

## **Antidepressant-Associated Sexual Dysfunction: A Review**

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## **ABSTRACT**

Sexual dysfunction has been reported to occur in approximately 30-70% of patients receiving antidepressant medications. The highest incidence of sexual dysfunction is seen primarily in patients receiving serotonin reuptake inhibitors (SSRIs) where up to 50-70% of these patients have been shown to have difficulties in sexual functioning. The occurrence of medication-associated sexual dysfunction increases the likelihood of medication non-compliance (or adherence) in patients, which may contribute to untreated depression and/or disease relapse. The goal of this review is to summarize and evaluate the current literature on the occurrence of antidepressant-associated sexual dysfunction as well as to assess the treatment options available for this side-effect.

## **INTRODUCTION**

Antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) are effective for the treatment of depression, but have unfortunately been associated with the occurrence of sexual dysfunction. Awareness about this significant side-effect has recently increased due to the high utilization of SSRIs as well as the development of several pharmacologic agents that successfully treat erectile dysfunction (ED). Unfortunately, ED is not the only kind of sexual dysfunction seen from SSRI use, with additional forms including decreased sexual desire, orgasmic and ejaculatory dysfunction, lack of sexual arousal, and reduced sexual satisfaction<sup>1</sup>. In the general population, sexual dysfunction has been found to occur at a baseline rate between 5-35%<sup>2</sup>. Risk factors for the occurrence of sexual dysfunction include cigarette smoking, cardiovascular disease, diabetes, heavy ethanol consumption, hormone disorders, medications, depression, sexual trauma and other psychiatric diagnoses<sup>3</sup>. In this review we will discuss the incidence of this medication-associated adverse event, the effect of sexual dysfunction on antidepressant medication compliance, as well as review the currently available studies on treatments for this problem.

## **SEXUAL DYSFUNCTION IN GENERAL AND PSYCHIATRIC POPULATIONS**

In 1992, portions of the National Health and Social Life Survey (NHSLS) were performed to address the sexual behavior of adults in the United States and prevalence rates of sexual dysfunction were compiled. The survey included 1410 men and 1749 women between the ages of 18 and 59. As part of the NHSLS, the presence of at least one critical symptom in the previous 12 months in one or more of 7 response items was measured. Laumann et al<sup>4</sup> analyzed the data from this survey and found that sexual dysfunction was more prevalent in women (43%) than men (31%) in that study sample. Data examining psychiatric and medical diagnoses, as well as concomitant medications were not included in their analysis. An earlier review of 22 studies of sexual dysfunction found prevalence estimates of 15% and 35% inhibited sexual desire for males and females respectively, ED/ejaculatory disturbances in 35% of men, and orgasmic difficulties in 5-30% of women<sup>2</sup>. Risk factors that were associated with sexual dysfunction can be found in Table 1. Age was found to be a strong predictor of sexual dysfunction, in that young women and older men most commonly have sexual problems<sup>5</sup>. Taken together, these analyses indicate that sexual dysfunction is a significant public health concern, is affected by many health and psychosocial factors (see Table 1), and

further research needs to be done to determine the etiology behind why these factors affect sexual well-being.

Sexual dysfunction occurs in the general population, but is often confounded by psychiatric illnesses, particularly mood and anxiety disorders. Thus, pharmacological treatment of these mental health problems has the ability to improve sexual dysfunction resulting from psychiatric illness. Unfortunately, many medications that are used to treat psychiatric illnesses have side effects that negatively impact sexual functioning.

Although major depression has been associated with the occurrence of sexual dysfunction, many antidepressant agents can exacerbate or induce this problem. Therefore it is sometimes difficult to determine whether sexual difficulties in a medicated individual result from their psychiatric condition(s) or from the medications being used to treat them. This topic was addressed by Angst et al <sup>6</sup>, who examined 591 males and females between the ages of 20-35 in the general population to determine the prevalence of sexual problems in depressed individuals. By comparing those subjects with depression to non-depressed subjects they found over a two-fold difference in the prevalence of sexual dysfunction (50% vs 24% respectively). The subjects with depression were subsequently stratified based on whether they were currently being treated for their depression. This analysis showed that 62% of those receiving pharmacotherapy reported some sexual dysfunction, compared to 45% of those untreated, and 24% in the non-depressed controls.

Most recently, Williams and colleagues <sup>7</sup> examined the prevalence of antidepressant-associated sexual dysfunction in two different European populations. In a cross-sectional study including 500 patients from France and the United Kingdom receiving antidepressants, these authors found that 26.6% of the French population and 29.2% of the UK population were experiencing antidepressant-associated sexual dysfunction. In this study sample, 32.4% of the women and 32.5% of men in this sample had sexual dysfunction. The patients with antidepressant-associated sexual dysfunction reported that their changes in sexual functioning negatively affected self-esteem, mood, and relationships, as well as sexual satisfaction of their partner. Thus, antidepressant-associated sexual dysfunction can not only negatively impact the individual with depression, but also others involved in the patients' lives as well.

## **PSYCHOPHARMACOLOGY OF ANTIDEPRESSANT ASSOCIATED SEXUAL DYSFUNCTION**

Broadly speaking, there are 3 stages of sexual functioning [Stage 1: interest and desire (libido), Stage 2: physiologic arousal, and Stage 3: orgasm] and five primary neurotransmitters, dopamine (Stage 1), nitric oxide and acetylcholine (Stage 2), serotonin (Stage 2 and 3), and norepinephrine (Stage 3), which are believed to play the most crucial roles in antidepressant-associated sexual dysfunction <sup>8</sup>. During Stage 1, increased levels of central dopamine are associated with an increase in sexual desire due to effects on the dopamine reward center in the mesolimbic system. Agents which block the action of dopamine have negative effects on sexual functioning. In Stage 2, nitric oxide (NO) and acetylcholine (Ach) affect physiologic arousal by increasing genital blood flow. Ach provides parasympathetic innervation of vascular tissues, and NO promotes additional blood flow to this region, promoting erection in males and vaginal swelling and

lubrication in females. Therefore agents which promote the action of NO and Ach facilitate arousal, while agents that inhibit their production or action (e.g. anticholinergic compounds) negatively affect sexual functioning at this stage of the sexual experience. Serotonin also plays a role in this second stage of sexual functioning as well as having an effect in the third stage. Animal models have shown that activation of 5-HT<sub>2A</sub> receptors has an inhibitory action on sexual behavior (Stages 2 and 3)<sup>9,10</sup>. Furthermore, we know that agents which enhance activation at these receptors (e.g. SSRIs) have negative effects on arousal. Conversely, agents known to block 5-HT<sub>2A</sub> receptors (e.g. nefazodone, mirtazapine, cyproheptadine) are known to have a lower incidence of sexual dysfunction and in some cases reverse sexual dysfunction from agents that promote 5-HT<sub>2A</sub> transmission. The third stage of the sexual experience, orgasm, appears to be primarily mediated by the sympathetic nervous system. Therefore, agents that promote the actions of norepinephrine (e.g. stimulants) positively affect Stage 3, while agents that block sympathetic signal transmission (e.g. beta blockers) have negative effects. It also appears that serotonin signaling through 5-HT<sub>2A</sub> receptors also negatively affects orgasm, although this mechanism is not well defined.

