

FEMALE SEXUAL FUNCTION

Safety of Flibanserin in Women Treated With Antidepressants: A Randomized, Placebo-Controlled Study



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ABSTRACT

Background: Depression is often associated with sexual dysfunction, and pharmacologic treatment for hypoactive sexual desire disorder can be considered in women receiving treatment for depression.

Aim: To evaluate the safety of flibanserin in women treated for depression with selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors.

Methods: In this double-blinded, randomized, placebo-controlled trial, women with remitted or mild depression treated with selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors who were not postmenopausal and were experiencing symptoms of hypoactive sexual desire disorder (ie, decreased sexual desire and related distress) received flibanserin 50 mg at bedtime (qhs) for 2 weeks and up-titrated to 100 mg qhs, flibanserin 100 mg qhs for the entire treatment period, or placebo for up to 12 weeks.

Outcomes: Safety assessment included adverse events and symptoms of depression and anxiety.

Results: 73 patients were randomly assigned to flibanserin (both dose groups combined) and 38 to placebo. The sponsor terminated the study early at discontinuation of the development of flibanserin. Treatment duration was at least 8 weeks for 84.9% and 94.7% of patients in the flibanserin and placebo groups, respectively. The most common adverse events (incidence $\geq 2\%$ in the flibanserin group and higher than that in the placebo group) included dry mouth (5.5% for flibanserin vs 2.6% for placebo), insomnia (5.5% vs 2.6%), back pain (4.1% vs 2.6%), and dizziness (4.1% vs 0.0%). There were no serious adverse events and no instances of suicidal ideation or behavior. The proportions of patients with symptom worsening in the flibanserin and placebo groups, respectively, were 6.9% and 21.6% for depression and 1.4% and 2.7% for anxiety. Remission of depression at study end point, as measured by the Quick Inventory of Depressive Symptomatology—Self Report, was experienced by 19.4% of flibanserin-treated patients and 10.8% of patients receiving placebo; remission of anxiety based on the Beck Anxiety Inventory was noted in 16.4% and 2.7% of patients, respectively.

Clinical Implications: The results of this study support the safety of flibanserin in premenopausal women being treated with a serotonergic antidepressant. No increased risks were observed when adding flibanserin to a stable selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor treatment regimen.

Strengths and Limitations: This was a well-designed, randomized, placebo-controlled trial. The primary limitation was the early study discontinuation by the sponsor, which decreased the sample size and duration of treatment.

Conclusion: In this small trial, flibanserin 100 mg qhs was generally safe and well tolerated in premenopausal women with mild or remitted depression taking a serotonergic antidepressant. **Clayton AH, Croft HA, Yuan J, et al. Safety of Flibanserin in Women Treated With Antidepressants: A Randomized, Placebo-Controlled Study. J Sex Med 2018;15:43–51.**

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Key Words: Antidepressants; Flibanserin; Safety

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INTRODUCTION

The hallmark symptoms of hypoactive sexual desire disorder (HSDD) are decreased sexual desire and associated distress.¹ As defined by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR), HSDD is a persistent or recurrent deficiency (or absence) of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty and is neither better accounted for by another psychiatric condition nor due exclusively to the direct physiologic effects of a substance, medication, or general medical condition.²

Flibanserin is a postsynaptic 5-hydroxytryptamine (5-HT)_{1A} agonist and 5-HT_{2A} antagonist that decreases serotonin activity and enhances dopamine and norepinephrine activity in certain regions of the cerebral cortex.^{3–6} In contrast to most serotonergic antidepressant medications, flibanserin is not active at the serotonin transporter.^{7,8} Flibanserin is approved by the US Food and Drug Administration (FDA) for the treatment of acquired, generalized HSDD in premenopausal women.^{9–11} It is hypothesized that flibanserin acts to modulate the activity of excitatory and inhibitory neurotransmitter systems involved in a healthy sexual response.^{12,13} The efficacy and safety of flibanserin have been demonstrated in randomized clinical trials.^{14–19}

