Clinically Relevant Changes in Sexual Desire, Satisfying Sexual Activity and Personal Distress as Measured by the PFSF, SAL, and PDS in Postmenopausal Women with Hypoactive Sexual Desire Disorder

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Running title: Clinical Relevance of Treatment Effects in Women with HSDD

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Abstract

Introduction. Transdermal testosterone patch (TTP) treatment produced statistically significant improvements in satisfying sexual activity (SSA), sexual desire, and personal distress in postmenopausal women suffering from hypoactive sexual desire disorder (HSDD), but clinical significance of these changes was not determined.

Aim. To quantify the magnitude of change in 3 principal outcomes measures determined by HSDD-patients as associated with the perception of meaningful benefit with TTP therapy.

Methods. The criteria for defining responders were determined using anchoring methodology and receiver operating characteristics (ROC) analysis to establish minimum important differences (MIDs) in a representative subsample of 132 patients in 2 randomized, controlled trials in surgically menopausal women with HSDD (N=1094). Perceived benefit was established based upon the question "Overall, would you say that you experienced a meaningful benefit from the study patches?" These data defined responders and established MIDs for changes in sexual desire, SSA, and personal distress. The MIDs were applied to the 2 trials to establish responder rates in each treatment group.

Main Outcome Measures. Changes in score that correspond to the MID for sexual desire, SSA, and personal distress, and responder rates in each treatment group based upon these values.

Results. Increases in frequency of SSA of greater than 1 activity/4-weeks, increases in sexual desire score of ≥8.9, and decreases in the personal distress score of ≥20.0 were identified as threshold improvements best able to differentiate responders and non-responders. The responder rate was significantly higher ($p<0.001$) in the testosterone group versus placebo for all three outcomes measures (sexual desire, 50% vs. 34%; SSA, 44% vs. 30%; personal distress, 51% vs. 39%).

Conclusions. Changes in sexual desire, SSA, and personal distress observed with transdermal testosterone patch treatment in surgically menopausal women with HSDD were clinically significant and were associated with a meaningful treatment benefit.

Introduction

Women who have undergone menopause may experience decreased levels of sexual desire. Loss of ovarian sex steroid production following surgery (if surgically menopausal), or the natural aging process are the most credited biological contributors to loss of sex drive. Such women commonly report diminished sexual desire, reductions in sexual activity, feelings of concern, and dissatisfaction. When distressed as a result of their diminished desire, these women meet the criteria for a diagnosis of hypoactive sexual desire disorder (HSDD) as defined by the DSM-IV.[1]

The development of effective clinical treatments to address HSDD in postmenopausal women requires that reliable and valid instruments be available to assess critical aspects of desire, sexual activity, and associated distress in this population. To meet this need, 3 inventories -- the Profile of Female Sexual Function© (PFSF©), the Sexual Activity Log© (SAL©), and the Personal Distress Scale© (PDS©) -- were developed and validated in a series of multinational studies in this patient population.[2-5]

Clinical trials have shown the PFSF, SAL, and PDS to be sensitive to therapeutic changes in these aspects of sexual functioning observed in patients receiving pharmacological treatment with a testosterone patch compared with changes in patients receiving placebo.[6-11] Additionally, evaluation of the significance of these benefits in a clinical relevance study has shown significantly greater increases in frequency of satisfying sexual activity and sexual desire and decreases in distress (the three defining components of HSDD) in patients who experienced a meaningful treatment benefit as compared with those who did not experience a meaningful benefit.[12]

Although changes associated with testosterone patch treatment in the three central components of HSDD have been demonstrated to be statistically superior to those seen with placebo, it is uncertain what magnitudes of change are associated with patient perception of a meaningful benefit. Defining this magnitude of change would provide a clinically appropriate definition of a responder. This issue of what defines clinically important change has been debated under the rubric of *clinical significance* or *clinical relevance*, and is a pivotal issue from the perspectives of both clinical trials researchers and government regulators alike.[13,14] Definitions of clinically meaningful change represent essential information for clinicians who are attempting to effectively treat women with HSDD, enabling them to make informed judgments as to their patients' therapeutic progress.

A concept that has become central to the clinical significance question is the concept of minimum important difference (MID) or minimal clinically important difference (MCID). Originally, the MID was defined as the smallest difference in score on the outcomes measure of note that patients perceive as beneficial, and which would mandate, in the absence of significant adverse events and excessive cost, a change in the patient's management.[15] This definition is clearly patient-oriented, and a patient-oriented perspective continues to dominate contemporary approaches to defining a MID.[16,17] Also, although it does not represent an exclusive approach, MIDs are often utilized to operationalize the definition of a treatment responder.