In general, the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs) seem to affect all stages of sexual functioning<sup>3</sup>. For sexual dysfunction related to SSRI use, difficulties seem to occur most commonly in relation to Stages 2 and 3<sup>8</sup> due to their ability to enhance neurotransmission of serotonin. In contrast to these medications, recent research suggests that bupropion, nefazodone, and possibly mirtazapine may not have the same propensity to cause sexual dysfunction due to differences in the mechanisms of action of these drugs compared to the more traditional TCAs, MAOIs, or SSRIs<sup>3</sup>. For a more thorough review of the pharmacology of antidepressant-associated sexual dysfunction, please see Zajecka 2001<sup>3</sup> and Meston and Frohlich 2000<sup>11</sup>.

### **ANTIDEPRESSANT USE AND GENERAL SEXUAL DYSFUNCTION**

Although sexual dysfunction associated with antidepressant use is seen fairly commonly in practice, the rates included in the package inserts, which are based on the initial clinical trials for each agent may not represent this. Package insert data for SSRIs and other newer antidepressants show rates of sexual dysfunction as a result of antidepressant use ranging from 0% to about 15% depending of the type of sexual dysfunction and the SSRI studied, with a mean rate of less than 10% (Figure 1). These rates are likely artificially low since they are based on inaccurate measures of sexual dysfunction, such as spontaneous reports of adverse effects in Phase 3 trials. Thus there is a discrepancy between what is reported in package inserts and what is reported in the literature. This may indicate that if patients were educated about these potential side-effects and specifically asked questions about their sexual health, the incidence rates would be more accurate, which has been the goal of many recent studies.

In one of the largest prospective studies of antidepressant-associated sexual dysfunction to date, Montejo et al<sup>12</sup> published a prospective analysis of 1022 patients with major depression, dysthymia, panic disorder, or obsessive-compulsive disorder, taking fluoxetine (n=279), sertraline (n=159), fluvoxamine (n=77), paroxetine (n=208), citalopram (n=66), venlafaxine (n=55), mirtazapine (n=49), nefazodone (n=50), amineptine (an atypical tricyclic antidepressant that blocks DA reuptake) (n=29), or

moclobemide (n=26). The Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) was the primary assessment tool while the Clinical Global Impression (CGI) and Hamilton Rating Scale for Depression (HAM-D) assessments were secondary measures performed to assess construct validity of the PRSexDQ. This study found that when asked directly, 59.1% of the patients experienced some form of sexual dysfunction after antidepressant initiation. However, only 20.2% of patients reported their problem spontaneously and the remaining 79.8% would have gone undiscovered. Antidepressants with the highest rates of dysfunction were citalopram (72.7%), paroxetine (70.7%), and venlafaxine (67.3%). Mirtazapine had a lower rate of dysfunction (24.4%) than the SSRIs as did nefazodone (8.0%), amineptine (6.9%), and moclobemide (3.9%). The most common adverse sexual effects of the SSRIs and venlafaxine were decreased libido and delayed orgasm. Paroxetine was associated with significantly higher rates of erectile dysfunction/decreased vaginal lubrication ( $p < 0.05$ ) compared to the other antidepressants. Males had a higher rate of dysfunction than females (62.4% vs. 56.9%), but females experienced more severe decreases in libido, delayed orgasm, and anorgasmia ( $p < 0.05$ ). Twenty-seven percent of the patients showed good tolerance to the sexual side effects, 34.5% accepted it with some objection, and 38.3% considered it unacceptable and suggested that this significantly affected their desire to continue therapy with their current medication.

An earlier prospective, observational, open label study assessing sexual dysfunction was performed with 344 patients taking fluoxetine, sertraline, fluvoxamine, or paroxetine<sup>13</sup>. The variables assessed were loss of libido, delayed orgasm or ejaculation, absence of orgasm or ejaculation, impotence, and patient's tolerance of sexual dysfunction. The incidence of sexual dysfunction was significantly increased when patients were asked directly from the questionnaire (58.1%) compared to spontaneous reports (14.2%). Greater than 50% of subjects receiving sertraline (56.4%), fluoxetine (54.4%), and paroxetine (64.7%) reported sexual dysfunction, with paroxetine being associated with a significantly higher incidence and severity of impotence and anorgasmia or no ejaculation ( $p < 0.05$ ). Overall, there was a higher incidence of sexual dysfunction in males (61.8%) than females (52.5%), but the sexual dysfunction experienced in females was more severe. Fifteen patients were switched to moclobemide with 12 (80%) experiencing a disappearance of sexual dysfunction. Five patients with antidepressant-associated sexual dysfunction were switched to amineptine. Three (60%) had complete resolution of their sexual difficulties while one had partial improvement, suggesting that switching to another class of antidepressants may be an effective strategy for dealing with SSRI-associated sexual dysfunction. In addition, these authors found that spontaneous reporting of sexual dysfunction was extremely low, and that direct questioning resulted in more powerful assessment of this side-effect.

Landen et al<sup>14</sup> assessed the incidence of sexual side effects in patients not responding to four weeks of citalopram or paroxetine in a randomized, double-blind, placebo-controlled bupropion augmentation trial. The patients were evaluated before and after they received four weeks of placebo or bupropion treatment. Outcomes were assessed with the CGI-S, Montgomery Asberg Depression Rating Scale (MADRS), Visual Analog Scale (VAS) to assess sexual functioning, and Global Assessment of Functioning (GAF). Side-effects were also assessed by asking a non-leading question that was followed by more direct questions with the UKU Side Effect Rating Scale. Forty-one percent of the patients

reported sexual dysfunction in response to direct questioning compared to only 6% of patients reporting sexual dysfunction with spontaneous report ( $p < 0.001$ ). There was no statistically significant difference in the sexual side effects between the two SSRIs (44% vs 36%). Overall the authors found that sexual dysfunction correlated with the duration of the current depressive episode ( $r = 0.19$ ,  $p = 0.043$ ), but did not correlate with age, dose of citalopram or paroxetine, plasma levels of either drug, duration of treatment with SSRI, or sexual functioning scores. The authors report that the patients' depression at baseline might contribute to sexual dysfunction.

Kennedy et al.<sup>15</sup> conducted a study comparing the effects of moclobemide, paroxetine, sertraline, and venlafaxine on sexual drive/desire and arousal/orgasm in 107 patients with a diagnosis of major depressive disorder. The SFQ and HAMD were administered before antidepressant treatment and after eight and 14 weeks. Antidepressant selection was based on the clinician's choice. Gender analysis at the end of 14 weeks showed that men reported significantly more impairment in drive/desire than women ( $p < 0.05$ ), but not on the arousal/orgasm scale. Women experienced more drive/desire and arousal/orgasm dysfunction while taking sertraline and paroxetine compared to moclobemide and venlafaxine, but overall the difference was only significant on a few items in each scale.

