See accompanying article by Kronstein et al p1050

Regulatory and Scientific Issues in Studies to Evaluate Sexual Dysfunction in Antidepressant Drug Trials

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ABSTRACT

Objective: Sexual dysfunction is an important side effect of serotonergic antidepressants, as it often leads to treatment nonadherence. However, sexual dysfunction is often underestimated in clinical trials submitted in support of drug approval. This is because such assessments are based mainly on unsolicited reporting. As a result, the characterization of sexual adverse events has become an important component of many of the development programs for new antidepressants. The purpose of this article is to discuss US Food and Drug Administration's (FDA's) current thinking on possible approaches to characterizing the effects of drugs on sexual function in depression drug trials.

Participants: FDA's Division of Psychiatry Products, together with the Division of Biometrics I, in particular the authors of this article.

Evidence: The above-referenced FDA divisions conducted a regulatory science forum on measuring sexual dysfunction in depression trials.

Consensus Process: Considering the evidence presented and discussed at the forum, we developed our preliminary regulatory views on the scientific issues with regard to study design, study population, use of available scales, testing strategy, and statistical analysis plans.

Conclusions: Sexual dysfunction associated with antidepressants is an important entity that should be adequately assessed during clinical trials with the use of available instruments and described in product labels. It is important to appreciate the need for a positive control to establish assay sensitivity for any trial evaluating the impact of antidepressant medications on sexual function. Methodological improvement and additional data as well as experience with these approaches will be needed prior to further consideration of a formal regulatory guidance document by the FDA.

J Clin Psychiatry 2015;76(8):1060–1063
dx.doi.org/10.4088/JCP.14cs09700

Submitted: December 1, 2014; accepted April 1, 2015.
Online ahead of print: July 7, 2015.

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Sexual dysfunction, one of the side effects of antidepressant treatment, appears more prominent for the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) than for other antidepressants such as bupropion and mirtazapine.[1,2]

However, given that assessment of sexual dysfunction is based mainly on unsolicited reporting in the controlled clinical trials supporting drug approval, sexual dysfunction is often underreported and the rates underestimated (range, 3%–26% SSRI/SNRI vs 0%–2% placebo) in the product labeling of these 2 classes of antidepressants.[3] Much higher rates of sexual dysfunction associated with SSRIs and SNRIs have been reported in the literature, generally between ~30%–60% (ranging up to over 80%), when the trials were specifically designed to assess this adverse effect.[2,4,5] Adequate assessment of sexual dysfunction in controlled trials is essential if this distressing side effect is to be properly described in labeling.

The substantial overlap between sexual dysfunction and depression in the general population complicates the evaluation of sexual dysfunction during antidepressant treatment. A recent cross-sectional study indicated that approximately 40% of people with sexual dysfunction (a disorder of desire, arousal, or orgasm) have concurrent depression, underscoring the importance of evaluating patients with sexual problems for depression in clinical practice.[6] In addition, there seems to be agreement in the psychiatric community that a significant proportion of patients with depression may have sexual dysfunction (most commonly decreased libido) as part of the clinical picture.[7]

To find better ways to assess and characterize sexual dysfunction caused by antidepressant drugs, US Food and Drug Administration's (FDA's) Division of Psychiatry Products and Division of Biometrics I conducted a literature search to characterize rates of sexual dysfunction with SSRIs and SNRIs when sexual function was ascertained by methods other than unsolicited reporting, that is, methods such as direct questioning and standardized assessment instruments. FDA also conducted exploratory analyses of in-house data from studies that utilized standardized instruments to assess sexual dysfunction in registration trials. The results of FDA's analyses were discussed with expert clinicians and statisticians from academia and industry at a Regulatory Science Forum, held August 2012 on the FDA White Oak Campus, Silver Spring, Maryland. That discussion is summarized in a separate article.[8] Although the available data were limited, SSRIs and SNRIs did not consistently show increases in sexual dysfunction compared to placebo of the magnitude expected on the basis of published reports; however, the reported frequencies were higher for individual drugs in some studies. The reason for this disparity is not clear.

