Antidepressant-Related Erectile Dysfunction: Management via Avoidance, Switching Antidepressants, Antidotes, and Adaptation

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The ideal antidepressant would control depression with no adverse effect on sexual function. Erectile dysfunction and other sexual dysfunction associated with antidepressant medication treatment are problems with many antidepressants and can lead to patient dissatisfaction and decreased compliance with treatment. A computerized MEDLINE search (English language, 1966–2003) was performed using the terms *antidepressive agents*, *erectile dysfunction*, and *sexual dysfunction*. Emphasis was placed on studies with specific sexual function measurements taken before and after treatment and placebo control. Mixed mediator, nonserotonergic antidepressants that block postsynaptic serotonin type 2 receptors (nefazodone, mirtazapine) or that primarily increase dopamine or norepinephrine levels (bupropion) were thought to be good choices for avoiding antidepressant-associated sexual dysfunction or for switching patients in whom antidepressant-associated sexual dysfunction emerged. Comparisons with serotonin reuptake inhibitors (SRIs) have revealed less desire and orgasm dysfunction with nonserotonergic bupropion, less orgasm dysfunction with nefazodone, and superior overall satisfaction with sexual functioning with bupropion or nefazodone. However, most of these studies have design flaws that make evidence-based claims of efficacy difficult to substantiate. Agents proposed for antidote use in antidepressant-associated sexual dysfunction have either not been studied in men or not proved efficacious in randomized placebo-controlled trials. Switching to and augmentation with bupropion or nefazodone have also not clearly shown efficacy in controlled trials and require care and monitoring to avoid SRI discontinuation symptoms and loss of antidepressant efficacy. Few proposed treatment options, apart from avoidance, have proved effective for antidepressant-associated sexual dysfunction, which can have negative consequences on depression management. *(J Clin Psychiatry 2003;64[suppl 10]:11–19)*

Before the discovery of the role of nitric oxide, the key central nervous system neurotransmitters involved in sexual function were considered to be dopamine, norepinephrine, acetylcholine, and serotonin.[1–3] Dopamine increases sexual drive and desire, and may affect erection by acting on neurons in the hypothalamus or on the proerectile sacral parasympathomimetic nucleus in the spine.[4] In animal studies, drugs that increase dopamine increase sexual motivation, arousal, and copulatory behavior.[4] Norepinephrine appears to have a positive effect on sexual arousal and orgasm via both central (spinal) actions and peripheral actions in the genitalia.[1,2] Drugs that stimulate norepinephrine release seem to stimulate sexual activity.[2]

Serotonin, in general, has an inhibiting effect on sexual function, including arousal and orgasm.[2,3] It had been proposed that the decreased libido and impaired ejaculation associated with selective and nonselective serotonin reuptake inhibitors (SRIs) are secondary to an increase in serotonin neurotransmission produced by serotonin reuptake inhibition in the lateral hypothalamus.[3] However, such oversimplification does not recognize that there are 7 known families of serotonin receptors (5-$HT_{1–7}$) and 14 subtypes.[5] Animal studies report that activation of different serotonin receptor subtypes has different effects on sexual behavior; stimulation of 5-HT_{1A} receptors lowers the threshold for arousal and ejaculation, but stimulation of subtypes 5-HT_{1B}, 5-HT_2 (including 5-HT_{2A} and 5-HT_{2C}),

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Support was provided by Pfizer Inc, New York, N.Y.

Dr. Labbate has received grant/research support from Eli Lilly and Pfizer, has received honoraria from Pfizer, and has been a speakers/advisory board member for Pfizer, GlaxoSmithKline, Forest Laboratories, and Janssen. Dr. Croft has been a consultant for Pfizer, Glaxo, and Eli Lilly; has received grant/research support from Merck, Pfizer, Pharmacia, Eli Lilly, and Glaxo; has received honoraria from Forest, Pfizer, Glaxo, and Upjohn; and has been a speakers/advisory board member for GlaxoSmithKline and Pfizer.

