Prevalence of Antidepressant-Associated Erectile Dysfunction

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Sexual dysfunction in general and erectile dysfunction in particular are common problems in the overall population but also frequent symptoms of both untreated and treated depression. Erectile dysfunction and associated sexual dysfunction secondary to antidepressant therapy may occur in up to 90% of men with antidepressant-emergent sexual side effects; accurate assessment of prevalence rates depends on taking a detailed history regarding erectile dysfunction and other aspects of sexual function prior to treatment. In this review, we examine the available data on prevalence of erectile dysfunction and related sexual dysfunction in untreated depression and secondary to antidepressant medications compared with healthy populations. Possible mechanisms involved in serotonin reuptake inhibitor (SRI)–associated erectile dysfunction are examined. The assessment of SRI-associated erectile dysfunction is presented to aid in the management of this important and prevalent side effect. Treatment of antidepressant-associated erectile dysfunction can greatly increase the likelihood that patients will continue the medication that effectively treats their depression.

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Over the past decade, the medical community has increasingly recognized the problem of erectile dysfunction and other sexual dysfunction associated with antidepressant therapy. Although early generation antidepressant agents such as monoamine oxidase inhibitors or tricyclic antidepressants frequently elicit erectile dysfunction and related sexual dysfunction,[1] these problems are overshadowed by more troublesome and debilitating side effects that limit their utility.[2] In response, serotonin reuptake inhibitors (SRIs) were developed and have become the most commonly prescribed antidepressants worldwide.[3] SRIs offer comparable efficacy, improved dose titration, and a significantly better safety margin. However, with their widespread use, it has become apparent that SRIs are not without sexual side effects.[2,4] Antidepressant-associated erectile dysfunction and sexual dysfunction are well-described effects in patients taking SRIs, and approximately 10 to 15 million patients taking SRIs are likely to develop sexual side effects each year.[4]

Antidepressant-associated erectile dysfunction can play a disruptive role in the often long-term treatment of depression. Current recommendations indicate prolonged continuation treatment for 6 to 9 months after the acute phase, as well as a long-term maintenance phase (1 year to lifetime) for patients with recurring episodes of depression.[5] Moreover, it has been reported that approximately 25% of patients taking SRIs or other antidepressants do not complete treatment with the initially prescribed agent and switch to another.[6] Less than half of patients taking an antidepressant fill more than 3 prescriptions, an indication that treatment is not adhered to for more than 3 months.[7]

Treatment of antidepressant-associated sexual dysfunction should include a complete sexual history to determine the type of erectile dysfunction as well as effects on desire, arousal, orgasm, and satisfaction; potential contributing factors; and a management strategy suitable for the individual patient. Successful management can improve adherence to antidepressant therapy and potentially prevent increased morbidity and relapses.

PREVALENCE OF ERECTILE DYSFUNCTION IN HEALTHY POPULATIONS

Erectile dysfunction is a common problem in the general population and a common symptom of depression. The National Health and Social Life Survey indicated that 31% of men aged 18 to 59 years report sexual dysfunction, with 5% of those men reporting erectile dysfunction.[8] However, erectile dysfunction is highly correlated with

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Table 1. Prevalence of Erectile Dysfunction in Healthy Populations

Study	Age, y	N	Sexual Dysfunction, %	Any ED, %	Moderate and Complete ED, %
NHSL Survey[8]	18–59	1410	31	5	…
MMAS[9]	40–70	1290		52	35
Cross National Study[41]	40–70	~600			
Japan		…	…	…	34
Malaysia		…	…	…	22
Italy		…	…	…	17
Brazil		…	…	…	15
Turkey[42]	40–70+	1982	…	69	36
Belgium[43]	40–69	799	…	…	34
Rancho Bernardo Study[44]	30–80+	976	…	…	27
United Kingdom survey[45]	18–75	654	34	…	…
General medical patients[46]	59	199	…	36	…
Thailand[47]	40–70	1250	…	38	…

Abbreviations: ED = erectile dysfunction, MMAS = Massachusetts Male Aging Study, NHSL = National Health and Social Life Survey. Symbol: … = not determined.

aging. The Massachusetts Male Aging Study (MMAS) reported an overall erectile dysfunction prevalence (mild, moderate, and complete) of 52% in men between the ages of 40 and 70 years; 35% of men reported moderate and complete erectile dysfunction.[9] Studies in other countries support these prevalence numbers (Table 1).