As noted above, it is well known that sexual dysfunction is underreported when patients are not queried specifically on the topic. Thus, studies intended to assess sexual dysfunction must be designed to query patients directly. Moreover, it is essential to include a positive control in all trials evaluating the impact of antidepressant medications on sexual function in order to assess assay sensitivity, that is, to confirm that the trial had the ability to demonstrate sexual dysfunction for a drug known to cause it.

The characterization of sexual adverse events has been an important component of many of the development programs for new antidepressants. Specifically, drug sponsors have sought to show and claim an advantage for their drug in causing fewer sexual side effects, a claim that would offer significant marketing advantages and that, if well documented, would in fact be an important clinical benefit.

Of note, the term *sexual dysfunction* includes several distinct domains (ie, drive/desire, arousal, and orgasm), and for any given patient it can be difficult to determine whether sexual dysfunction is part of the MDD being treated or a side effect of drug treatment. Moreover, drugs and underlying depression could have different effects on distinct aspects of sexual function. For example, some drugs may have important effects on orgasm but little effect on desire. If drug development programs seek to evaluate effects on sexual dysfunction, a desirable goal, these separate domains need to be addressed.

Here, we discuss possible approaches to characterizing the effects of drugs on sexual function in depression trials. We also discuss preliminary FDA views on scientific issues with regard to study design, study population, use of available scales, testing strategy, and statistical analysis plans. When methodological development and experience support such specific approaches, we will consider preparation of formal guidance.

POTENTIAL LABELING CLAIMS

All drug labeling claims sought must be well supported by data. In general, a claim would focus on specific sexual functions, such as desire or orgasm. There are 2 possible claims a sponsor could pursue in characterizing the effects of a drug on sexual function:

1. Comparative claim: the drug is superior (ie, causes less sexual dysfunction) to the active/positive control (SSRIs, SNRIs). Such a claim could be investigated in unselected patients or in an "enriched" population, ie, patients known to have sexual dysfunction while taking the control drug.
2. No effect claim: the drug causes no sexual side effect compared to placebo. A study to support this would always need a positive control to establish assay sensitivity.

Our current thinking is discussed below.

SCALES TO MEASURE SEXUAL FUNCTION

At our discussion with experts on sexual dysfunction at the FDA Regulatory Science Forum, there was a consensus that sexual function can be evaluated using quantitative measures and that the existing scales appear to be useful in evaluating patients' sexual function. The forum discussion was focused on the results from the two most widely used scales in registration trials for drugs in psychiatry, the Arizona Sexual Experiences Scale (ASEX)[9,10] and the Changes in Sexual Functioning Questionnaire (CSFQ).[11,12]

Clinical Points

- Sexual dysfunction is a clinically important side effect of serotonergic antidepressant drugs.
- Adequate assessment of sexual dysfunction in antidepressant trials is vital.
- Meaningful research into treatment-emergent sexual dysfunction with antidepressants is needed to generate the evidence the psychiatric community now lacks in addressing this very important issue.

The Arizona Sexual Experiences Scale

The ASEX comprises 5 domains of sexual function (sexual drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and orgasmic satisfaction), each with 1 question, assessed with a 6-point Likert scale scored from 1 (hyperfunction) to 6 (extreme hypofunction). An ASEX total score of 19 or greater is used to categorize a patient as having clinically relevant sexual dysfunction.[9,10]

Changes in Sexual Functioning Questionnaire-Short Form (CSFQ-14)

The CSFQ-14 is a gender-specific questionnaire, comprising 5 domains of sexual function (pleasure, desire/frequency, desire/interest, arousal/excitement, and orgasm completion).[11] This is a shorter, 14-item version of the original CSFQ questionnaire.[12] A higher total score indicates better sexual functioning. Total scores of < 47 for men and < 41 for women (out of a possible 70) are considered by the CSFQ authors to represent clinically relevant sexual dysfunction.