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Table 1. Observed Frequency of Sexual Dysfunction in Large Observational Studies, % (Total N)

	Montejo et al[8]					Clayton et al[9a]
			Orgasm/Ejaculation			
Antidepressant	Desire	Arousal	Delayed	None	Overall	Overall
Bupropion IR	…	…	…	…	…	20 (51)
Bupropion SR	…	…	…	…	…	24 (584)
Citalopram	62 (66)	35 (66)	64 (66)	52 (66)	73 (66)	38 (730)
Fluoxetine	50 (279)	22 (279)	50 (279)	39 (279)	58 (279)	36 (1521)
Fluvoxamine	48 (77)	21 (77)	55 (77)	38 (77)	62 (77)	…
Mirtazapine	20 (49)	14 (49)	18 (49)	8 (49)	24 (49)	40 (64)
Moclobemide	…	…	…	…	4 (26)	…
Nefazodone	6 (50)	0 (50)	2 (50)	2 (50)	8 (50)	29 (342)
Paroxetine	64 (208)	41 (208)	64 (208)	53 (208)	71 (208)	42 (1132)
Sertraline	55 (159)	29 (159)	57 (159)	47 (159)	63 (159)	40 (1098)
Venlafaxine	60 (55)	40 (55)	62 (55)	42 (55)	67 (55)	40 (629)

[a]Data derived from Clayton et al.,[9] Figure 2.
Abbreviations: IR = immediate release, SR = sustained release.

Table 2. Causes of Sexual Dysfunction[a]

Physiologic
Depression
Other psychiatric conditions (eg, anxiety)
Other medical conditions
Hormonal changes (estrogen in women, testosterone in both sexes)
Pharmacologic
Prescription medications (eg, antidepressants, antihypertensives)
Nonprescription chemicals and medications (eg, alcohol, opiates)
Psychological
Relationship issues
Stress, anger, frustration
Concerns about pregnancy and sexually transmitted diseases

[a]Based on Nurnberg.[11]

and 5-HT_3 inhibit arousal and ejaculation.[2,6] Postulated mechanisms for the effects of serotonin include modulation of dopamine levels in the brain,[3] and activity on the smooth muscles of the vascular system and genitals and on the nerves innervating the sexual organs.[2] There is speculation that serotonin may inhibit nitric oxide synthase and hence nitric oxide production.[7]

Antidepressant-associated sexual dysfunction often manifests as complex, polymorphic dysfunctions of libido, arousal, erection, and orgasm (Table 1). Often, antidepressant-associated sexual dysfunction may manifest as more than 1 of these dysfunctions. Erectile dysfunction has been found to be of equal or greater prevalence among men with SRI-associated sexual dysfunction.

Prior to definition of the roles of dopamine, norepinephrine, serotonin, and nitric oxide in sexual function, management of antidepressant-associated sexual dysfunction was limited to 4 widely used strategies of pharmacotherapy: (1) avoidance of the problem by selecting an antidepressant that has little or no associated sexual dysfunction, (2) switching to such an antidepressant, (3) use of adjunctive antidote pharmacotherapy with an antagonist/agonist or non-SRI antidepressant that has little or no associated dysfunction, and (4) adaptation. The empirical evidence base for each strategy is reviewed for the treatment of antidepressant-associated sexual dysfunction, with a specific focus on antidepressant-associated erectile dysfunction in men.

METHOD

A computerized literature search using MEDLINE (English language, 1966–2003) was performed using the terms *antidepressive agents*, *erectile dysfunction*, and *sexual dysfunction*. Additional abstracts not yet published were also reviewed.

Most of the available data, particularly those regarding the benefits of switch and antidote therapy for treatment of antidepressant-associated sexual dysfunction, are of limited value. Placebo-controlled data are the exception, and methodological flaws are common, such as the description of successful cases without reporting the outcome in all treated patients, the failure to employ rating instruments (e.g., specific sexual function measurements) or to validate or measure baseline sexual function, and a focus on young, healthy patients. For example, when physicians systematically and directly asked patients about sexual function, 58% reported antidepressant-associated sexual dysfunction; however, only 14% of patients spontaneously reported antidepressant-associated sexual dysfunction as a side effect.[10] Baseline data can control for the underlying level of sexual function, which can be compromised by many factors (Table 2). Use of placebo quantifies any placebo effect on underlying sexual function and confirms efficacy. Therefore, emphasis was placed on studies with the following methodological features: specific sexual function measurement before and after treatment and placebo control.