More recently this group has examined the effects of bupropion versus paroxetine on sexual functioning in men and women receiving these medications under double-blind conditions for eight weeks<sup>16</sup>. A total of 141 subjects (68 women and 73 men) were included in this study. Bupropion SR was dosed at 150-300mg/day and paroxetine was dosed at 20-40mg/day. Subjects were assessed with the HAMD, Sex Effects Scale (SEFX) and the Investigator-Rated Sexual Desire and Functioning Scale (IRSD-F) every two weeks. Prior to treatment, the women reported significantly lower sexual functioning than the male subjects ( $p < 0.001$ ). There were also baseline treatment differences for the women, with those in the paroxetine group reporting significantly lower levels of sexual functioning than women in the bupropion SR group ( $p < 0.01$ ). With drug treatment the women reported no statistical differences between the medications in terms of sexual functioning, however the men reported a worsening with paroxetine treatment ( $p < 0.05$ ). The women experienced an inverse relationship between the HAMD and sexual functioning scores over the eight weeks, confirming this group's previous results<sup>15</sup> that women experience better sexual functioning with treatment response. This relationship was not seen with the men and in fact with paroxetine treatment, the men experienced reduced sexual functioning compared to the bupropion group.

Bupropion is the only antidepressant with approval from the Federal Drug Administration (FDA) to state that it has a lower risk of sexual side effects within its package insert. The first placebo-controlled study comparing sustained-release bupropion and sertraline in the treatment of depression that specifically examined sexual dysfunction was published by Croft et al.<sup>17</sup> Bupropion, which is generally not associated with sexual dysfunction, is believed to exert its antidepressant activity via enhanced norepinephrine and dopamine neurotransmitter activity. The placebo control in this study is an advantage over other studies because it allowed the researchers to show that the change in sexual function is a result of the antidepressant and not due to the natural course of depression or any other external factors. The 360 patients who entered the trial had a diagnosis of moderate-to-severe depression and a score of  $\geq 18$  on the HAMD. They were randomized to receive

bupropion SR (150-400 mg/day), sertraline (50-200 mg/day), or placebo. Between 39% and 46% of patients in each treatment group suffered from a sexual desire disorder at baseline. By day 42, only 19% of bupropion SR treated patients continued to have problems with desire compared to approximately one-third of the sertraline and placebo groups ( $p < 0.05$ ). At baseline no one was considered to have sexual arousal disorder, however by day 14 and thereafter significantly more patients treated with sertraline experienced a problem with arousal ( $p < 0.05$ ). The incidence of arousal disorders with bupropion SR was significantly higher than placebo, but this difference did not become statistically significant until day 56 ( $p < 0.05$ ). Although sertraline did have a nominally higher incidence than bupropion, this was not statistically significant. There were also no reports of orgasmic dysfunction at baseline, but by day seven and thereafter, a significantly greater number of sertraline-treated patients experienced orgasmic dysfunction compared to those treated with placebo or bupropion ( $p < 0.001$ ). Sixty percent of patients were satisfied with their sexual function at baseline. From days seven through 42, more patients treated with bupropion SR were satisfied with their functioning compared to sertraline ( $p < 0.05$ ). However, on day 56 the difference between the two drugs was no longer significant, and significantly more placebo treated patients were satisfied compared to the sertraline group, while there was no difference seen between bupropion and placebo.

Recently, bupropion was also compared to escitalopram in terms of sexual functioning and antidepressant efficacy<sup>18</sup>. A total of 830 patients were randomized to either bupropion XL (300-450mg/day), escitalopram (10-20mg/day), or placebo for eight weeks in two identical but individual randomized, double-blind, treatment trials. Data from these trials were analyzed prospectively for the individual trials as well as looking at the pooled data. Overall the results of this study are very similar to the Croft study<sup>17</sup> previously discussed, except statistically significant differences were seen at week eight. Worsening of sexual dysfunction was statistically lower for the bupropion group compared to escitalopram (36% vs 20% respectively,  $p < 0.05$ ), while no statistical difference was seen between bupropion and placebo (20% vs. 15% respectively,  $p \geq 0.067$ ). Worsening of sexual functioning was also statistically higher with escitalopram compared to placebo ( $p \leq 0.001$ ). Thus, these studies confirm what has been reported in other studies, that bupropion is relatively lacking in sexual side-effects and therefore may be appropriate for antidepressant treatment when sexual functioning is a concern. Furthermore, escitalopram is not without effects on sexual functioning.

Mirtazapine is an antidepressant that exerts its effect by blockade of noradrenergic neurotransmission at presynaptic central alpha 2 adrenergic receptors<sup>19</sup>. Given that this medication also blocks post-synaptic 5-HT<sub>2A</sub> receptors, the risk of antidepressant-associated sexual dysfunction is felt to be relatively low. Initial case reports indeed suggested that there was a relatively low incidence of sexual dysfunction with mirtazapine treatment<sup>20</sup> and that switching from SSRIs to mirtazapine was useful in some patients experiencing sexual dysfunction from SSRI therapy<sup>21</sup>. Recently this was examined in a six month open label study involving 78 patients being treated with 15-60mg/day of mirtazapine for major depression<sup>22</sup>. Effectiveness was assessed using the HAMD rating scale along with the CGI and PRSexDQ. Over 60% of the subjects reported sexual dysfunction at baseline with a return to normal sexual functioning being seen in more than 70% of subjects completing the study. Improvement in sexual

functioning was independent of depression scores as only 47.4% of those included in this study experienced complete remission of their depression. A previous trial of oral disintegrating mirtazapine versus sertraline in 345 subjects with the Changes in Sexual Functioning Questionnaire (CSFQ)<sup>23</sup>. These authors found that in the first two weeks of the trial both males and females treated with mirtazapine had significantly greater improvements in the frequency of sexual activity as well as sexual arousal ( $p < 0.05$  for both CSFQ subscale measures). Total CSFQ scores were not statistically different, although the mean scores for sertraline met the gender-specific thresholds for having sexual dysfunction, while mirtazapine-treated participants had average scores above this threshold, indicating no dysfunction.

Recently, duloxetine has been added to our armamentarium for the treatment of depression. The primary mechanism of action for this medication is dual inhibition of both serotonin and norepinephrine reuptake transporters with lack of significant affinity for muscarinic, histaminic, or alpha receptors<sup>24</sup>. In a recently published review<sup>25</sup> of four eight week placebo or paroxetine controlled trials of duloxetine, the rate of sexual dysfunction associated with treatment was significantly less than that seen with paroxetine ( $p = 0.015$ ), but the rates in both the active medication arms were significantly higher than placebo ( $p = 0.007$  and  $p < 0.001$  for duloxetine and paroxetine, respectively). Overall, 61.4% of paroxetine subjects, 46.4% of duloxetine subjects, and 28.8% of placebo subjects experienced sexual dysfunction during acute treatment. The doses of medication used in these trials were 40-120mg/day of duloxetine and 20mg/day of paroxetine. Thus, although duloxetine showed a lower risk for sexual dysfunction than paroxetine, this risk was still significantly greater than that seen with placebo.

