REVIEWS

Satisfying Sexual Events as Outcome Measures in Clinical Trial of Female Sexual Dysfunction

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ABSTRACT

Introduction. Assessing the sexual response in women with female sexual dysfunctions (FSDs) in clinical trials remains difficult. Part of the challenge is the development of meaningful and valid end points that capture the complexity of women's sexual response.

Aim. The purpose of this review is to highlight the shortcomings of daily diaries and the limitations of satisfying sexual events (SSEs) as primary end points in clinical trials of women with hypoactive sexual desire disorder (HSDD) as recommended by the Food and Drug Administration (FDA) in their draft guidance on standards for clinical trials in women with FSD.

Methods. Clinical trials in women with HSDD using SSEs as primary end points were reviewed.

Main Outcome Measures. The agreement between three outcome measures (SSEs, desire, and distress) was assessed to illustrate to what degree improvements in SSEs were in agreement with improvements in sexual desire and/or personal distress.

Results. Nine placebo-controlled randomized trials in women with HSDD were reviewed: seven with transdermal testosterone and two with flibanserin. In four trials, all using transdermal testosterone 300 μg/day had agreement between changes in SSEs, desire, and distress. In five studies (testosterone 300 μg/day, n = 2; testosterone 150 μg/day, n = 1; flibanserin n = 2), changes in SSEs did not correlate with changes in desire and/or distress and vice versa. It should be noted that in the flibanserin trials, SSEs did correlate with desire assessed using the Female Sexual Function Index but not when it was assessed using the eDiary.

Conclusions. Findings in the literature do not uniformly support the recommendations from the FDA draft guidance to use diary measures in clinical trials of HSDD as primary end points. Patient-reported outcomes appear to be better suited to capture the multidimensional and more subjective information collected in trials of FSD. **Kingsberg SA and Althof SE. Satisfying sexual events as outcome measures in clinical trial of female sexual dysfunction. J Sex Med 2011;8:3262–3270.**

Key Words. Hypoactive Sexual Desire Disorder; Testosterone; Flibanserin; Diary

Introduction

Female sexual dysfunctions (FSDs) are complex conditions with clinical assessment continue to be a challenge. The only guidance on standards for clinical trials in women with FSD was issued in 2000 by the US Food and Drug Administration (FDA) and is currently still only available in draft form [1]. The FDA draft guidance states, among other recommendations, that the number of satisfactory sexual events (SSEs), collected using daily diaries, should be the primary end point in clinical trials of FSD, while patient-reported outcomes (PROs) are recommended as secondary end points. These recommendations have received much criticism from experts in the FSD field [2,3]. The concerns focus mainly on five areas [3]: (i) SSEs are being recommended as primary end points,

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although they are not part of the criteria for a FSD, recognized by experts or the DSM-IV-TR (Diagnostic and Statistical Manual, 4th ed, Text Revision). (ii) A DSM-IV–recognized FSD symptom should be selected as a primary end point, e.g., improvement in sexual desire, accompanied by a reduction in distress, in women with hypoactive sexual desire disorder (HSDD). (iii) The emphasis on daily recording of symptoms, e.g., sexual desire in women with HSDD, should be replaced with a longer recall period, as it has been shown that women with HSDD find a 1- to 4-week recall meaningful [4], and there is the potential for measurement contamination from daily assessments. (iv) Psychometric concerns, i.e., the concept of SSEs is several steps removed from the components being studied, such as desire or arousal.

Objective

The purpose of this review is to assess the limitations of daily diaries and of SSEs as primary end points in clinical studies of women with HSDD and to recommend the use of PROs as primary end points.

Daily Diaries vs. Self-Administered Questionnaires

Daily diaries or event logs have historically been used in clinical trials of conditions with well-defined end points, such as overactive bladder [5], irritable bowel syndrome [6], and sexual dysfunction [7,8]. Use of daily diaries is appropriate when events such as frequency of orgasms, incontinence episodes, or bowel movements are counted; they are much less suited for collecting subjective data. Simply counting is an unsophisticated form of assessing a complex and multidetermined construct such as desire.

It has been suggested that PROs, such as the Sexual Function Questionnaire [9] or the Female Sexual Function Index (FSFI), [10] are better suited to obtain multidimensional and more subjective information. This is supported by a trial in women with HSDD using transdermal testosterone that noted disagreement between sexual desire results obtained from diary measures and a validated PRO, the Brief Index of Sexual Function [11]. More recently, in two separate trials of flibanserin, the sexual desire score obtained from the diary disagreed with that from the FSFI in both trials; only when data from the studies were pooled did the two measures agree (Tables 1 and 2) [21]. Furthermore, a study assessing the sensitivity of different types of outcome measures (event logs, PROs, physiological measures of arousal, and self-reported changes in subjective sexual arousal in a laboratory setting) for detecting treatment-induced changes in women with female sexual arousal disorder found that the FSFI was the only instrument to demonstrate treatment response [22].

SSEs are determined by asking women to record their subjective experience and frequency of sexual activity by paper or electronic diary, such as the Sexual Activity Log (SAL), which records the number of intercourse and nonintercourse sexual events, number of orgasms, level of sexual desire, and satisfying sexual activity experienced (Table 3) [23]. However, questions about intensity and frequency of sexual desire collected daily may not be conceptually relevant to HSDD; neither the daily time frame nor the measurement of intensity is closely linked to the HSDD construct. Recent evidence showed that women with HSDD did not find a 24-hour recall, the most appropriate time frame for assessing their perceived desire, and instead preferred a period of 1–4 weeks [4].

Besides determining the number of events, the use of SSEs as an end point also requires the determination of a woman's perception of success or satisfaction, a highly subjective matter. Women might experience improved desire but choose not to engage in sexual activities or may not perceive the activity as satisfactory for reasons not related to their desire, such as still being upset over an argument with their partner. Alternatively, women might describe a sexual encounter as successful or satisfactory despite not experiencing improved desire. Moreover, a satisfying event does not necessarily motivate women to want to have another sexual encounter. In women with HSDD, the construct of low desire is only indirectly related to the number of sexual events because most sexual events in women with HSDD are initiated by the partner [3]. Many women agree to lovemaking out of a sense of obligation or love for their partner, not because they feel sexual desire.

Thus, the concept of an SSE appears to be several steps removed and not necessarily related to the sexual response component being examined in a trial, such as desire or arousal.

Male vs. FSD Trials

There are noteworthy discrepancies between the end points utilized in clinical trials of male sexual function, such as erectile dysfunction and premature ejaculation, and trials of FSD with

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