From our experience with the use of such scales in depression trials conducted to support recent New Drug Applications (NDAs), however, it remains uncertain whether these scales would be successful in distinguishing the effect of antidepressant drugs on different types of sexual dysfunction in clinical trials.[8]

Development of additional scales, such as the Derogatis Interview for Sexual Functioning, Sex Effects Scale, and others, was also reported.[13–15]

CLINICAL TRIAL DESIGN ISSUES

Study Population

The choice of the study population is critical because both the underlying depression and the treatment can affect aspects of sexual dysfunction. A study in normal volunteers can assess specific drug effects and avoid the confounding influences of the underlying depression but would not be able to detect potential interactions between the drug and the depression. Given that the principal problem is not the short-term effect on sexual function that could occur during treatment of acute depression, but rather the longer term effects that occur during drug maintenance, an argument could be made that antidepressant effects on sexual function should be studied in patients with a history of depression who are not having an acute episode.

Patient Population: MDD Patients in the Acute Setting

There are a number of articles in the literature, going as far back as 1999, demonstrating the use of sexual function assessments in patients with major depressive disorder (MDD) in the acute setting, for example, using direct questioning to compare bupropion versus sertraline versus placebo.[16,17] Recently, sponsors have included sexual function assessments in the controlled trials intended to support drug approval. One of the concerns with using acute MDD studies to assess treatment-emergent sexual dysfunction is adequately assessing abnormal baseline sexual function, as many MDD patients would be expected to have sexual dysfunction as a feature of their acute illness. Moreover, it would be expected that some of the sexual symptoms (eg, decreased desire) would improve as drug treatment improves the depression and as the acute episode resolves. It seems possible that these disease-related components of sexual dysfunction could make drug effects harder to detect.

Nonetheless, a randomized comparison of 2 antidepressants that showed a clear advantage of a drug over an active control in an acute setting would be informative. The inability to detect a statistically significant difference from placebo, however, would not be interpretable as evidence of an absence of sexual dysfunction, unless there was an active control that did show a sexual dysfunction effect, supporting assay sensitivity, ie, that the study could in fact detect the effect of a drug (the control drug) on sexual function.

Patient Population: MDD Patients in the Maintenance Setting

As noted, acute sexual dysfunction is not the main problem. It would therefore be of interest to study patients who have had sexual dysfunction during maintenance use of an antidepressant, that is, to conduct a trial enriched with patients who are responding to an antidepressant but demonstrate sexual dysfunction while taking that particular drug. The enrichment design,[18,19] which could be carried out in patients experiencing general sexual dysfunction (or perhaps some particular type, such as erectile dysfunction or anorgasmia), would then randomize patients to continued treatment with the sexual dysfunction–inducing drug or to a test drug. A showing of less sexual dysfunction on the test drug would support a claim of less sexual dysfunction in patients who experienced the problem on the initial drug. A placebo group could be used to assess whether the test drug was simply superior to the control or appeared to cause little or no sexual dysfunction (within some specified confidence interval). It would also be essential to assess continued antidepressant effectiveness. A clear difference in sexual dysfunction, but with similar maintenance effectiveness (which would also need a placebo comparison), would support an advantage for the test drug in the population studied. The other study option in this enriched population is an add-on design in which a test agent to alleviate sexual dysfunction (or placebo) would be added to the sexual dysfunction–inducing antidepressant maintenance therapy.[20,21]

Nonpatient Population: Normal Healthy Volunteers

It may be informative to study normal healthy adults (with no sexual dysfunction at baseline) in one of the studies characterizing the effect of a drug on sexual function. Dunn et al[22] demonstrated apparent deterioration in all domains of sexual function in healthy young men who received an SSRI (paroxetine 20 mg/d) compared to placebo, with sexual function assessed by the CSFQ-14 at day 21. In designing such studies, it is important to ensure that no subjects have sexual dysfunction or hyperfunction at baseline and that men do not have premature ejaculation. It is also important to ensure that sufficient numbers of subjects of both genders are enrolled in this type of study.

It can be anticipated that, whatever the study design, a claimed advantage of causing less sexual dysfunction would need to be supported by 2 independent, adequate, and well-controlled trials and that at least 1 of the trials would be in a patient population with depression.