Reboxetine is another new antidepressant approved for the treatment of depression in Europe. Mechanistically this medication is a selective norepinephrine reuptake inhibitor that exerts little effect on serotonin neurotransmission<sup>26</sup>. The effects of this medication versus paroxetine were recently reported by Baldwin et al<sup>27</sup>. For this investigation, 70 patients from the United Kingdom were recruited for a randomized double-blind eight week study of reboxetine (4mg/day) or paroxetine (20mg/day). Assessments consisted of the HAMD and CGI completed at all study visits, and the Visual Analog Scale of the Rush Sexual Inventory (RSI) completed at baseline, day 28 and day 56. In terms of sexual functioning, subjects within the reboxetine group reported greater improvements with the item measuring the subjects' ability to become sexually excited showing increases for both treatment groups (7.1% increase for paroxetine vs. 66.5% for reboxetine,  $p < 0.05$ ). Overall, there were no other statistical differences seen between these two groups and lack of a placebo control made it difficult to determine if the improvements seen with the reboxetine group were due to the medication or simply a placebo effect. Additionally, the potential for lack of equivalent dosing for reboxetine and paroxetine make comparisons between these two agents difficult<sup>28</sup>.

Nefazodone has also been suggested as an alternative to the SSRIs due to reportedly lower rates of sexual dysfunction associated with this drug. The first study performed which showed a difference was by Feiger et al<sup>29</sup> and found that nefazodone was associated with fewer sexual adverse effects than sertraline. Ferguson et al<sup>30</sup> also examined sexual functioning with nefazodone treatment and included 105 patients who had previously experienced sexual dysfunction with sertraline. After a one week washout

period, subjects then underwent a seven to 10 day single blind placebo phase. Those who were not experiencing sexual dysfunction at the end of this phase were randomized to treatment with either nefazodone (400mg/day) or sertraline (100mg/day) for eight weeks. After this time period, 76% of the sertraline treated patients experienced a reemergence of sexual dysfunction compared to 26% of the nefazodone treated patients ( $p < 0.001$ ). Subjects treated with nefazodone were more satisfied with their sexual functioning and neither of the patients in either treatment group experienced a relapse of depressive symptoms. Unfortunately, recent reports of a relationship between this medication and the occurrence of fatal hepatitis have significantly decreased its use for the treatment of depression<sup>31</sup>.

Lastly, it should be noted that antidepressant-associated sexual dysfunction is not only associated with newer antidepressants (SSRIs, etc). One of the few randomized, double-blind, placebo-controlled studies examining the sexual side-effects of the tricyclic and MAOI classes of antidepressants was reported by Harrison et al in 1986<sup>32</sup>. A total of 82 moderately-depressed patients were randomized to receive imipramine (200-300 mg/day), phenelzine (60-90 mg/day), or placebo for six weeks. The effects on sexual functioning were assessed using the investigators' Sexual Function Questionnaire (SFQ) assessment. The HAMD, Symptom Check List, and CGI were also done before and after the trial. Five of seven items on the SFQ showed significant decreases in sexual function following treatment. Phenelzine caused more impairment than imipramine in the questions regarding interest ( $p = 0.02$ ), enjoyment ( $p = 0.03$ ), and ability to achieve orgasm with either intercourse or masturbation ( $p = 0.00$ ). The rates of patients reporting decreases in sexual functioning were 30% for imipramine ( $p = 0.02$  vs. PLB), 40% for phenelzine ( $p = 0.002$  vs. PLB), and 6% for PLB. Overall, the authors found a dose-dependent effect of decreased sexual function for imipramine, but not phenelzine. This study suggests that phenelzine and imipramine are associated with a high incidence of adverse effects on sexual functioning, and that these changes occur more frequently with phenelzine than imipramine.

Antidepressant associated sexual dysfunction appears to occur with most antidepressant medications, although most of the focus has been on SSRIs. In looking at this literature both bupropion and nefazodone and perhaps mirtazapine tend to "stand out" as medications approved in the United States that cause the least amount of sexual dysfunction. Most importantly to this literature is the discordance between the rates of sexual dysfunction reported in the package inserts and that actually seen in these clinical trials.

### **ANTIDEPRESSANT USE AND PREMATURE EJACULATION**

In looking at the types of sexual dysfunction seen with SSRIs, delayed ejaculation is a problem that has been reported to occur. Therefore, these medications have been the focus of research involving the treatment of premature ejaculation. Although occurrence of this "adverse effect" may be beneficial in males suffering from premature ejaculation, we may also look to this literature to assess the subtle differences that antidepressants may have in this area of sexual functioning.

Waldinger et al<sup>33</sup> conducted a double-blind, placebo-controlled study in 48 men with lifelong rapid ejaculation, defined as an intravaginal ejaculation latency time (IELT) of

one minute or less. The men received paroxetine (20 mg/day), sertraline (50 mg/day), nefazodone (400 mg/day), or placebo for six weeks. The female partner used a stopwatch to measure IELT. The mean baseline IELT was  $21 \pm 15$  seconds. After six weeks of treatment, there was a significant difference in IELT between placebo and sertraline (IELT=58 seconds,  $p=0.024$ ) and placebo and paroxetine (IELT=146 seconds,  $p<0.001$ ), but not nefazodone (IELT=23 seconds) and placebo. This indicates that there are differences in the amount of delay that occurs between different agents, even those in the same class, where paroxetine may cause more delay than other SSRIs. The delay in IELT seen with medication was evident within the first week of treatment and at a dose half of what is considered effective for treatment of depression. In this study, both paroxetine and sertraline caused marked increases in IELT, which is beneficial for those with premature ejaculation, but may predispose men to experience delayed ejaculation if they previously had a normal IELT. Although nefazodone is often considered a serotonergic antidepressant, it did not reduce IELT, which suggests that if one is concerned about delay in ejaculation, nefazodone may be preferred over a SSRI.

Waldinger et al.<sup>34</sup> also published a study comparing the effects of paroxetine and citalopram on IELT. Thirty men received paroxetine (20 mg/day) or citalopram (20 mg/day) for five weeks, following one week of half the dose previously mentioned. The mean IELT at baseline for paroxetine was 17.6 seconds and for citalopram was 20.7 seconds. At the end of six weeks, the IELTs for paroxetine and citalopram were 152.3 and 42.8 seconds, respectively. The difference from baseline for paroxetine was significant ( $p<0.001$ ), while the citalopram group's IELT did not increase significantly ( $p=0.07$ ). There was also a difference in IELT between the two groups at the end of six weeks ( $p=0.0004$ ). Thus, paroxetine treatment produced a significant delay in ejaculation, while the effect seen with citalopram was mild, and not significant. This study suggests that neither potency nor selectivity plays a critical role in the differences in ejaculation delay that are seen with the various SSRIs.

In contrast to this, Sarfarinejad and Hosseini<sup>35</sup> recently reported that citalopram was more effective than placebo in the treatment of premature ejaculation. For this investigation, 58 potent men were randomized to either citalopram (20mg/day) or placebo for 12 weeks. The efficacy of the two treatments was measured every two weeks during the study and at the study endpoint. The primary measures of efficacy were IELT and the International Index of Erectile Function (IIEF). After eight weeks of treatment the mean IELT for the placebo group changed from 28 seconds to 38 seconds, while in the citalopram group the IELT changed from 32 to 268 seconds ( $p<0.001$ ). Additionally, those in the citalopram group reported greater intercourse satisfaction as reported on the IIEF ( $p<0.05$ ). Thus, although the previous authors suggest that citalopram may not be effective for the treatment of premature ejaculation, the differences in treatment duration for each of these investigations (five weeks vs twelve weeks) may help explain the discrepancies in these results.

