

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

Lawrence A. Labbate, M.D.; Harry A. Croft, M.D.;
and Marvin A. Oleshansky, M.D.

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-HT₂ (including 5-HT_{2A} and 5-HT_{2C}),

From the Department of Psychiatry and Behavioral Science, Medical University of South Carolina and Veterans Administration Medical Center, Charleston, S.C. (Dr. Labbate); San Antonio Psychiatric Research Center, San Antonio, Tex. (Dr. Croft); and the Department of Psychiatry, Walter Reed Army Medical Center, Washington, D.C. (Dr. Oleshansky).

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.

Corresponding author and reprints: Lawrence A. Labbate, M.D., Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, VAMC, Mental Health Service, 109 Bee St., #116, Charleston, SC 29401 (e-mail: labbatel@muscedu).

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

Antidepressant	Montejo et al ⁸					Clayton et al ^{9a} Overall
	Desire	Arousal	Orgasm/Ejaculation		Overall	
			Delayed	None		
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)

⁹Data 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

^aBased on Nurnberg.¹¹

and 5-HT₃ 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

^aOnly 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.

^bData 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.

^cAmong the subgroup without sexual desire disorder at baseline.

^dData 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-HT₂ and 5-HT₃ 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, norepi-

nephrine 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 reinstatement 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 report³⁷ 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 anti-parkinsonian 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-HT₂-receptor agonist),^{54–56} nefazodone,⁵⁷ mirtazapine,⁵⁸ psychostimulants (such as methylphenidate,^{59,60} dextroamphetamine,⁶¹ and pemoline⁶¹), 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 study⁷¹ 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-HT₃ 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 report⁷⁶ and a small crossover study with sumatriptan⁷⁷ 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 Levine⁷⁹ 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-HT₂ 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).

REFERENCES

1. Stahl SM. The psychopharmacology of sex, pt 1: neurotransmitters and the 3 phases of the human sexual response [BRAINSTORMS]. *J Clin Psychiatry* 2001;62:80–81
2. Meston CM, Frohlich PF. The neurobiology of sexual function. *Arch Gen Psychiatry* 2000;57:1012–1030
3. Hull EM, Lorrain DS, Du J, et al. Hormone-neurotransmitter interactions in the control of sexual behavior. *Behav Brain Res* 1999; 105:105–116
4. Giuliano F, Allard J. Dopamine and male sexual function. *Eur Urol* 2001;40:601–608
5. Wolf H. Preclinical and clinical pharmacology of the 5-HT₃ receptor antagonists. *Scand J Rheumatol Suppl* 2000;113:37–45
6. Fabre-Nys C. Steroid control of monoamines in relation to sexual behaviour. *Rev Reprod* 1998;3:31–41
7. Angulo J, Peiro C, Sanchez-Ferrer CF, et al. Differential effects of serotonin reuptake inhibitors on erectile responses, NO-production, and neuronal NO synthase expression in rat corpus cavernosum tissue. *Br J Pharmacol* 2001;134:1190–1194
8. Montejo AL, Llorca G, Izquierdo JA, et al, for the Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. *J Clin Psychiatry* 2001;62(suppl 3):10–21
9. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 2002;63:357–366
10. Montejo-Gonzalez AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther* 1997;23:176–194
11. Nurnberg HG. Managing treatment-emergent sexual dysfunction associated with serotonergic antidepressants: before and after sildenafil. *J Psychiatr Pract* 2001;7:92–108
12. Mackay FR, Dunn NR, Martin RM, et al. Newer antidepressants: a comparison of tolerability in general practice. *Br J Gen Pract* 1999;49: 892–896
13. Nieuwstraten CE, Dolovich LR. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. *Ann Pharmacother* 2001; 35:1608–1613
14. Dong J, Blier P. Modification of norepinephrine and serotonin, but not dopamine, neuron firing by sustained bupropion treatment. *Psychopharmacology (Berl)* 2001;155:52–57
15. Fiorino DF, Phillips AG. Facilitation of sexual behavior in male rats following *d*-amphetamine-induced behavioral sensitization. *Psychopharmacology (Berl)* 1999;142:200–208
16. Settle EC, Stahl SM, Batey SR, et al. Safety profile of sustained-release bupropion in depression: results of three clinical trials. *Clin Ther* 1999;21:454–463
17. Coleman CC, Cunningham LA, Foster VJ, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. *Ann Clin Psychiatry* 1999;11:205–215
18. Coleman CC, King BR, Bolden-Watson C, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. *Clin Ther* 2001;23:1040–1058
19. Croft H, Settle E Jr, Houser T, et al. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin Ther* 1999;21:643–658
20. Segraves RT, Kavoussi R, Hughes AR, et al. Evaluation of sexual functioning in depressed outpatients: a double-blind comparison of sustained-release bupropion and sertraline treatment. *J Clin Psychopharmacol* 2000;20:122–128
21. Kavoussi RJ, Segraves RT, Hughes AR, et al. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psychiatry* 1997;58:532–537
22. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J Clin Psychiatry* 1996;57 (suppl 2):53–62
23. Gardner EA, Johnston JA. Bupropion: an antidepressant without sexual pathophysiological action. *J Clin Psychopharmacol* 1985;5:24–29
24. Clayton AH, McGarvey EL, Abouesh AI, et al. Substitution of an SSRI