While there are numerous specific methods for estimating a MID, they generally fall into 2 distinct classes: anchor-based methods and distribution-based approaches. The former category of techniques relates the magnitude of change on the principal outcomes measure to an independent measure (anchor), often reflecting the presence or extent of patient-perceived benefit. Anchors are usually cross-sectional, assessed at the completion of treatment; however, they may be defined longitudinally as well.[13] Distribution-based approaches utilize statistical methods to ascertain the meaningfulness of differences in change between treatment groups on the principal outcomes measure, relative to some indicator of the measure's variance. A number of distinct indicators of variability have been recommended for use in distribution-based techniques.[17]

In this study, we have used anchoring methodology and ROC analysis to establish MIDs for 3 principal outcome measures, using data from a subset of patients enrolled in 2 large randomized, controlled trials of the transdermal testosterone patch in surgically menopausal women with HSDD.[8, 9] These MIDs were then applied as responder definitions in order to determine differences in the proportion of patients who experienced a meaningful benefit in the testosterone versus placebo groups in the clinical trials. Although this study was conducted earlier, recent thinking at the FDA and the agency's formal Patient Related Outcomes (PRO) guidelines suggest that formally defining a treatment responder represents an important step in establishing treatment benefit.[18]

Aim

The aim of this work was to quantify the magnitude of change in each of 3 principal measures that was determined by patients with HSDD to be associated with the perception of meaningful benefit. These values provide a basis for determining the clinical significance of the treatment effect observed with transdermal testosterone in clinical trials and may be valuable to clinicians and regulators when assessing individual patient response to treatment.

Methods

Patients/Study Design

Two multicenter, 24-week, double-blind, placebo-controlled, phase III trials (SM1 and SM2) were conducted in 1094 surgically menopausal women with HSDD to evaluate the efficacy and safety of a testosterone transdermal system. These studies have been described and the primary results reported previously.[8,9] Frequency of satisfying sexual activity was assessed in a weekly diary throughout the trials while sexual desire and personal distress were assessed at weeks 4, 8, 12, and 24. Changes in each of these outcomes at 24 weeks in the intent-to-treat population constituted the primary analysis and substantive secondary analyses for these clinical studies.

At the end of the 24-week double-blind treatment period a representative subset of 132 women from study centers across the United States participated in face-to-face interviews (selected based of the timing of their 24- week study visit and accessibility to the study interviewer) or telephone interview (random selection). This follow-on clinical relevance study assessed the clinical significance of treatment benefits, as previously described.[12] All participants gave written, informed consent to be interviewed. This study was conducted under a separate protocol from the original Phase III drug studies. Approvals by Institutional Review Boards were obtained before participants were approached concerning participation in the interviews. Women in the study were interviewed by a single trained, experienced, female interviewer using a semistructured interview with a discussion guide, within 2 weeks of exiting the blinded portion of the study. The interviewer was an independent, third party, employed by the sponsor specifically for this purpose. The interviews began with an open-ended discussion of the woman's sexual feelings and behaviors, both before and during the clinical trial. A series of direct questions followed, including a global assessment question regarding whether or not they had "experienced a meaningful benefit from the study patches". Those who answered "Yes" that they had experienced a meaningful benefit were termed "treatment responders"; those who answered "No" they did not perceive a meaningful benefit from the study patches were termed "treatment non-responders".

Statistical Methods

The ability of each of the three outcome measures to differentiate subjects experiencing a meaningful benefit from those who did not was assessed using ROC analysis. In order to ensure that selection of a cutoff was appropriate, the overall discriminatory ability of the outcome measures was evaluated by computing the area under the ROC curve (AUC). In order to identify the threshold improvements in frequency of satisfying sexual activity (SAL), sexual desire (PFSF), and personal distress (PDS) that would correspond to a patient experiencing a clinically meaningful effect, sensitivity and specificity corresponding to varying increasing criteria were computed. Overall correct classification was also evaluated; in this evaluation, accurate classification of women with and without meaningful treatment benefit was given equal weight.

Analyses to determine the threshold criteria were performed before the SM1 and SM2 study databases were locked and unblinded with regard to treatment assignment. Hence treatment assignment was unknown to the moderator, patients, and sponsor personnel. Following unblinding, treatment effects observed in these studies were compared with the threshold changes. The odds ratio of patients with increases in frequency of satisfying sexual activity and sexual desire and decreases in personal distress exceeding the identified thresholds in the testosterone group relative to the placebo group was compared using a logistic regression model adjusted by route of administration (oral vs. transdermal) of concomitant estrogen (stratification variable in original studies) for individual study analyses and adjusted by estrogen route of administration and study for an analysis of pooled studies. Additionally, the percentages of testosterone and placebo patients exceeding none of the 3 threshold criteria, at least one criterion, at least two criteria, and all three criteria were computed and the odds ratio of exceeding more criteria on testosterone than on placebo was compared using a logistic regression model adjusted by estrogen route of administration and study. Only patients with non-missing data on all three endpoints were included in this analysis.

Main Outcome Measures

Main outcome measures were changes in the score that correspond to the MIDs for sexual desire, SSA, and personal distress, and the responder rates in each treatment group based upon these values.