Recently, Kilic et al.<sup>36</sup> reported on the use of venlafaxine SR 75mg for the treatment of premature ejaculation. By using a two week placebo controlled crossover design in 31 subjects, these authors found significant increases in IELT from baseline ( $60.1 \pm 39.1$  sec to  $126.9 \pm 98.3$  and  $178.1 \pm 122.8$  seconds) for both placebo and venlafaxine ( $p<0.0001$  for each comparison). Thus, venlafaxine's effect on IELT seems to be primarily due to a

placebo effect and that perhaps a higher dosage of medication is required before ejaculatory difficulties can occur.

Although these studies were designed to assess premature ejaculation in non-depressed males, they may serve to illustrate subtle pharmacologic differences in the effects of agents within and between antidepressant classes on ejaculation. This may be useful as we assess pharmacological alternatives to agents that cause undesirable ejaculatory delay in persons taking these medications for mental illnesses.

### **ANTIDEPRESSANT DOSE AND SEXUAL DYSFUNCTION**

When we see patients experiencing antidepressant-associated sexual dysfunction, the question is often asked about the relationship between sexual dysfunction and medication dose. In looking at the premature ejaculation studies previously discussed, the investigators often found that the doses needed to reverse this sexual dysfunction were lower than those used for the treatment of depression. Thus, one would expect that the occurrence of sexual dysfunction associated with antidepressant use would be dose related. Package insert rates of spontaneously reported adverse sexual effects for paroxetine and venlafaxine showed that rates of dysfunction increased with increasing dosage. Clayton et al<sup>37</sup> also assessed the possibility of a dose relationship between sexual dysfunction and antidepressant medication in a cross-sectional study of 6297 patients using the CSFQ. In general, higher dosages of medication were associated with higher rates of dysfunction. However the variability in this data resulted in non-significant statistical comparisons.

### **SEXUAL DYSFUNCTION AND ANTIDEPRESSANT COMPLIANCE OR ADHERENCE**

Overall, antidepressant use for the treatment of depression seems to have an independent risk for the occurrence of sexual dysfunction, above and beyond what is seen in those with untreated depression. This increased risk for the development of sexual dysfunction with antidepressant use is troubling as antidepressant-associated sexual dysfunction can adversely affect the patients' quality of life, interpersonal relationships, self-esteem, as well as their satisfaction with treatment, and compliance with medication regimens. Persistence of antidepressant-associated sexual dysfunction after depressive symptoms have been alleviated may lead to a recurrence of depression<sup>17</sup>.

Sleath et al<sup>38</sup> conducted a study examining how patient sources of information (such as that obtained from health care professionals, friends and family, or the internet) were related to antidepressant adherence. They found that patients experiencing more side-effects were significantly less likely to adhere to their antidepressant regimens. Seventy-two percent of the patients in this study were taking an SSRI and had been taking their antidepressant for an average of two years. They experienced an average of 2.7 side effects, with change in sex drive being most frequent (35.8%). The average adherence rate in the previous week was 94.3%, with a range from 0 to 100, while 10% were less than 80% adherent. Overall, they found that the number of side effects experienced was a significant predictor of medication non-compliance.

Bull et al<sup>39</sup> found that more than half (55%) of patients receiving antidepressants experienced one or more adverse effect that was described as "occurring a lot" or

“extremely bothersome” and that 29% had one or more “extremely bothersome” adverse effect. This suggests that prescribers should expect that approximately half of their patients will experience serious medication-related side-effects that may need to be addressed. These authors also found that a third of those in this study were not taking their original antidepressant, primarily due to adverse effects, and of those, 70% stopped using their medication without consulting their physician. However, they also found that patients who discussed antidepressant-associated adverse effects with their prescriber were less likely to discontinue their medication than those who did not discuss these problems.

Similar to the Bull and colleagues study<sup>39</sup>, a study by Ruscher et al<sup>40</sup> found that nearly two-thirds of the patients (65.8%) receiving a psychiatric medication had changed their drug regimens without discussing this change with their psychiatrist and almost half (47.3%) of subjects discontinued their medication at some time in the past without informing their physician. Thirty-one percent of subjects in this study discontinued because of unwanted physical effects and 36.5% reported no negative side effects from their medication. This population included patients diagnosed with affective psychosis, schizophrenia, personality disorder and various other diagnoses.

Demyttenaere et al<sup>41</sup> investigated when and why patients stopped treatment with antidepressants and whether they informed their physicians. By the end of the study 53% of the respondents had discontinued their antidepressant, most commonly because they were feeling better (55%), and secondly because of adverse effects (23%). Twenty-four percent of the patients did so without telling their physician.

Overall these studies found that between 24-70% of patients who discontinued their antidepressant did so without informing their prescriber, and that 36% of those who discontinued their medication did so because of adverse effects<sup>39</sup>. Although untreated depression in and of itself is a significant risk factor for non adherence, this may only be worsened by bothersome adverse effects associated with antidepressant treatment, often necessitating dosage adjustments, switching classes of medication, the use of adjunctive treatment, or medication discontinuation.

## **MANAGEMENT OF SSRI ASSOCIATED SEXUAL DYSFUNCTION**

Because of the significant effect of sexual dysfunction on compliance to antidepressant therapy, there have been many investigations into strategies to manage or treat this unfortunate side-effect.

### Non-pharmacological Treatments

There are several non-drug treatment measures that have been investigated for management of antidepressant-associated sexual dysfunction. These include waiting for tolerance to develop (adaptation) which may take three to six months, employing a drug holiday, and reducing the dose of or discontinuing the antidepressant. Overall, the utilization of non-pharmacologic measures needs to be seriously considered before addition of any other pharmacologic agents, as these medications carry with them additional cost and the risk of further adverse drug reactions. The decision of how to proceed with therapy needs to be done in consultation with the patient as some of these

measures require a considerable amount of time, patience, and preparation on the patient's part.

### *Adaptation and Reemergence*

As part of non-pharmacologic management for antidepressant-associated sexual dysfunction, patients are encouraged to continue treatment with no changes to determine if this adverse effect is transient. This method is currently termed accommodation or adaptation. Montejo-Gonzalez et al<sup>13</sup> performed a prospective study of 344 outpatients being treated with SSRIs. Fifty-eight percent of patients had some decrease in sexual function at follow-up. They also found that within six months 5.8% of patients reported that sexual dysfunction had resolved completely, moderate improvement was found in 12.8%, and 81.4% showed no improvement. Thirteen patients in this study were switched to other SSRIs, of which four (30.7%) showed improvement in sexual dysfunction. Ashton et al<sup>42</sup> published a brief report of 97 outpatients who were taking antidepressants. Sexual function was measured at baseline and then followed for two to 38 months. They found that 9.8% of patients had accommodation to sexual dysfunction over the entire course of follow-up; however the definition of accommodation was not given. A later study published by Montejo et al<sup>12</sup> had similar findings. After six months of treatment with the antidepressant, 9.7% of patients had total improvement or spontaneous remission, 11.2% had partial improvement, and 79.1% showed no improvement in sexual dysfunction. Unfortunately, accommodation to the side-effect of sexual dysfunction seems to occur in only approximately 10% of patients within six months, although up to 15-20% of patients experience some type of improvement in symptoms in this time frame.