- with bupropion sustained release following SSRI-induced sexual dysfunction. *J Clin Psychiatry* 2001;62:185–190
25. Walker PW, Cole JO, Gardner EA, et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. *J Clin Psychiatry* 1993;54:459–465
 26. Rogoz Z, Wrobel A, Dlaboga D, et al. Effect of repeated treatment with mirtazapine on the central dopaminergic D2/D3 receptors. *Pol J Pharmacol* 2002;54:381–389
 27. Millan MJ, Gobert A, Rivet JM, et al. Mirtazapine enhances frontocortical dopaminergic and corticolimbic adrenergic, but not serotonergic, transmission by blockade of alpha2-adrenergic and serotonin 2C receptors: a comparison with citalopram. *Eur J Neurosci* 2000;12:1079–1095
 28. Fawcett J, Barkin RL. Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. *J Affect Disord* 1998;51:267–285
 29. Koutouvidis N, Pratikakis M, Fotiadou A. The use of mirtazapine in a group of 11 patients following poor compliance to selective serotonin reuptake inhibitor treatment due to sexual dysfunction. *Int Clin Psychopharmacol* 1999;14:253–255
 30. Gelenberg AJ, Laukes C, McGahuey C, et al. Mirtazapine substitution in SSRI-induced sexual dysfunction. *J Clin Psychiatry* 2000;61:356–360
 31. Owens MJ, Ieni JR, Knight DL, et al. The serotonergic antidepressant nefazodone inhibits the serotonin transporter: in vivo and ex vivo studies. *Life Sci* 1995;57:PL373–PL380
 32. Bagdy G, Kalogeras KT, Szemerédi K. Effect of 5-HT1C and 5-HT2 receptor stimulation on excessive grooming, penile erection and plasma oxytocin concentrations. *Eur J Pharmacol* 1992;229:9–14
 33. Robinson DS, Roberts DL, Smith JM, et al. The safety profile of nefazodone. *J Clin Psychiatry* 1996;57(suppl 2):31–38
 34. Ferguson JM, Shrivastava RK, Stahl SM, et al. Reemergence of sexual dysfunction in patients with major depressive disorder: double-blind comparison of nefazodone and sertraline. *J Clin Psychiatry* 2001;62:24–29
 35. Schreiber S, Getslev V, Weizman A, et al. The antinociceptive effect of moclobemide in mice is mediated by noradrenergic pathways. *Neurosci Lett* 1998;253:183–186
 36. Atmaca M, Kuloglu M, Tezcan E, et al. Switching to tianeptine in patients with antidepressant-induced sexual dysfunction. *Hum Psychopharmacol* 2003;18:277–280
 37. Ramasubbu R. Switching to moclobemide to reverse fluoxetine-induced sexual dysfunction in patients with depression. *J Psychiatry Neurosci* 1999;24:45–50
 38. Philipp M, Kohnen R, Benkert O. A comparison study of moclobemide and doxepin in major depression with special reference to effects on sexual dysfunction. *Int Clin Psychopharmacol* 1993;7:149–153
 39. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987;334:1–100
 40. Philipp M, Tiller JW, Baier D, et al, and the Australian and German Study Groups. Comparison of moclobemide with selective serotonin reuptake inhibitors (SSRIs) on sexual function in depressed adults. *Eur Neuropsychopharmacol* 2000;10:305–314
 41. Kennedy SH, Eisfeld BS, Dickens SE, et al. Antidepressant-induced sexual dysfunction during treatment with moclobemide, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry* 2000;61:276–281