AVOIDANCE AND SWITCHING

Different antidepressants have different effects on the various neurotransmitters involved in sexual function. Understanding the effects of neurotransmitters on sexual function provides a theoretical basis for the choice of antidepressants to avoid or eliminate (via switching) antidepressant-associated sexual dysfunction. Furthermore, comparative data from large observational studies, prescription-event monitoring, and analyses of pooled clinical trial data suggest differences between antidepressants in the incidence and risk of sexual dysfunction (Table 1).[8–10,12,13] The antidepressants most commonly mentioned for avoidance or switch therapy are bupropion (a weak dopamine reuptake inhibitor) and nefazodone and mirtazapine (mixed receptor modulator, third-generation antidepressants). Antidepressants not approved in the

Table 3. Double-Blind Randomized Studies of the Incidence of Antidepressant-Associated Sexual Dysfunction Developing in Patients With Moderate-to-Severe Depression Treated With SRIs Compared With Bupropion or Nefazodone

Reference	Dosage, Mean (range), mg/d	Duration	N Evaluated/ Randomized	Sexual Dysfunction at End of Treatment[a]			Overall Satisfaction[a]
				Desire	Arousal	Orgasm	
Bupropion							
Coleman et al[17]							
Bupropion SR	290 (100–365)	8 wk	118/122	16% (*vs sertraline)[b]	6%	10% (*vs sertraline)[b]	85% (*vs sertraline)
Sertraline	106 (42–167)	8 wk	109/118	31%[b]	9%	37%[b]	62%
Placebo	…	8 wk	117/124	19%[b]	10%	14% (*vs sertraline)[b]	81% (*vs sertraline)
Coleman et al[18]							
Bupropion SR	319	8 wk	136/150	15% (*vs fluoxetine)[b]	7%[b]	10% (*vs fluoxetine)[b]	97% (*vs fluoxetine, placebo)[b]
Fluoxetine	26	8 wk	146/154	24%[b]	12%[b]	31%[b]	78%[b]
Placebo	…	8 wk	145/152	13% (*vs fluoxetine)[b]	9%[b]	10% (*vs fluoxetine)[b]	91%[b]
Croft et al[19]							
Bupropion SR	293 (150–400)	8 wk	116/120	18% (*vs placebo)[b]	6% (*vs placebo)[b]	15% (†vs sertraline)[b]	75% (*vs sertraline)[b]
Sertraline	121 (50–200)	8 wk	116/119	28%[b]	12% (*vs placebo)[b]	42% (†vs placebo)[b]	65% (*vs placebo)[b]
Placebo	…	8 wk	116/121	32%[b]	1%[b]	9%[b]	77%[b]
Segraves et al,[20] Kavoussi et al[21]							
Bupropion SR	238 (10–300)	16 wk	119/122	3% (*vs sertraline)[c]	Cumulative: 7% (*vs sertraline)	Cumulative: 10% (†vs sertraline)	79% (†vs sertraline)[d]
Sertraline	114 (50–200)	16 wk	122/126	22%[c]	Cumulative: 19%	Cumulative: 61%	58%[d]
Nefazodone							
Feiger et al[22]							
Nefazodone	456 (100–600)	6 wk	50/78	Not assessed	1.96 ± 0.25	4.04 ± 0.22 (‡vs sertraline)	2.44 ± 0.20 (‡vs sertraline)
Sertraline	148 (50–200)	6 wk	50/82	Not assessed	2.04 ± 0.24	2.63 ± 0.31	3.43 ± 0.27

[a]Only Feiger et al. and Segraves et al. reported results separately for men; the other data are combined results in men and women. Data represent incidence, except for those of Feiger et al., which represent mean ± SD scores on a 5-point scale from 1 (always) to 5 (never) for erection achieved, 1 (always) to 5 (rarely or never) for delayed ejaculation, and 1 (completely) to 5 (not at all) for satisfaction with sexual functioning.
[b]Data derived from Coleman et al.[17] Figures 2 and 3; Coleman et al.[18] Figures 2, 4, 5, and 6; Croft et al.[19] Figures 3, 4, 5, and 6.
[c]Among the subgroup without sexual desire disorder at baseline.
[d]Data for men and women combined.
*$p \leq .05$ between treatments and/or vs. placebo.
‡$p \leq .01$ between treatments and/or vs. placebo.
†$p \leq .001$ between treatments and/or vs. placebo.
Abbreviations: SR = sustained release, SRI = serotonin reuptake inhibitor.

