

Reassessing the approach to SSRI treatment-emergent sexual dysfunction

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Maintaining patient compliance with a recommended treatment regimen is a common and long-standing concern in medical practice. Despite the general awareness of this widespread problem—a recent article cites 60,000 examples since 1980¹—only a paucity of data suggests how to overcome it. At best, regardless of disease, treatment, age, or risk level, only 50% of patients with chronic diseases comply with their physicians' recommended regimens.

About 25 to 30 million Americans suffer from depression annually; of these, 18 to 25 million are treated with antidepressants, but less than one half fill three prescriptions, and less than one third complete the recommended guideline for 6-months treatment following resolution of the acute phase.² Treatment-emergent side effects (ie, sexual dysfunction, weight gain, sleep disturbance) account for 66% to 75% of premature treatment terminations.³ This significantly increases risk for relapse, recurrence, and morbidity or mortality associated with treatment failure. The 25% to 70% reemergence rate occurs incrementally, and is significantly higher among patients who have terminated treatment prematurely than among those completing the drug regimens. Sexual dysfunction (SD), one of the most common adverse effects of the selective serotonin reuptake inhibitors (SSRIs), occurs in 40% to 70% of Americans using SSRIs,⁴ suggesting that 10 to 15 million patients annually may develop iatrogenic SD, and 87% will not follow their prescribed regimens.

Antidepressant-associated SDs generally occur early in treatment and subsequently remit, improve, change, or persist. Decreased libido, erectile dysfunction (ED), vaginal dryness, delayed orgasm, and discomfort or pain are common complaints. Although the specific mechanisms

remain to be clarified, serotonin (5-HT) levels and receptor function are considered to underlie SSRI effects for depression and treatment-emergent SD. (Many other agents participate in the complex pathways that signal sexual function sequencing.)

Much has been made of the different serotonergic effects of individual SSRIs on sexual function. Although all the SSRIs are similar in terms of transporter inhibition, their other pharmacokinetic properties may nevertheless be different, resulting in differences in side effects. However, perhaps with the exception of paroxetine, which may confer greater adverse effects, no adequate controlled studies are available that can allow us to determine significant differences among the SSRIs' efficacy regarding treatment-emergent SD. Unlike other experts,⁵ my opinion is that the data are inconclusive and cannot establish the significance of any differences among SSRIs on treatment-emergent SD. We must also remember that patients, too, have different responses,

even when taking the same agent. As we are beginning to better understand individual genotype variation influencing drug response and side effects, any claim for superiority among the SSRIs must be critically evaluated and clinically replicated.

W. Finger's able review⁶ in the September 2001 issue of the journal concerning the different treatment strategies for antidepressant-induced SD was comprehensive, but all these approaches are quite weak, and further inquiry for supporting evidence reveals sparse empirical data, which can be methodologically challenged. To date, fewer than 15 double-blind, placebo-controlled studies have been conducted on these approaches, and none has demonstrated a level of efficacy that would substantially improve the condition in more than 50% of subjects. The prevail-

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ing approaches in this country to serotonin reuptake inhibitor (SRI) antidepressant treatment-emergent SD can be divided into the following four major categories.

Antidote—using a specific agonist or antagonist agent acting on receptors conjectured to promote or oppose SRI-inducing SD mechanisms (eg, yohimbine, bupropion, cyproheptadine, stimulants, bethanechol, pindolol, amantadine, granisetron, or herbals).

Avoidance—a strategy used to prevent SRI-emergent SD by selecting an antidepressant with receptor profile that is less likely to be associated with SD (eg, bupropion, nefazodone, mirtazapine, moclobemide, mianserin).

Antidepressant augmentation/switching—a variant of the antidote approach, it uses non-SSRI antidepressants with different receptor profiles to “add-to” or replace an SSRI that is effective for the depression but is causing treatment-emergent SD.

Adaptation—“watchful waiting,” dose reduction, or “drug holiday” are methods used to allow patients to adjust to treatment-emergent SD.

The disjunction between current “clinical wisdom” and evidence-based data becomes poignant when we consider essentially none of these approaches has demonstrated an overall significant, clinically meaningful treatment efficacy in randomized, double-blind, placebo-controlled trials.^{3,7} Only two studies investigating initial treatment of major depression by comparing bupropion with an SSRI and a placebo have been able to demonstrate reduced orgasm dysfunction with bupropion at 8 weeks, as compared with the SSRI.^{8,9} Several reports of add-on of bupropion to an SSRI showed no difference compared with placebo, or a 0.05 improvement in sexual desire or fantasy only, using high daily dose.¹⁰

Therefore, when applying any of these four approaches we must consider the potential of new or heightened adverse effects inherent in the involved agents or methods: for example, yohimbine may induce anxiety; cyproheptadine can exacerbate major depression; bupropion is associated with agitation; stimulants develop dependency; mirtazapine may result in weight gain; nefazodone shows greater treatment drop out, with neutral rather than antidote effects on SD; and granisetron, amantadine, and bupropion only equal placebo. Waiting for spontaneous remission, drug holiday, or dose reduction are rarely effective.

The SRIs remain the agents of choice; nefazodone has, perhaps, the most neutral effect on sexual function,

and bupropion is less likely to be associated with treatment-emergent SD. Until the arrival of the novel non-adrenergic-noncholinergic (NANC)-enhancing agents, there were no effective treatments for iatrogenic antidepressant SD. Untreated sexual problems remain a major obstacle to patient compliance with antidepressant regimens.

Psychiatrists have been using antidepressants for close to 50 years, yet only a paucity of new data has emerged to address the problem of SSRI-induced SD. Research into NANC signal transduction led in 1998 to the introduction of sildenafil citrate for the treatment of diverse etiologies of ED. Several studies reported highly significant efficacy compared with placebo in men with ED associated with diabetes, hypertension, multiple sclerosis, depression, Peyronie’s disease, stable angina, and other conditions.

Enhanced NANC signal transduction suggests a potential application to iatrogenic SRI-emergent SD. Sildenafil’s mechanism of action as well as its well-tolerated and broad-spectrum efficacy for ED further suggest that it might be clinically effective in alleviating SSRI-induced SD. A number of open-label studies reported that male and female patients with major depression in remission with SRI treatment-continuation responded well to sildenafil treatment.^{3,11,12}

Although encouraging, final conclusions await results of our research group’s recently completed prospective, multicenter, double-blind, placebo-controlled study^{13,14} that compared sildenafil with a placebo for the treatment of antidepressant SRI-associated SD in men with major depression in remission, on continuation of an SRI treatment. Over 90% of study-completed patients were able to remain on the SRI antidepressant and maintain depression remission for over 23 weeks without recurrence or relapse.¹⁴ These results indicate a new potential first-line therapy for antidepressant treatment-emergent ED and associated sexual dysfunctions. Several replications of this study are either completed or in progress.¹⁵

Because many patients on SSRIs are women, the question of their effects on women must be addressed. Our open-label studies, using the same protocol as on men, were positive. Results from our double-blind, placebo-controlled study on women will be available soon. We must emphasize, however, that sildenafil has only been approved by the FDA for the treatment of ED; therefore, any other application, such as for SSRI-induced SD in women, is off label. ☐

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