### *Drug Holiday*

Given that some reports have shown an association between SSRI dose and the incidence of sexual dysfunction, another strategy that has been suggested as a treatment for antidepressant-associated sexual dysfunction is altering the timing of the dose, or stopping the medication for a specified time period (drug holiday), such that the drug nadir occurs near the time of expected or usual sexual activity. The efficacy of a drug holiday was evaluated by Rothschild<sup>43</sup> who studied 30 outpatients (16 women and 14 men) who reported worsening sexual function with SSRI treatment. Ten patients each were taking paroxetine, fluoxetine, and sertraline. Participants were instructed to take the total SSRI dose in the morning, but to discontinue the SSRI after the Thursday morning dose and to restart it on Sunday at noon. They were also told to have sexual relations between Thursday evening and Monday morning and that they may see improvement in their sexual functioning. There were no significant differences in mean HAMD scores between Thursday and Sunday. In regards to sexual functioning, 50-60% of patients taking paroxetine and sertraline reported their sexual functioning was "much" or "very much" improved, while none of six women and one of four men taking fluoxetine reported improved functioning for at least 50% of four different weekend drug holidays. There was no difference in the rates of improvement between sertraline and paroxetine. The difference in the number reporting improvement was significantly greater with sertraline and paroxetine compared to fluoxetine. There was no placebo against which to compare these results. However, the consistent improvement in the paroxetine and sertraline groups and failure in the fluoxetine group fail to support a possible placebo

effect as use of a drug holiday is not recommended with fluoxetine due to its long half life. This study shows that a drug holiday may be efficacious for those taking the antidepressants with shorter half lives without allowing depressive symptoms to return. It must be noted that in this study, the doses of medications were relatively low [fluoxetine (n=10, 24 mg/d mean), paroxetine (n=10, 26 mg/d mean), sertraline (n=10, 60 mg/d mean)]. Because antidepressant-associated sexual dysfunction is often a dose-related phenomenon, and the likelihood for antidepressant discontinuation symptoms increases with higher doses, the drug holiday method of sexual dysfunction management is not an optimal option for the majority of patients experiencing these medication effects. Furthermore, healthcare providers must also consider the consequences of empowering patients to discontinue medications as needed, especially in light of previously discussed compliance data by Bull et al <sup>39</sup>.

### *Dosage Reduction*

In addition to the previous mentioned methods to treat antidepressant-associated sexual dysfunction such as accommodation, and drug holidays, dosage reduction is another possible treatment modality. Very little research has been done on specifically using this technique to treat this troubling and serious medication-associated side-effect. However, in looking at the previously mentioned data on sexual dysfunction and antidepressant dosage <sup>37</sup>, it would seem prudent that instituting a dosage reduction of medication may be a viable therapeutic option for some patients despite the lack of scientific literature specifically supporting this option.

### Switching Medications

In addition to the non-pharmacologic methods for the treatment of SSRI-associated sexual dysfunction listed above, there are several case reports in the literature that suggest switching to a different antidepressant may be a useful treatment. As outlined earlier, nefazodone, bupropion, and mirtazapine have all been consistently associated with lower rates of sexual dysfunction. Recently, Ashton et al <sup>44</sup> published a case controlled retrospective review of 47 patients who were switched to escitalopram for the management of antidepressant-associated sexual dysfunction. This review consisted of 26 males and 21 female patients who had been receiving fluoxetine, paroxetine, citalopram, sertraline, or venlafaxine for at least four weeks. Overall, 68% of these patients experienced mild or marked improvement in sexual dysfunction after switching therapy and in those patients that switched to the lowest dose of escitalopram (10mg/day), 73% experienced a reversal of sexual dysfunction. Given that this is a retrospective case report, the results do need to be interpreted cautiously, but may suggest that reducing the dosage of medication or switching to a different medication may be helpful in the treatment of SSRI associated sexual dysfunction.

### Adjunctive Therapy

Although the use of non-pharmacologic measures for the treatment of antidepressant-associated sexual dysfunction is generally considered first line, the use of adjunctive treatments is becoming more popular as more research into these treatments evolves. Before adding another agent to current antidepressant therapy, clinicians might consider a trial of medication such as bupropion or mirtazapine (if clinically appropriate) as sole therapeutic agent since these antidepressants appear to be associated with a lower risk of

sexual dysfunction. However, switching to another antidepressant or antidepressant class is not always possible and adjunctive treatment needs to be considered despite very little research within this area.

### *Bupropion*

In terms of adjunctive therapy with antidepressants, the medication most commonly examined has been bupropion. Kennedy et al<sup>45</sup> reported a trial of 18 patients who had received at least six weeks of paroxetine, fluoxetine, or venlafaxine XR and had documented sexual dysfunction. Bupropion SR was added at 150 mg/day for eight weeks given in an open manner. The primary outcome variables used were the HAMD, CGI, and the Sexual Functioning Questionnaire-Version 2 (Sex-FX). Overall, addition of the bupropion SR resulted in a clinically significant decrease in HAMD scores in 14 (78%) of the subjects and six (33%) achieved a full response ( $p=0.017$ ). The mean HAMD score at baseline was  $16.2 \pm 5.1$  which decreased to  $11.3 \pm 5.8$  after eight weeks of bupropion SR treatment ( $p=0.001$ ). In terms of sexual functioning, all three domains of the SEX-FX (desire, arousal, and orgasm) showed improvement after eight weeks of bupropion SR treatment but for the women, only the orgasm scores were statistically improved ( $p = 0.02$ ) while for the men the global functioning scores improved ( $p = 0.017$ ).

Masand et al<sup>46</sup> assessed the efficacy of bupropion SR in 39 patients who had been taking an SSRI for at least six weeks and whose MDD was in remission. Patients were randomized to receive 150 mg of bupropion SR or placebo for three weeks. The outcome measures used were the ASEX and the HAM-D. The investigators found that bupropion was no different than placebo for all measures of sexual function, as both agents showed significant improvement from baseline.

In 2004, Clayton et al<sup>47</sup> reported on the use of bupropion SR 150 BID as an “antidote” for SSRI associated sexual dysfunction. This study included 42 patients who had responded to their SSRI and were experiencing sexual dysfunction as measured by the CSFQ. After four weeks of adjunctive treatment with the bupropion, there were no differences in the total CSFQ scores between treatment groups. At four weeks the only measures which showed statistical differences were desire, as measured by self-report feelings, and frequency of sexual activity ( $p=0.024$ ) with the bupropion group experiencing significantly greater improvement compared to placebo.

DeBattista et al<sup>48</sup> entered 41 patients into a six week randomized, double-blind trial to assess the utility of adding a 150 mg morning dose of bupropion SR to current antidepressant therapy. To be included patients had to have been taking a fixed, therapeutic dose of fluoxetine, paroxetine, citalopram, or sertraline for at least six weeks and complain of sexual adverse effects. Sexual functioning was assessed using the total and individual item Arizona Sexual Experiences Scale (ASEX) score. Response was considered an improvement of 25% or more in total ASEX score and significant improvement was considered a 50% reduction in total ASEX score. None of the assessments of sexual functioning were found to be significantly different over time in both treatment groups and only five of 20 and six of 21 in the bupropion group and placebo group, respectively responded. This study failed to show that there was consistent improvement in SSRI-induced sexual dysfunction following the addition of

bupropion SR. However, the dose of bupropion used in this study was potentially too low to conclude that bupropion at any dose is ineffective and a larger study with higher doses is needed.