United States that have been studied for avoidance and/or switch therapy are moclobemide (a monoamine oxidase inhibitor) and tianeptine (a serotonin reuptake accelerator).

Bupropion

Bupropion, an aminoketone, is chemically unrelated to other antidepressants. It is a putative dopamine reuptake inhibitor that also enhances the release of norepinephrine and subsequently enhances the firing of serotonin neurons via a norepinephrine-dependent mechanism.[14,15]

Avoidance. Pooled clinical trial data from placebo-controlled studies that did not measure pretreatment and posttreatment sexual functioning reported that sexual dysfunction is rare with bupropion.[16] These findings were confirmed by a series of 4 double-blind randomized studies,[17–21] which compared the effect of bupropion with that of an SRI in sexually active patients with moderate-to-severe depression and normal baseline sexual function with the exception of decreased sexual desire (e.g., no difficulty with arousal or orgasm), (Table 3). Criteria based on definitions from the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, were used to measure pretreatment and posttreatment sexual function.

Placebo controls in 3 of these studies[17–19] established that the incidence of sexual dysfunction with bupropion is generally no different from that of placebo. However, results from the individual studies suggested a lower incidence of sexual desire dysfunction (18% vs. 32%; $p \leq .05$),[19] a lower incidence of overall dissatisfaction with sexual function (3% vs. 9%; $p \leq .05$),[18] and a higher incidence of sexual arousal dysfunction (6% vs. 1%; $p \leq .05$)[19] with bupropion relative to placebo. The results indicated that bupropion treatment had little absolute effect on sexual function other than to improve the sexual desire dysfunction associated with major depressive disorder (MDD) and, based on results from 1 of the studies,[19] a small negative effect on arousal.

Bupropion was at least as efficacious as the comparator SRI in antidepressant activity but was associated with a 36% to 86% lower incidence of desire dysfunction, a 33% to 65% lower incidence of arousal dysfunction, a 64% to 84% lower incidence of orgasm dysfunction (delay or failure), and a 15% to 37% higher incidence of overall satisfaction with sexual function.[17–21] The differences between bupropion and the comparator SRI were generally statistically significant except for differences in arousal

dysfunction. A pooled data analysis of 3 of these studies, which compared bupropion with sertraline, determined that on day 56 of treatment, the relative risks of desire dysfunction, arousal dysfunction, and orgasmic dysfunction were 0.65 (95% CI = 0.51 to 0.84), 0.46 (95% CI = 0.26 to 0.83), and 0.22 (95% CI = 0.12 to 0.40), respectively, for bupropion and that satisfaction with sexual functioning was significantly less in the sertraline group (relative risk 1.28; 95% CI = 1.16 to 1.41).[13] However, in both antidepressant groups over time, sexual desire disorder decreased and orgasmic dysfunction increased (all 3 of the studies),[17,19–21] sexual arousal disorder increased (2 of the studies),[19–21] and satisfaction with sexual functioning increased (2 of the studies).[17,19] Unfortunately, data from 2 of the trials are flawed, as Segraves et al.[20] and Kavoussi et al.[21] lack a placebo control and in Coleman et al.[17] the administered dose of sertraline failed to efficaciously treat the underlying depression.