 42. Balon R. Intermittent amantadine for fluoxetine-induced anorgasmia. *J Sex Marital Ther* 1996;22:290–292
 43. Shrivastava RK, Shrivastava S, Overweg N, et al. Amantadine in the treatment of sexual dysfunction associated with selective serotonin reuptake inhibitors [letter]. *J Clin Psychopharmacol* 1995;15:83–84
 44. Gross MD. Reversal by bethanechol of sexual dysfunction caused by anticholinergic antidepressants. *Am J Psychiatry* 1982;139:1193–1194
 45. Segraves RT. Reversal by bethanechol of imipramine-induced ejaculatory dysfunction [letter]. *Am J Psychiatry* 1987;144:1243–1244
 46. Lauerma H. Successful treatment of citalopram-induced anorgasmia by cyproheptadine. *Acta Psychiatr Scand* 1996;93:69–70
 47. Steele TE, Howell EF. Cyproheptadine for imipramine-induced anorgasmia [letter]. *J Clin Psychopharmacol* 1986;6:326–327
 48. McCormick S, Olin J, Brotman AW. Reversal of fluoxetine-induced anorgasmia by cyproheptadine in two patients. *J Clin Psychiatry* 1990;51:383–384
 49. Arnott S, Nutt D. Successful treatment of fluvoxamine-induced anorgasmia by cyproheptadine. *Br J Psychiatry* 1994;164:838–839
 50. Aizenberg D, Zemishlany Z, Weizman A. Cyproheptadine treatment of sexual dysfunction induced by serotonin reuptake inhibitors. *Clin Neuropharmacol* 1995;18:320–324
 51. Ashton AK, Ahrens K, Gupta S, et al. Antidepressant-induced sexual dysfunction and ginkgo biloba [letter]. *Am J Psychiatry* 2000;157:836–837
 52. Balon R. Ginkgo biloba for antidepressant-induced sexual dysfunction? *J Sex Marital Ther* 1999;25:1–2
 53. Cohen AJ, Bartlik B. Ginkgo biloba for antidepressant-induced sexual dysfunction. *J Sex Marital Ther* 1998;24:139–143
 54. Aizenberg D, Gur S, Zemishlany Z, et al. Mianserin, a 5-HT2a/2c and alpha 2 antagonist, in the treatment of sexual dysfunction induced by serotonin reuptake inhibitors. *Clin Neuropharmacol* 1997;20:210–214
 55. Aizenberg D, Naor S, Zemishlany Z, et al. The serotonin antagonist mianserin for treatment of serotonin reuptake inhibitor-induced sexual dysfunction in women: an open-label add-on study. *Clin Neuropharmacol* 1999;22:347–350
 56. Dolberg OT, Klag E, Gross Y, et al. Relief of serotonin selective reuptake inhibitor induced sexual dysfunction with low-dose mianserin in patients with traumatic brain injury. *Psychopharmacology (Berl)* 2002;161:404–407
 57. Reynolds RD. Sertraline-induced anorgasmia treated with intermittent nefazodone [letter]. *J Clin Psychiatry* 1997;58:89
 58. Farah A. Relief of SSRI-induced sexual dysfunction with mirtazapine treatment [letter]. *J Clin Psychiatry* 1999;60:260–261
 59. Roeloffs C, Bartlik B, Kaplan PM, et al. Methylphenidate and SSRI-induced sexual side effects [letter]. *J Clin Psychiatry* 1996;57:548
 60. Bartlik BD, Kaplan P, Kaplan HS. Psychostimulants apparently reverse sexual dysfunction secondary to selective serotonin re-uptake inhibitors. *J Sex Marital Ther* 1995;21:264–271
 61. Gitlin MJ. Treatment of sexual side effects with dopaminergic agents [letter]. *J Clin Psychiatry* 1995;56:124
 62. Segraves RT. Reversing anorgasmia associated with serotonin uptake inhibitors [questions and answers]. *JAMA* 1991;266:2279