In summary, despite positive effects that were seen in open label, uncontrolled trials, randomized, placebo-controlled trials of adjunctive bupropion do not support its efficacy as treatment for antidepressant-associated sexual dysfunction. Improvement in sexual dysfunction in these trials occasionally resulted in statistically-significant improvements in some symptoms, but improvements in placebo groups as well suggest that a significant placebo effect may also play a role in symptom improvement.

### *Trazodone*

There is very little information on the role of trazodone for the treatment of erectile dysfunction. Recently a meta-analysis was published looking at this issue in men without depression<sup>49</sup>. This analysis included almost 400 men who were enrolled in six different randomized placebo controlled trials. Overall the authors found that three of the six trials showed a clinically meaningful benefit of trazodone for the treatment of erectile dysfunction, although only two of these studies reached statistical significance. In looking at the pooled data, trazodone showed a relative benefit increase of 1.6 (95% confidence interval 0.8-3.3) which was not statistically significant. The subgroup analyses showed that trazodone may be more beneficial in men when used at higher doses (150-200mg/day) and in men with psychogenic erectile dysfunction. Thus, these lackluster results may not support the use of trazodone for this purpose.

### *Phosphodiesterase Inhibitors*

The most commonly recognized agents for treating sexual dysfunction are the phosphodiesterase inhibitors. Until recently, sildenafil was the sole agent available, but now tadalafil and vardenafil are included in this class of medications. There is fairly convincing evidence that use of these agents as adjunctive treatment in males with SSRI-associated sexual dysfunction is effective, with the most significant effects in those patients with erectile dysfunction as their primary complaint. The first randomized controlled report of this was by Nurnberg et al<sup>50</sup> who combined data from 10 phase II and phase III trials to retrospectively identify men receiving 25-200mg/day of sildenafil or placebo and concomitant SSRIs. This analysis included 98 patients with SSRI-associated sexual dysfunction where efficacy of the sildenafil treatment was measured using the IIEF. Overall, sildenafil was better than placebo for ability to achieve and maintain erection ( $p=0.006$ ), ejaculation frequency ( $p=0.02$ ), and orgasm frequency ( $p=0.008$ ). However, sildenafil and placebo were no different when assessing desire frequency ( $p=0.65$ ).

In 2003, Nurnberg et al<sup>51</sup> reported a trial of 90 male outpatients who had been taking an SSRI for at least 12 weeks and suffering from sexual dysfunction for at least four weeks. Subjects were randomized to receive either 50-100 mg of sildenafil or placebo before sexual activity for six weeks. None of the patients discontinued the study medication because of side effects; however 40% reported headache and 7% flushing. Differences in sexual functioning was measured with the Clinical Global Impression-Sexual Function (CGI-SF) and the ASEX. There was no significant difference between placebo at baseline, sildenafil at baseline, and placebo at the endpoint. However, the CGI-SF scores

for the sildenafil group were significantly better at the end of the six weeks ( $p < 0.001$ ) than the three time points mentioned above. Scores on the ASEX were also significantly improved with sildenafil treatment in regards to desire, arousal, erectile function, and ability to orgasm ( $p < 0.02-0.001$ ).

Tignol et al.<sup>52</sup> saw comparable results with sildenafil treatment for antidepressant-associated sexual dysfunction. This study included 168 men with erectile dysfunction who were randomized to receive either sildenafil (50-100mg/day) or placebo for 12 weeks. All subjects included in this study were in remission from their major depressive disorder, indicated by a MADRS score of less than 12 at baseline. Assessment measures included the MADRS at baseline and 12 weeks, intercourse success rates, global efficacy, the IIEF and Life Satisfaction Checklist (LSC). After 12 weeks of treatment those receiving the sildenafil experienced higher rates of intercourse success (74% vs. 29%,  $p = 0.0001$ ) and about 83% of the sildenafil treated patients reported improved erections versus 34% of the placebo patients ( $p = 0.0001$ ). The IIEF and LSC scores also improved in the sildenafil group compared to the placebo patients.

Most recently, Fava et al.<sup>53</sup> reported on the short term use of sildenafil in treating antidepressant-associated erectile dysfunction (ED). For this study, 142 men were randomized to receive six weeks of either sildenafil (50-100mg/day) or placebo. The primary outcome for this study were questions three (frequency of penetration) and four (frequency of maintained erections after penetration) from the IIEF. Overall, these authors found very similar results to previous reports in that those receiving sildenafil reported significant improvement on the outcome measures versus placebo ( $p = 0.003$ ) and there were no changes in depression scores over the six weeks of treatment.

Along the lines of their previous research, Nurnberg and colleagues have also examined the economical advantages of using sildenafil for the treatment of SSRI-associated ED.<sup>54</sup> In this study, the investigators completed an economic analysis of 1000 hypothetical patients taking SSRIs and compared the costs of stopping the medication, switching to another SSRI, adding a non-SSRI on to treatment, or using sildenafil. Overall these authors found that after six months of treatment, adding on sildenafil was the most cost effective means of treating antidepressant-associated ED compared to the other therapeutic options. Their analysis suggests that patients who stop their medications due to ED and subsequently experience disease relapse incur substantial distress (psychological and financial) and that those that add on an additional antidepressant or switch antidepressants also incur treatment failures and additional costs. Thus, these authors concluded that sildenafil for the treatment of SSRI-associated ED is the most cost effective option in their model. However, it should be noted that in this industry-sponsored study, the cost-effectiveness of switching to an agent of a different medication class (e.g. bupropion or mirtazapine) was not assessed in this analysis.

Thus, it would appear from the numerous studies in males that sildenafil is an effective treatment for SSRI-associated ED and that this medication also has an effect on overall sexual satisfaction and functioning. Unfortunately in females, this may not be the case. Although there are case reports of phosphodiesterase inhibitors working in females with antidepressant-associated sexual dysfunction (<sup>55, 56, 57</sup>) in unpublished data from the drug manufacturer, a randomized, placebo-controlled trial found that it was not effective for treating antidepressant-associated sexual dysfunction in females. In information obtained

from [www.clinicalstudyresults.org](http://www.clinicalstudyresults.org), all of the drug manufacturer's currently ongoing studies examining sildenafil were terminated due to the "a decision by the sponsor to discontinue development of sildenafil for treatment of female sexual arousal disorder". Thus, although the phosphodiesterase inhibitors may be effective for some women with antidepressant-associated sexual dysfunction, there are no other studies in women registered with the clinical studies results webpage for any of the medications included in this class, nor have any been published.

#### *Additional Treatments*

In addition to adjunctive bupropion and the phosphodiesterase inhibitors, the scientific literature surrounding antidepressant-associated sexual dysfunction has also included reports of improvement with amantadine (dopamine agonist), buspirone (suppresses serotonergic activity while enhancing noradrenergic and dopaminergic cell firing), cyproheptadine (antiserotonergic), yohimbine (alpha 2- receptor antagonist<sup>58, 59</sup>), and L-arginine (nitric oxide precursor). Unfortunately the majority of the references within the literature supporting the use of these agents are based on open studies or case reports. Thus, many therapies have been utilized to manage sexual dysfunction but there is little positive evidence of their effectiveness and those that do show positive results are often small, unrandomized, and without controls.