For women treated with an antidepressant medication, the safety of flibanserin co-administration is of concern. Depression is often associated with sexual dysfunction.^{20–22} A systematic review and meta-analysis examined the association between depression and sexual dysfunction and found a bidirectional relationship.²⁰ In this meta-analysis, study participants with sexual dysfunction had a 130% to 210% increased risk of developing depression, and those with depression had a 50% to 70% increased risk of developing sexual dysfunction. Because pharmacologic treatment for HSDD can be considered in women who are already receiving treatment for depression, and information on concomitant use of depression treatments was not available from previous studies of flibanserin (major depressive disorder and antidepressant medication use were exclusion criteria),^{14–16} the FDA required a study to evaluate the safety of concomitant use of flibanserin with antidepressant medications.

AIM

This placebo-controlled study evaluated the safety of flibanserin in women with symptoms of HSDD (ie, decreased sexual desire and related distress) who were being treated for depression with a selective serotonin reuptake inhibitor (SSRI) or a serotonin and norepinephrine reuptake inhibitor (SNRI).

METHODS

Patients

Potential study participants were identified from new or existing patients who were receiving treatment for depression at investigative sites, referred by other physicians, or recruited through advertising.

Eligible patients were women 18 to 50 years of age who were not postmenopausal (ie, did not meet the criterion of 12 consecutive months of amenorrhea) and had been taking the same SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline) or SNRI (duloxetine, desvenlafaxine, or venlafaxine) for at least 3 months (with a stable dose for ≥ 2 months). All patients had mild or remitted depressive disorder (with or without concurrent mild anxiety disorder or premenstrual dysphoric disorder) for at least 12 weeks based on medical records or other documentation and supported by scores lower than 11 on the 16-item Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR₁₆)²³ and lower than 16 on the Beck Anxiety Inventory.²⁴ All patients reported decreased sexual desire and related distress for at least 4 weeks as determined by the Clinical Interview for Female Sexual Desire—Depression and DSM-IV-TR criteria² and supported by scores of at least 15 on the Female Sexual Distress Scale—Revised (FSDS-R) and no higher than 9 on the Changes in Sexual Functioning Questionnaire—14-item self-report (CSFQ-14) desire/interest items. Investigators were required to determine, by history taken at screening, whether HSDD symptoms predated the depressive disorder and/or SSRI or SNRI use; however, a diagnosis of HSDD made before the onset of depressive symptoms was not required for participation in this safety study. All patients were required to be in a stable, communicative, monogamous, heterosexual relationship of at least 1 year's duration with a sexually functional partner who was expected to be physically present for at least 50% of every month during the study.

Exclusion criteria included other sexual dysfunction (eg, lifelong history of decreased sexual desire, arousal disorder, or orgasm disorder; sexual aversion disorder; substance-induced sexual dysfunction other than SSRI- or SNRI-induced sexual dysfunction; and sexual dysfunction from a general medical condition other than depression); current suicidal ideation or history of suicidal behavior; history of drug abuse or dependence (including alcohol) in the past 12 months; and history of another psychiatric disorder that could affect sexual function. Women were excluded if they had pelvic inflammatory disease, urinary tract or vaginal infection or vaginitis, cervicitis, interstitial cystitis, vulvodynia, or significant vaginal atrophy; were currently pregnant or had a pregnancy within the past 6 months; had a history of cancer within the past 5 years; or had electrocardiographic or blood abnormalities. The use of certain medications within the previous 4 weeks was prohibited, including sex hormones (except for hormonal contraceptives), anticoagulants, central nervous system stimulants, dopamine agonists, antidepressants (other than SSRIs or SNRIs), antipsychotics, benzodiazepines, prescription hypnotics, mood stabilizers, anti-epileptics, triptans, St John's wort, metoclopramide, or narcotics (except for short-term use in acute situations).

Study Design

This multicenter, randomized, double-blinded, placebo-controlled, 12-week, phase 3 safety study ([ClinicalTrials.gov](https://clinicaltrials.gov), NCT01040208) was conducted from January 2010 through

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