Switching. There is no convincing evidence for the use of bupropion as switch therapy in patients with antidepressant-associated sexual dysfunction. Data are limited to results from small, uncontrolled, open-label studies in which antidepressant-associated sexual dysfunction was alleviated after a switch to bupropion from an SRI or a tricyclic antidepressant.[23–25]

Mirtazapine

Mirtazapine, an α_2-antagonist, is also a unique antidepressant that enhances noradrenergic and 5-HT_{1A}–activated neurotransmission; it does not inhibit norepinephrine or serotonin reuptake.[26–28] In addition, mirtazapine causes blockade of postsynaptic 5-HT_2 and 5-HT_3 receptors, which should spare sexual function.[26,28]

Analysis of pooled clinical trial data suggests that sexual dysfunction is uncommon with mirtazapine.[28] However, in a large observational study, patients treated with mirtazapine experienced sexual dysfunction at a frequency similar to or greater than that of patients treated with selective SRIs (Table 1).[9] The absence of placebo-controlled or active-controlled studies that assess sexual function with specific measurements taken before and after treatment makes it impossible to determine the absolute or relative incidence of sexual dysfunction with mirtazapine. Furthermore, studies of switch therapy are limited to 2 small, uncontrolled, open-label studies[29,30] in which patients experiencing SRI-induced sexual dysfunction, mostly anorgasmia, were switched to mirtazapine titrated up to 45 mg/day for up to 6 weeks; mirtazapine successfully controlled depressive symptoms and improved sexual functioning in many patients, but was associated with emergent adverse reactions of weight gain, irritability, and sedation.

Nefazodone

Nefazodone is a phenylpiperazine derivative that inhibits the reuptake of serotonin and, to a lesser degree, norepinephrine and also acts by antagonism of 5-HT_{2A} receptors.[31] Improvement in sexual function is theoretically achieved by increasing the sensitivity of 5-HT_{1A} receptors and decreasing the sensitivity of 5-HT_{2A} receptors. In addition, *m*-chlorophenylpiperazine, a metabolite of nefazodone, appears to provoke sexual excitement in animals.[32] Analysis of pooled clinical trial data suggests that sexual dysfunction is rare with nefazodone.[33] However, the uncommon possibility of hepatic toxicity has limited its use.

Avoidance. Although the absence of placebo-controlled studies limits conclusions regarding the potential for nefazodone to cause sexual dysfunction, a double-blind randomized comparison with sertraline provides data on the relative potential.[22] Patients with single or recurrent moderate-to-severe nonpsychotic MDD were randomly assigned to 6 weeks of treatment with nefazodone or sertraline; sexual function and satisfaction were evaluated at baseline and weekly with a questionnaire (Table 3). By the last week of treatment, scores for most questions answered by men indicated significantly less sexual dysfunction with nefazodone. A higher proportion of men treated with nefazodone compared with sertraline fully or sometimes enjoyed sex (100% vs. 57%; $p < .01$), were moderately to completely satisfied with their sexual functioning (89% vs. 50%; $p < .01$), and experienced delayed ejaculation at most only occasionally (82% vs. 33%; $p < .01$). Ejaculation difficulty was experienced by 19% of nefazodone recipients (an increase from 13% at baseline) compared with 67% of sertraline recipients (an increase from 18% at baseline; $p < .01$). However, as with the results of most of the bupropion studies, there was no significant difference between nefazodone and sertraline in measures of arousal dysfunction; an erection was achieved never or only some of the time in 19% and 20% of nefazodone- and sertraline-treated patients, respectively, and 22% and 30% of patients reported that it took a long time to achieve an erection. Both drugs were well tolerated, with similar rates of discontinuation because of adverse events. Study methodological problems include the lack of a placebo control and the use of a higher mean dose of sertraline (148 mg/day) than was generally used in similar studies.

Switching. One hundred five patients with MDD underwent a 1-week washout period and a 7- to 10-day single-blind placebo period to document remission of sertraline-associated sexual dysfunction (with the exception of decreased sexual desire—a known symptom of MDD).[34] Sexual function was assessed using the Rush Sexual Function Inventory and a Physician-Rated Sexual Dysfunction Symptoms questionnaire. Of the 75 patients who qualified for random assignment to double-blind treatment with nefazodone (initially 200 mg/day, doubling after 7 days) or reinstitution of sertraline (initially 50 mg/day, doubling after 7 days), 72 were included in the sexual function analysis. Both treatments demonstrated a

similar and sustained improvement in symptoms of depression. More sertraline recipients (76%; 25/33) than nefazodone recipients (26%; 10/39) experienced reemergence of antidepressant-associated sexual dysfunction (ejaculatory and/or orgasmic difficulty; $p < .001$). However, rechallenge with the same SRI rather than an alternative limits the conclusions to this study.

