheral, hormonal or dopaminergic activities of these drugs and sexual functioning. Evidence is provided that supports the role of serotonin in these drug-induced sexual side effects.

From a review of the drugs' specific serotonergic effects, it is evident that a link exists between these effects and human sexual functioning. In a broad sense, several drugs that act as serotonin agonists inhibit sexual behavior, while several of those that act as serotonin antagonists facilitate it. The tricyclics, MAOIs, fluoxetine, and fenfluramine all act as serotonin agonists and inhibit sexual functioning. Similarly, lithium, methysergide, PCPA, and cyproheptadine act as serotonin antagonists and facilitate sexual functioning. However, this apparent correlation may be coincidental. The major tranquilizers block some serotonin receptors and inhibit sexual behavior, and several of the drugs, such as trazodone, lisuride and LSD, exert both agonistic and antagonistic effects.

The most dramatic finding, and one that may account for this discrepancy, is the correlation that exists between the drugs' effects on specific serotonin receptor sites and their effects on sexual behavior. Virtually all drugs that decrease the density of 5-HT₂ receptors inhibit sexual behavior. The tricyclics, MAOIs, fluoxetine, trazodone, phenothiazines, and thioxanthenes all act as 5-HT₂ antagonists and have been described in association with decreased sexual functioning. Additionally, lisuride and ECT increase the density of 5-HT₂ receptors and have been shown to facilitate sexual behavior. In a similar manner, lithium, buspirone, ECT, and lisuride act as 5-HT_{1A} agonists and have also been described in association with an increase in sexual functioning. LSD may act as both a 5-HT_{1A} agonist and a 5-HT₂ antagonist. Interestingly, LSD has been shown to both facilitate and inhibit sexual behavior. These findings are consistent with studies on the male rat that have linked the 5-HT_{1A} receptor to a facilitatory role in sexual behavior. However, these findings contrast with the apparent inhibitory role of the 5-HT_{1A} receptor in the female rat and the 5-HT₂ receptor in the male rat.

A secondary finding of this review is the absence of an obvious sex difference in the effects of these drugs on sexual behavior. Such sex differences have been reported in the rat (Gorzalka, Mendelson & Watson 1990). Changes in sexual desire seen among males are matched with similar changes seen among females; changes in ejaculation are paralleled with changes in orgasm reported among females. In terms of the incidence of sexual side effects, an apparently disproportionately higher number of side effects is reported among males than females. This finding may be attributable to the higher susceptibility of males to the placebo effect or to the fact that males may be more willing to report sexual side effects.

An interesting finding of this review is that the reported effects on human sexual behavior seem more consistent with the effects on male rat sexual behavior than female rat sexual behavior. Cyproheptadine, lisuride, methysergide, and PCPA have all been shown to facilitate sexual behavior in the human male and also in the male rat. Similarly, lithium has been reported to reduce the latency to ejaculate in both the human male and in the male rat, and both clomipramine and thioridazine have been shown to inhibit ejaculation in the human male and to prolong ejaculation in the male rat. In marked contrast, cyproheptadine has been shown to reverse anorgasmia in the human female but to inhibit lordosis behavior in the female

rat. Buspirone has been shown to enhance sexual behavior in the human female but to inhibit sexual behavior in the female rat, and lisuride and methysergide have been shown to enhance sexual behavior in the human male but to inhibit sexual behavior in the female rat. This finding may relate to the fact that in female rats, only lordosis is usually measured as a sexual response. Lordosis is a spinal reflex and is largely not analogous to the various aspects of human female sexual behavior. Perhaps it would be worthwhile for animal researchers to look at other aspects of female rat sexual behavior.

In conclusion, specific alterations in serotonin receptor binding sites resulting from treatment by the various drugs reviewed provide a possible explanation for some sexual side effects that appear secondary to the use of these drugs. Future receptor binding studies that assess the effects of these drugs on specific serotonin subtypes may generate new insight into the pathophysiologic processes of sexual dysfunctions and the development of agents that may enhance sexual functioning.

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