PREVALENCE OF ERECTILE DYSFUNCTION IN UNTREATED DEPRESSION

The relationship between erectile dysfunction and depression is complex, and the causal relationship is not clear. The stress and anxiety that accompany erectile dysfunction may cause secondary depression, or erectile dysfunction can be 1 of the symptoms of major depressive disorder (MDD), or both conditions can coexist in a related or unrelated fashion.[10]

In a subgroup of men with MDD, a reversible loss of nocturnal penile tumescence was reported, further suggesting that depression can directly affect erectile function.[10] Epidemiology studies have demonstrated an association between erectile dysfunction and depression independent of age or the presence of comorbidities.[9,11,12] In the MMAS, men with depression had a 1.8 times higher chance of experiencing erectile dysfunction than those without depression, and the prevalence rates of erectile dysfunction increased as the severity of depression increased.[12] In a Brazilian study of sexual behavior, a bivariate age-adjusted analysis showed a significant association between a history of depression and an increased prevalence of erectile dysfunction.[13]

In 2 studies of men with MDD that assessed the occurrence of sexual dysfunction prior to antidepressant therapy, 46% of men reported an inability to sustain an erection[14] and 65% reported some sexual dysfunction at baseline.[15] Finally, in a randomized controlled trial of 90 men with MDD, baseline prevalence of some degree of erectile dysfunction was reported at 87%. In addition, the mean number of sexual problems reported by these men was 3.6, emphasizing that in depression, single sexual complaints are rare.[16]

PREVALENCE OF ERECTILE DYSFUNCTION IN TREATED DEPRESSION

A worsening of preexisting erectile dysfunction has been reported with various agents from all antidepressant classes, including monoamine oxidase inhibitors, tricyclic antidepressants, and SRIs.[1] While SRIs have transformed the treatment of depression since their release in the late 1980s and are now the most commonly prescribed antidepressants worldwide,[3] sexual function disturbances associated with these agents have been prevalent. Postmarketing surveillance and clinical trials have shown the occurrence of sexual dysfunction associated with SRI use.

One surveillance study of almost 2500 patients treated with fluoxetine indicated that the incidence of sexual dysfunction was < 1.5%, an example of the inadequacy of postmarketing studies in estimating the incidence of antidepressant-associated sexual dysfunction.[17] However, this type of study has the potential of distinguishing differences in the relative incidence of sexual dysfunction among different antidepressants. For example, a cohort study by the Drug Safety Research Unit of the United Kingdom comparing 4 antidepressants found that erectile dysfunction was reported significantly more often with paroxetine than with other SRIs.[17] Similarly, in a comparison of the postmarketing safety profiles of antidepressants using the spontaneous adverse drug reaction reports to the United Kingdom Committee on Safety of Medicines, reports of erectile dysfunction were higher for paroxetine compared with other SRIs.[17]

Prerelease and early clinical studies rarely reported any SRI-associated sexual dysfunction; in fact, initially the

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Table 2. Prevalence of SRI-Associated Erectile Dysfunction

Study	Men, N	Type of Study	SRI Used	Overall Sexual Dysfunction, %	ED, %
Ashton et al, 1997[18]	167	Retrospective		23.4	10
			Fluoxetine		
			Paroxetine		
			Sertraline		
			Venlafaxine		
Jacobsen, 1992[19]	160	Prospective	Fluoxetine	34	
Montejo-Gonzalez et al, 1997[20]	152	Prospective		58 (14)[a]	
			Fluoxetine		16
			Fluvoxamine		9.5
			Paroxetine		34
			Sertraline		16
Fava et al, 1998[22]	63	Double-blind, placebo-controlled	Paroxetine	25	
			Fluoxetine	7	
Labbate et al, 1998[21]	12	Prospective		ND	58/38[b]
			Fluoxetine		
			Sertraline		
			Paroxetine		
Clayton et al, 2002[23]	183	Cross-sectional, observational	Citalopram	30	
			Venlafaxine	30	
			Sertraline	27	
			Paroxetine	27	
			Fluoxetine	24	
			Bupropion	7	
			Overall	24	ND

[a]Number in parentheses indicates percentage of patients reporting sexual dysfunction/ED without prompting.
[b]58% and 38% of patients had decreased erection scores after 1 and 2 months of SRI therapy, respectively.
Abbreviations: ED = erectile dysfunction, ND = not determined, SRI = serotonin reuptake inhibitor.