Other Antidepressants

Two other antidepressants are occasionally considered for avoidance or switch therapy. Moclobemide, a monoamine oxidase inhibitor that preferentially inhibits monoamine oxidase type A, is an antidepressant that affects the monoaminergic cerebral neurotransmitter system, thereby decreasing the metabolism and increasing the extracellular concentrations of norepinephrine, dopamine, and serotonin.[35] The absence of placebo-controlled studies prevents comment on the absolute potential of moclobemide to cause sexual dysfunction, but a double-blind randomized comparison with doxepin and 2 open-label comparisons with SRIs, described in this section, provide data on the relative potential. Tianeptine, a dibenzothiazepine tricyclic, increases the presynaptic uptake of serotonin in the absence of any binding to 5-HT receptors and does not bind to α_1- or α_2-receptors.[36] It is not possible to determine the absolute or relative incidence of sexual dysfunction with tianeptine because no placebo-controlled or active-controlled studies were found that assessed sexual function with specific measurements taken before and after treatment. Study of switch therapy with these agents is limited to a moclobemide case report[37] and a small, uncontrolled, open-label study of tianeptine.[36]

Avoidance with moclobemide. A total of 237 adults with MDD underwent a 4-day run-in period with placebo and assignment to treatment with moclobemide or doxepin.[38] Although the study was stated to be double-blind, the method of treatment assignment was not reported. Among the 169 patients who completed the 6-week treatment phase with no protocol violations, the mean daily dose of study medication was 430 mg (range, 240–580 mg) for moclobemide and 103 mg (range, 33–138 mg) for doxepin. Antidepressant efficacy was similar in the 2 treatment groups, but the moclobemide group showed greater improvements from baseline in sexual desire (42% vs. 9%; $p < .001$), penile erection (23% vs. 5%; $p = .003$), ejaculation (20% vs. 6%; $p = .016$), and orgasm (28% vs. 13%; $p = .021$), measured using the Udvalg for Kliniske Undersogelser Side Effect Rating Scale.[39]

In 2 open-label studies,[40,41] moclobemide was compared with other antidepressants, including various SRIs (i.e., fluoxetine, fluvoxamine, paroxetine, sertraline) and venlafaxine, a serotonin and norepinephrine reuptake inhibitor, in sexually active patients with depression whose sexual function was assessed before and after antidepressant use by means of physician and patient questionnaires developed by the investigators. In 1 of the studies,[40] 138 moclobemide recipients and 130 SRI recipients were evaluable from a population of 315 patients who received at least 1 dose of study drug. Baseline sexual function values were similar among users of moclobemide and the comparator antidepressants. However, the incidence of treatment-emergent sexual dysfunction was lower in the moclobemide group compared with the pooled SRI group ($p < .001$) and compared favorably with each SRI separately for other measurements of sexual dysfunction at most weeks ($p < .05$), according to physicians' and patients' ratings. In the second study,[41] 107 of 174 enrolled patients were treated for at least 8 weeks with moclobemide, paroxetine, sertraline, or venlafaxine and completed a sexual function questionnaire at baseline and after 8 or 14 weeks of antidepressant therapy. Levels of sexual dysfunction in men did not differ to a statistically significant extent, across drugs at baseline or during treatment, for either the drive/desire items or the arousal/orgasm items (chi-square analysis). All antidepressant medications were similarly effective in reducing depressive symptoms, but nonresponders reported greater sexual dysfunction than responders.