#### *Non-prescription Therapies*

In addition to prescription medications, the literature has included several non-prescription medications available to help manage sexual dysfunction. Most of these preparations are classified as dietary supplements by the FDA and thus are not strictly regulated by this federal agency in terms of efficacy or safety. The list includes Zestra® (a botanical oil for females), ginkgo biloba, Enzyte®, Horny Goat Weed, and Avlimil®. Unfortunately only a few of these have been systematically studied and are included here.

A study by Ferguson et al<sup>60</sup> looked at the efficacy of Zestra®, which is applied topically before sexual activity, in 20 women, 10 with and 10 without sexual arousal disorder. Three in the control group and four in the treatment group were taking an SSRI. The study was double-blind, crossover, placebo-controlled study that involved five doses of active drug followed by five doses of placebo (or vice versa). Zestra® was significantly better than placebo for arousal ( $p < 0.0006$ ), lubrication ( $p < 0.047$ ), and orgasm ( $p < 0.0013$ ), regardless of whether the subject had a previous arousal disorder.

Kang et al<sup>61</sup> assessed the efficacy of ginkgo biloba in 37 patients treated with fluoxetine, paroxetine, or nortriptyline experiencing drug-induced sexual dysfunction. They received ginkgo or placebo for eight weeks and were assessed by an investigator questionnaire. They found no difference between placebo and Ginkgo for all outcome measures. This study was followed up by a "triple-blind (investigator, patient, and statistician) study of ginkgo biloba in 24 patients who received either active treatment or placebo for 12 weeks<sup>62</sup>. The author created a new scale to measure "the most important aspects of sexual dysfunction" and administered this scale seven times during the 12 week trial. Overall, the conclusion was that "There were some spectacular individual responses in both groups, but no statistically significant differences, and no differences in side-effects".

## CONCLUSION

In summary, sexual dysfunction is a very common problem among users of SSRIs, with rates ranging from 30-70%, which is significantly higher than the rates reported in package inserts. The highest rates of sexual dysfunction occur in persons taking agents with serotonin reuptake inhibition as a primary mechanism of action. The incidence of sexual dysfunction is positively correlated with increasing doses of SSRIs, in that as the dose increased the incidence of sexual dysfunction may so as well. In regards to the non-SSRI medications, bupropion has the most data to support the claim that it has a lower incidence of sexual side effects than other antidepressants, although the scientific literature suggests that this may also be true to other non-SSRI medications such as mirtazapine. Other potential antidepressants which may have a lower risk of sexual dysfunction include duloxetine and reboxetine, although very little work has been done to confirm this.

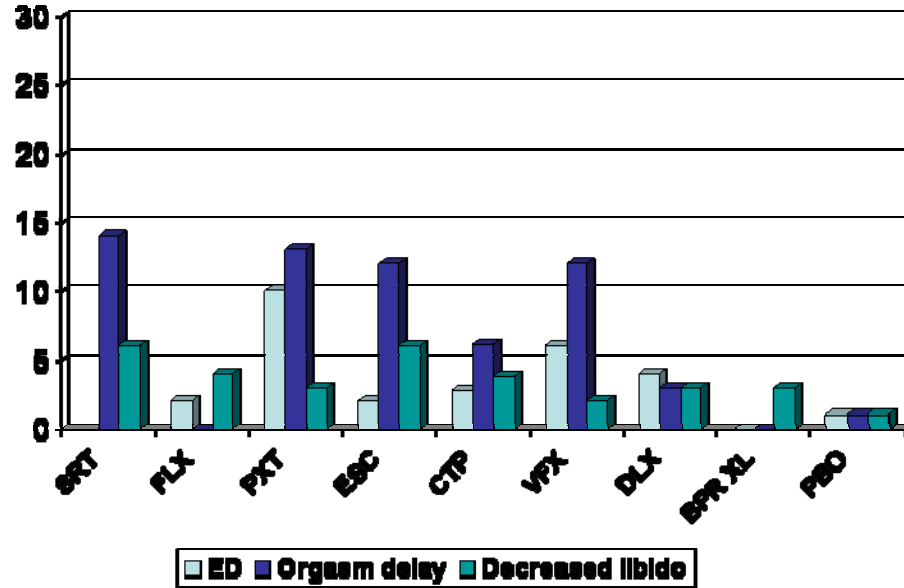
In terms of treatment strategies for antidepressant-associated sexual dysfunction, several have been outlined in the literature. Adaptation to the sexual dysfunction seems to occur in only approximately 10% of patients with 15-20% experiencing some improvement in symptoms. Additional therapeutic options include altering the timing of the dose, lowering the dose if possible, or switching to other non-SSRI related antidepressants. For adjunctive treatments, bupropion SR and sildenafil have been the most studied. Unfortunately placebo-controlled trials of bupropion have not been as positive as previous open label studies and case reports. Adjunctive treatment with sildenafil appears to be an option for males suffering from SSRI associated sexual dysfunction. The use of this medication has not been as successful in women.

Most importantly, communication between prescribers and patients is critical as there needs to be an open discussion regarding the potential for these side effects and what can be done to prevent or treat them. Patients need to be informed that, if appropriate, therapy may be adjusted when and if these adverse events become bothersome. They should be encouraged to let their prescriber know when problems arise so as to not interrupt antidepressant therapy. The prescribers should also be aware of baseline sexual functioning and at follow-up ask the patient if they are experiencing any adverse effect specifically related to sexual functioning, just as they would ask about any other side effect. If problems related to sexual functioning occur, a plan of action needs to be developed between the prescriber and the patient as research has shown that up to 70% of patients will discontinue therapy without consulting their physician. Sexual dysfunction associated with SSRI or other antidepressant therapy is an important issue that needs to be addressed promptly and seriously by every person prescribing antidepressants so as to avoid the vicious cycle of depression, sexual dysfunction, and potentially disease relapse.

| <b>Table 1: Risk Factors Identified For The Occurrence Of Sexual Dysfunction</b>   |  |
|--|--|
| <p><b>Specific to Women</b></p> <ul style="list-style-type: none"> <li>UTI in last year</li> <li>Decreased income, more than 20%, over last 3 yrs</li> <li>Previous sexual abuse</li> </ul>  | <p><b>Specific to Men</b></p> <ul style="list-style-type: none"> <li>Partner ever having an abortion</li> <li>Sexually touched before puberty</li> <li>Any same sex activity ever</li> </ul> |
| <p><b>Common Risk Factors for Both Genders</b></p> <ul style="list-style-type: none"> <li>Poor to fair health</li> <li>Emotional problems or stress</li> <li>Smoking</li> <li>Alcohol use</li> <li>Diabetes Mellitus</li> <li>Cardiovascular disease</li> <li>Age</li> </ul> |  |

From Laumann et al <sup>4</sup> and Lewis et al <sup>5</sup>

**Figure 1: Reported Incidence of Sexual Dysfunction for SSRIs and Newer Antidepressant Agents from Package Insert Information**



SRT=sertraline; FLX=fluoxetine; PXT=paroxetine;  
ESC=escitalopram; CTP=citalopram, VFX=venlafaxine,  
DLX=duloxetine; BPR=bupropion, PBO=placebo (per package  
inserts available 8/2006)

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