incidence of sexual dysfunction with fluoxetine in controlled trials was reported as 1.9%,[17] probably owing to the fact that no structured or validated questionnaires were used. Few studies have systematically evaluated the incidence of sexual side effects with antidepressant use (Table 2). A large-scale, nonrandomized, retrospective study of 167 men using 1 of 4 SRIs (fluoxetine, paroxetine, sertraline, or venlafaxine) for ≥ 6 months showed that 23% reported overall sexual dysfunction and 10% reported erectile dysfunction specifically.[18] In a prospective study of fluoxetine in 160 outpatients, 13% of patients reported decreased sexual response.[19] Similarly, in another prospective multicenter study of 152 male outpatients taking 1 of 4 SRIs, incidence of erectile dysfunction ranged from 10% (fluvoxamine) to 34% (paroxetine) depending on the SRI used.[20] Labbate et al.[21] reported reduced erection scores in 12 patients with MDD after 1 and 2 months of antidepressant use compared with baseline values, and Fava et al.[22] demonstrated a 25% and 7% incidence of sexual dysfunction with paroxetine and fluoxetine, respectively, in a double-blind study involving 63 men. More recently, a cross-sectional, observational study conducted in > 1000 U.S. primary care clinics involving > 6000 outpatients (1763 men) receiving antidepressant therapy concluded that in a subpopulation (N = 798 [183 men]) unlikely to have predisposing factors for sexual dysfunction, the prevalence of sexual dysfunction ranged from 7% to 30%, depending on the antidepressant used.[23]

PREVALENCE OF ERECTILE DYSFUNCTION SECONDARY TO OTHER SEXUAL DYSFUNCTIONS

It is well known that many antidepressants, including SRIs, cause other sexual dysfunction besides erectile dysfunction such as delayed ejaculation, anorgasmia, and decreased libido.[4,17] Montejo-Gonzalez et al.[20] reported in 344 patients a high incidence of loss of libido (40%–58%), delayed orgasm/ejaculation (46%–59%), or anorgasmia (31%–48%) depending on the SRI taken. These results are in agreement with other studies of patients taking antidepressants.[15,16,24]

Because the link between depression and sexual dysfunction is complex, it is possible that antidepressant-associated erectile dysfunction is a consequence of other comorbid sexual dysfunction. For example, on detailed inquiry some patients have revealed that their antidepressant-induced erectile dysfunction is associated with the inability to sustain an erection long enough to achieve orgasm and ejaculation[25]; thus, it could be considered that erectile dysfunction in these men occurs secondarily to prolonged ejaculatory latency.[17] Similarly, because desire is the first step in the sexual response cycle and is intimately connected with sexual arousal, its absence may preclude men from engaging in sexual activity and achieving erections. Therefore, erectile dysfunction in this situation may be labeled as secondary to hypoactive sexual desire.

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MECHANISMS OF ANTIDEPRESSANT-ASSOCIATED SEXUAL AND ERECTILE DYSFUNCTION

The neurochemistry of sexual function involves multiple integrated systems. Although the precise mechanisms mediating SRI-associated sexual dysfunction are not well understood, based on evidence from case reports, uncontrolled studies, and conclusions drawn from sexual side effects observed with the use of psychotropic drugs, a number of pathways have been implicated in this process. These include serotonergic, dopaminergic, and cholinergic systems, as well as prolactin and nitric oxide.[17,26]

Given the wide distribution and numerous serotonin receptor families located both centrally and peripherally, it is no surprise that serotonin mediates a number of aspects of the sexual response cycle. In general, serotonin exerts an inhibitory role on sexual function and, thus, drugs causing an increase in serotonergic activity, such as SRIs, lead to some form of sexual dysfunction.[26] In the brain, there is evidence that serotonin causes a decrease in dopamine levels (a neurotransmitter enhancing sexual function) in animal models. Peripherally, inhibition of α-adrenergic and cholinergic receptors in the genitourinary tract also impairs sexual function; cholinergic fibers aid blood flow in the corpora cavernosa, whereas α_1-receptors aid in the detumescence process.[20] Sexual side effects have consistently been observed with SRI use but not with serotonin (5-HT_{1A}) agonists. Apparently activation of 5-HT_{1A} receptors may facilitate sexual behavior in rats, whereas activation of 5-HT_2 receptors may be inhibitory.[17]

Dopamine neurotransmission has been reported to play a role in sexual function (i.e., libido, psychological arousal, and erection).[27] Agents that are potent SRI inhibitors but lack any effect on dopamine uptake inhibition, such as paroxetine, have an apparently greater incidence of sexual dysfunction than other agents with a more balanced profile.[28,29] In animal models, dopamine agonists have been linked to a decreased ejaculatory threshold, while removal of dopaminergic neurons is associated with increased ejaculatory latency.[30] Supporting these in vitro results are reports that dopamine antagonists, that is, antipsychotics, have a high incidence of erectile dysfunction.[31]