Potential Designs

All of the study designs would aim to show a difference between 2 active drugs, that is, a statistically significantly smaller deterioration of sexual function (or greater recovery) in patients receiving the drug compared to the active control. A potential study design in patients known to be sensitive to the sexual dysfunction effects of a particular drug was described above (see under Patient Population: MDD Patients in the Maintenance Setting). To show more general superiority (as opposed to superiority in patients with sexual dysfunction taking a particular drug), the test drug and active control would be compared directly in a randomized trial in newly treated subjects, either normal volunteers or patients with a history of depression, but generally not in patients with acute depression. In this case (superiority in a more general population), subjects should not have had a history of sexual dysfunction with the control drug. A significant advantage of the test drug to the control drug with respect to sexual dysfunction would demonstrate superiority, but the presence of a placebo group would be useful for 2 reasons. First, a placebo group would allow measurement of the actual sexual dysfunction effect (compared with no treatment) of the drugs, distinguishing between less effect and no effect. Second, if there were no difference between the drugs with respect to sexual dysfunction, a placebo group would permit assessment of the assay sensitivity of the trial; that is, was the trial able to detect sexual dysfunction with the control drug? If the trial could not detect an effect of the control drug on sexual dysfunction, then it would not have adequate assay sensitivity to determine whether the test drug was superior to control. With regard to the active control, paroxetine (an SSRI) 20 mg/d might be a good choice because it has been shown to have negative effects on sexual function compared to placebo on day 21, as assessed by the CSFQ total score, with a deterioration magnitude (relative to placebo) in the range of 7.2 to 13.1 (95% CI) in healthy male volunteers.[22]

Stratified Randomization

It would be useful to stratify subjects in a trial by gender because of potential heterogeneity between genders. In trials in MDD patients with a history of sexual dysfunction on drug treatment, further stratification by specific dysfunction may also be helpful. A detailed sexual history should be recorded at baseline (including affected domain) for each patient enrolled in depression trials so that the magnitude and type of sexual dysfunction present at baseline can be considered in the analysis of drug effects.

Statistical Analysis Plan

Prospective hypothesis testing with an appropriate control of the overall type 1 error rate is needed if the drug sponsor intends to draw multiple inferences about the sexual function outcome, for example, the study drug is superior to the active control (significantly less sexual dysfunction) and is not worse than the placebo in causing sexual dysfunction. The latter conclusion would need to specify what "no effect" would be, perhaps ruling out a fraction of the active control–placebo difference.

The multiple testing procedure would also need to take account of multiple doses in a trial in which characterization of a dose-response is contemplated, presumably using a sequential approach, for example, first comparing the lowest effective dose with the control and then proceeding to the next comparison if the difference is statistically significant.

Exposure-Response Considerations

If pharmacokinetic blood samples are being collected in a trial, the sponsor should consider conducting exposure-response analyses between the study drug level (including active control if data are available) and the sexual function scale total score, as well as the depression rating scale total score.

CONCLUSION

From both a regulatory and a scientific perspective, there was general consensus at the forum that sexual dysfunction associated with antidepressants is an important entity that should be adequately assessed during clinical trials with the use of available instruments and described in product labels. It is important to appreciate the need for a positive control to establish assay sensitivity for any trial evaluating the impact of antidepressant medications on sexual function. We hope this article will encourage meaningful research into treatment-emergent sexual dysfunction with antidepressants to generate the evidence the psychiatric community now lacks in addressing this very important issue.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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Potential conflicts of interest: None reported.

Funding/support: None reported.

Disclaimer: The views expressed in this paper are those of the authors and do not necessarily represent the official views of FDA.

Previous presentations: This topic was discussed at the following meetings: FDA Regulatory Science Forum on Measuring Sexual Dysfunction in Depression Trials held on August 22, 2012, at White Oak Campus in Silver Spring, Maryland; and NCDEU, An Annual Meeting of the American Society of Clinical Psychopharmacology, on May 30, 2013, in Hollywood, Florida.

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