 63. Jacobsen FM. Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. *J Clin Psychiatry* 1992;53:119–122
 64. Schiavi RC, White D, Mandeli J, et al. Effect of testosterone administration on sexual behavior and mood in men with erectile dysfunction. *Arch Sex Behav* 1997;26:231–241
 65. Aydin S, Odabas O, Ercan M, et al. Efficacy of testosterone, trazodone and hypnotic suggestion in the treatment of non-organic male sexual dysfunction. *Br J Urol* 1996;77:256–260
 66. Ashton AK, Rosen RC. Bupropion as an antidote for serotonin reuptake inhibitor-induced sexual dysfunction. *J Clin Psychiatry* 1998;59:112–115
 67. Bodkin JA, Lasser RA, Wines JD Jr, et al. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. *J Clin Psychiatry* 1997;58:137–145
 68. Labbate LA, Grimes JB, Hines A, et al. Bupropion treatment of serotonin reuptake antidepressant-associated sexual dysfunction. *Ann Clin Psychiatry* 1997;9:241–245
 69. Kennedy SH, McCann SM, Masellis M, et al. Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. *J Clin Psychiatry* 2002;63:181–186
 70. Masand PS, Ashton AK, Gupta S, et al. Sustained-release bupropion for selective serotonin reuptake inhibitor-induced sexual dysfunction: a randomized, double-blind, placebo-controlled, parallel-group study. *Am J Psychiatry* 2001;158:805–807
 71. Clayton AH, McGarvey EL, Warnock JK, et al. Bupropion SR as an antidote to SSRI-induced sexual dysfunction. Presented at the 40th annual meeting of the New Clinical Drug Evaluation Unit; May 30–June 2, 2000; Boca Raton, Fla
 72. Tunnicliff G. Molecular basis of buspirone's anxiolytic action. *Pharmacol Toxicol* 1991;69:149–156
 73. Norden MJ. Buspirone treatment of sexual dysfunction associated with selective serotonin re-uptake inhibitors. *Depression* 1994;2:109–112
 74. Landen M, Björling G, Agren H, et al. A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. *J Clin Psychiatry* 1998;59:664–668
 75. Landen M, Eriksson E, Agren H, et al. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. *J Clin Psychopharmacol* 1999;19:268–271
 76. Nelson EB, Keck PE Jr, McElroy SL. Resolution of fluoxetine-induced

- sexual dysfunction with the 5-HT₃ antagonist granisetron [letter]. *J Clin Psychiatry* 1997;58:496-497
77. Berk M, Stein DJ, Potgieter A, et al. Serotonergic targets in the treatment of antidepressant induced sexual dysfunction: a pilot study of granisetron and sumatriptan. *Int Clin Psychopharmacol* 2000;15:291-295
 78. Nelson EB, Shah VN, Welge JA, et al. A placebo-controlled, crossover trial of granisetron in SRI-induced sexual dysfunction. *J Clin Psychiatry* 2001;62:469-473
 79. Nurnberg HG, Levine PE. Spontaneous remission of MAOI-induced anorgasmia. *Am J Psychiatry* 1987;144:805-807
 80. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. *J Clin Psychopharmacol* 1999;19:67-85
 81. Rothschild AJ. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holiday. *Am J Psychiatry* 1995;152:1514-1516
 82. Hensley PL, Nurnberg HG. Formulary restriction of selective serotonin reuptake inhibitors for depression: potential pitfalls. *Pharmacoeconomics* 2001;19:973-982