ANTIDOTES

Agents studied for antidote efficacy in the treatment of antidepressant-associated sexual dysfunction have either unknown mechanisms (e.g., the herbal supplement *Ginkgo biloba*) or activities on various neurochemical pathways, such as inhibition of serotonin neurotransmission and/or enhancement of catecholamine neurotransmission. For most proposed antidote agents, available data on the treatment of antidepressant-associated sexual dysfunction in men are anecdotal or limited to case reports or small open case series. These agents include amantadine (an antiparkinsonian and antiviral drug),[42,43] bethanechol (an anticholinergic agent used to treat urinary retention),[44,45] cyproheptadine (used in the treatment of migraine and allergic conditions),[46–50] *Ginkgo biloba*,[51–53] mianserin (a tetracyclic antidepressant that is a strong 5-HT_2–receptor agonist),[54–56] nefazodone,[57] mirtazapine,[58] psychostimulants (such as methylphenidate,[59,60] dextroamphetamine,[61] and pemoline[61]), and yohimbine (a norepinephrine α_2-receptor antagonist with purported activity in the central nervous system and erectile tissue).[62,63]

Evidence for proposed antidote treatment of antidepressant-associated sexual dysfunction with testosterone is purely anecdotal, without even published case reports of efficacy. However, placebo-controlled studies suggest that testosterone may not be beneficial for improving sexual dysfunction in men with normal testosterone concentrations,[64,65] and the adverse effects of exogenous testosterone, including mood lability, hirsutism, acne, sleep apnea, and irritability, may limit its use for this indi-

cation. Before instituting testosterone therapy in a man older than 50 years, or in a man of any age who has a first-degree relative with prostate cancer, assessment by a urologist is appropriate. Only a few proposed antidote agents have been studied in controlled clinical trials of add-on therapy for the treatment of the manifestations of antidepressant-associated sexual dysfunction.

Bupropion

In addition to the aforementioned study of bupropion as avoidance or switch therapy for antidepressant-associated sexual dysfunction, it has also been studied as an antidote agent. In several small, open, uncontrolled trials and case series, addition of bupropion immediate release (75 or 150 mg 1 to 2 hours before sexual activity, or 75–450 mg/day)[66–68] or bupropion sustained release (150–300 mg/day)[24,69] was reported to improve SRI-induced sexual dysfunction. However, in a small (N = 31), randomized, placebo-controlled trial of patients who were euthymic but experiencing antidepressant-associated sexual dysfunction after 6 or more weeks of SRI therapy, bupropion sustained release, 150 mg, administered every evening for 3 weeks was not statistically superior to placebo in improving scores on any item of the Arizona Sexual Experience Scale.[70] Indeed, placebo recipients experienced greater improvement from baseline to week 2 in scores on the erectile function item ($p = .04$). It remains possible that higher doses of bupropion may be of benefit; 1 study[71] found that bupropion improved libido, but not arousal or orgasm, more than placebo.

Buspirone

Buspirone, a mixed or partial 5-HT_{1A}–receptor agonist, is an anxiolytic with some antidepressant activity. The ability of buspirone to improve sexual dysfunction may result from reduced serotonin transmission and enhanced dopaminergic activity.[72] A small case series suggested that SRI-induced sexual dysfunction manifest as decreased libido and delayed orgasm could be improved with addition of buspirone, 15 to 60 mg/day.[73] However, in a randomized, double-blind, placebo-controlled study of 119 MDD patients unresponsive to an SRI (paroxetine or citalopram for ≥ 4 weeks), add-on treatment with buspirone for 4 weeks was not statistically different from placebo in antidepressant response or in remittance of sexual dysfunction in the subgroup of 20 men who reported decreased libido or orgasmic dysfunction before they began buspirone.[74,75]

Granisetron

Granisetron is a 5-HT_3 antagonist used for treating nausea associated with cancer chemotherapy. It additionally demonstrates low-affinity binding for 5-HT_{1A} receptors.[5] Results of a case report[76] and a small crossover study with sumatriptan[77] suggest resolution of SRI-induced sexual dysfunction with administration of granisetron, 1 mg, an hour before intercourse. However, a small (N = 20), placebo-controlled, double-blind, crossover study did not support the efficacy of granisetron, 1 or 2 mg, administered before intercourse in reversing SRI-induced sexual dysfunction.[78]

ADAPTATION

Antidepressant-associated sexual dysfunction usually occurs early in treatment and then either persists or improves; spontaneous remission or development of tolerance to antidepressant-associated sexual dysfunction may occur.[11,79,80] However, it remains controversial whether adaptation, spontaneous remission, or tolerance develops at a clinically meaningful rate. Nurnberg and Levine[79] observed that patients who developed tolerance were treatment responders and suggested that spontaneous reversal of antidepressant-associated sexual dysfunction might be a marker for serotonin receptor down-regulation and an increased threshold for sexual dysfunction. Patients who did not respond to antidepressant therapy had greater levels of sexual dysfunction across all domains when compared with treatment responders.