Although the currently available evidence does not support a direct role for acetylcholine in sexual function, antidepressants with potent anticholinergic activity, such as tricyclic antidepressants and those SRIs with greater affinity for the cholinergic receptor, e.g., paroxetine, have shown a marked incidence of sexual dysfunction.[32,33]

The role of prolactin in the sexual response cycle remains uncertain. However, because serotonergic stimulation increases prolactin release from the hypothalamus and dopamine is the prolactin-inhibiting factor, any disturbance of the hypothalamic-pituitary-dopaminergic pathway is likely to affect prolactin secretion.[26] Hyperprolactinemia, which can be a consequence of SRI use,[34] is associated with a marked negative effect on sexual desire and performance in men. Consistent with these findings, studies have shown that paroxetine, a potent SRI but lacking effect on dopamine uptake inhibition, can cause marked increases in plasma prolactin levels in healthy volunteers and patients.[35,36]

Another possible explanation for the increased incidence of sexual dysfunction with SRIs is suggested by recent findings that certain SRIs are potent inhibitors of nitric oxide synthase both in vitro and in vivo[37]; nitric oxide is a critical element in the signal transduction cascade mediating penile erection.

ASSESSMENT OF ANTIDEPRESSANT-ASSOCIATED ERECTILE DYSFUNCTION

As recently as 20 years ago, medical school curricula did not include adequate information on how to properly elicit a sexual medical history from patients; even recent surveys among health care providers show that only 57% of physicians routinely obtain a sexual history from their patients.[38] The incidence of antidepressant-associated erectile dysfunction is often underestimated because few patients spontaneously report their problem[20]; in fact, many patients reported sexual difficulties only if specific questions were asked and sometimes only after repeated office visits.[18] Similarly, it has been reported that the incidence of sexual dysfunction was 58% when physicians asked their patients about sexual function compared with a 14% incidence when self-reported by patients.[20] Most patients clearly would like their physicians to bring up the topic of sexual health,[39] but in many cases embarrassment by physician and patient often prevents an open discussion of sexual health, thus limiting treatment opportunity. Obtaining a complete sexual history will aid the physician in determining what type of sexual dysfunction is present; whether it is a consequence of depression, antidepressants, or other medications; and what confounding factors may play a role.

In general, it is important for physicians to recognize the fact that sexual activity is important to patients with depression and that the prevalence of erectile dysfunction in this group can be high. It is, therefore, important to evaluate the sexual function of all patients with depression and to manage the depressive disorder in a way that optimizes sexual function. As a result, patients will be less likely to discontinue antidepressant treatment and, thus, to relapse.

METHODOLOGICAL AND CONCEPTUAL CHALLENGES

During a review of the literature on the incidence of SRI-associated erectile dysfunction and other sexual

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dysfunction, a number of challenges present themselves. These include nonrandom drug assignment, use of various unstructured or nonstandardized instruments resulting in a limited assessment of sexual function, varying treatment duration, concomitant medications, and lack of equivalence in dosages, making a comparison between different antidepressants and studies difficult if not impossible.

Postmarketing surveillance studies have historically reported very low incidences of sexual dysfunction and highlight the inadequacy of such measures for obtaining realistic incidences of antidepressant-associated sexual dysfunction. Cross-sectional studies may overlook beneficial effects of SRIs on sexual response and mistakenly attribute residual dysfunction to the medication used. In clinical studies, both trial design and endpoint assessment can have major impacts on the apparent incidence of sexual side effects with SRI use.[17] For example, none of the early clinical trials included in the product labeling of the SRIs used a structured instrument for the assessment of sexual dysfunction,[48] and this may have contributed to the underestimate of SRI-induced sexual dysfunction with fluoxetine (1.9%).[17] Finally, dosage of SRIs is an important point because the dose-response curve is relatively flat with respect to efficacy, whereas side effects such as sexual dysfunction are strongly dose related.[17]

SUMMARY

Significant advances have been made in the treatment of depression and other related affective disorders. Although newer antidepressant treatments have fewer side effects overall, erectile dysfunction is an important, highly prevalent, and potentially distressing occurrence for patients with depression and can limit adherence to antidepressant therapy. Thus, early detection of erectile dysfunction in men with depression, with the help of a suitable questionnaire such as the Sexual Health Inventory for Men,[40] can lead to successful management of erectile dysfunction and may increase the likelihood of antidepressant treatment continuation and minimize relapse.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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