For patients taking short-acting SRIs (e.g., sertraline, paroxetine), a possible approach is a brief drug holiday before anticipated sexual activity.[81] Among 30 outpatients who discontinued their SRI after the Thursday morning dose until Sunday at noon, at least half of those taking sertraline or paroxetine reported much or very much improvement for each of orgasm, satisfaction, and libido, whereas much or very much improvement was reported by only 1 patient taking fluoxetine and only for orgasm function. There was no loss of antidepressant efficacy in those patients taking the drug holiday.[81] Unfortunately, some patients have return of anxiety or depressive symptoms during drug holidays or experience SRI withdrawal symptoms such as dizziness or nausea. These uncontrolled open-label results require confirmation under double-blind controlled trial conditions. Placebo response rates under double-blind conditions would indicate the rate of spontaneous remission and adaptation. Additionally, the extent and significance of receptor adaptation over time remain to be determined.[11]

CONCLUSIONS

The ideal SRI antidepressant would control depression without adverse effects on sexual function. However, because of overlapping neuroregulatory mechanisms mediated by serotonin and multiple 5-HT receptors, this is seldom the case. Sexual adverse effects are a problem with many new-generation antidepressants and can lead to patient dissatisfaction and decreased compliance with treatment.

It remains controversial whether adaptation, spontaneous remission, or tolerance to antidepressant-associated sexual dysfunction develops at a clinically meaningful rate. Therefore, active intervention remains central to the management of antidepressant-associated sexual dysfunction. It has been suggested that antidepressants that block postsynaptic 5-HT_2 receptors (e.g., nefazodone, mirtazapine) or that primarily increase dopamine or norepinephrine levels (e.g., bupropion) might be good choices for either avoiding antidepressant-associated sexual dysfunction or switching patients from agents that cause antidepressant-associated sexual dysfunction. However, there are no placebo-controlled or active-controlled studies of mirtazapine as avoidance, switch, or antidote therapy in men. In contrast, bupropion and nefazodone have been shown to have a lower incidence of sexual dysfunction relative to SRIs. Bupropion was usually associated with significantly less dysfunction of desire. Bupropion and nefazodone were consistently associated with significantly less dysfunction of orgasm and significantly greater overall satisfaction with sexual functioning. The combined evidence suggests that patients receiving bupropion have much less sexual dysfunction than those receiving nefazodone. However, both drugs require multiple daily dosing, and bupropion is associated with other adverse effects, including anxiety, agitation, and sleep disturbance. Furthermore, most of the controlled studies had design deficiencies and were unable to demonstrate that bupropion or nefazodone offered any significant advantage compared with the SRIs in preventing the development of erectile dysfunction. Despite positive case reports and open-label studies, the few small placebo-controlled studies of agents proposed for antidote use in antidepressant-associated sexual dysfunction have been unable to demonstrate a significant difference from placebo in men.

When a patient is switched to bupropion or nefazodone from an SRI, the SRI should be tapered slowly to avoid discontinuation symptoms that are likely to affect compliance and only after the switch therapy has been maintained at therapeutic dose for several weeks to avoid loss of antidepressant efficacy. Fluoxetine, which has a long half-life, is exempt from this caution. After switching antidepressants, the patient should be monitored for depression relapse to ensure that the new therapy proves effective. This is especially true because antidepressants are not interchangeable, and patients are just as likely to get switched to a less effective antidepressant as they are to an equally effective one.[82]

Drug names: amantadine (Symmetrel and others), bethanechol (Urecholine), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa), cyproheptadine (Periactin), doxepin (Sinequan and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), granisetron (Kytril), methylphenidate (Ritalin, Concerta, and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), pemoline (Cylert), sertraline (Zoloft), sumatriptan (Imitrex), venlafaxine (Effexor), yohimbine (Aphrodyne and others).

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