Results

Demographic and baseline characteristics of the patient populations of the 2 large studies (SM1 and SM2, n=1094) are presented in Table 1. The characteristics of the subset of patients enrolled in the follow-on clinical relevance study (n=132) were representative to the overall study population (Table 1). Among the women in the clinical relevance study population, 33 of 64 women (52%) who received testosterone answered yes to the question about whether they had experienced an overall meaningful benefit from study patches, compared with 21 of 68 women (31%) who received placebo (p=0.025). Women who reported that they experienced an overall meaningful benefit also presented positive responses across all relevant aspects of sexual functioning as measured by the seven domains of the PFSF, while women who reported they did not have an overall meaningful benefit showed little or no effect across the same domains (Figure 1). This observation was equally true for both placebo and testosterone treated subjects.

The ROC curve for changes in frequency of satisfying sexual activity is given in Figure 2. The ROC curves for changes in sexual desire and personal distress were very similar (data not shown). The AUCs for changes in frequency of satisfying activity, sexual desire, and personal distress were 0.77, 0.77, and 0.78, respectively. The corresponding sensitivity, specificity, and overall correct classification rate for each outcome measure and potential threshold value are provided in Table 2.

Based on the ROC analysis and clinical rationale, increases in frequency of satisfying sexual activity of greater than 1 activity/4-weeks, increases in sexual desire score of 8.9 or greater, and decreases in the personal distress score of 20.0 or more were identified as the threshold improvements best able to differentiate responders and non-responders. Although an increase of 13.3 or greater in the sexual desire score was associated with a higher overall correct classification rate, this value caused the sensitivity rate to drop substantially, hence an increase of 8.9 or greater in this measure was considered the optimal value.

The percentages of patients in the SM1 and SM2 studies meeting the above identified threshold criteria (i.e., responders) for each individual outcome measure are provided in Table 3. For each criterion and study, significantly more patients receiving transdermal testosterone patch treatment responded to therapy compared with patients receiving placebo. The odds of responding to therapy with testosterone ranged from 1.6 to 2.2 times the odds of responding to placebo therapy. All odds ratios were statistically significant.

The percentages of testosterone and placebo patients exceeding none of the 3 threshold criteria, at least one criterion, at least two criteria, and all three criteria are shown in Figure 3. A woman receiving testosterone was more likely to experience meaningful changes in more aspects of HSDD than a woman receiving placebo. The ratio of the odds of having an additional criterion met for testosterone patients compared with placebo patients was 2.0 (95% confidence interval, 1.6 to 2.5, $p< 0.0001$).

Discussion

We have used an anchor-based approach to ascertain a series of MIDs for three primary outcomes measures in postmenopausal women with HSDD. These measures (the sexual desire domain of the PFSF, the SAL, and the PDS) were developed specifically in this population and reflect important aspects of sexual functioning in these women. The MIDs were then used to establish operational definitions of treatment responders and applied to the results of 2 large clinical treatment trials of the transdermal testosterone patch. These analyses showed that the proportion of patients responding in the active drug treatment group was significantly greater than the proportion responding in the placebo group. Appropriate definition of the criteria that identify a responder represents an important part of evaluating a treatment response. Beyond their value in directing research, the MIDs we've determined can be extremely important to clinicians attempting to treat HSDD, enabling them to better understand how a meaningful treatment benefit is defined by women with HSDD and also further appreciate the range of beneficial effects of testosterone therapy.

In a patient-centered perspective, it is the treated subject rather than the physician who determines the meaning of the treatment for her life. The concept of responder has therefore moved ahead: from the simple medical or clinical response that reaches statistical evidence to the perception of the impact of the treatment on real life. Understanding clinical relevance as meaningfulness for the patient fits well into the concept of shared decision making, a process in which therapeutic decisions are based on both the evidence (like statistical probabilities) and the weight given by the individual patient to the evidence, in relation to the personal concern/complaint that is being treated. Sharing treatment decisions is the prerequisite to adherence to treatment and consistency of use of treatment over time, two critical aspects of contemporary medicine. The minimum important difference (MID) or minimal clinically important difference (MCID) is, therefore, a patient-centered concept. In the sexual field, it inspires a concept of responder that is not based only on a statistically significant physical and psychosexual change but on the meaning the treatment has for the woman, her relationship and her life. In this current concept of responder, the perceived comprehensive reward from the treatment helps to understand and discriminate those who will or will not continue the treatment as opposed to those who respond to the treatment based on a scientific definition but will not use it for long in real life. The perceived clinical relevance is therefore of the highest importance for the clinician, to help him/her to understand and predict who will adhere to and comply with the treatment, thanks to the perceived personal satisfaction of use. It is not yet understood which factors contribute to the perception of reward or benefit and which others prevent an effective treatment for HSDD from being perceived as providing a meaningful benefit worthy of continued treatment. Some of the factors worthy of further study include the new onset of the partner's sexual dysfunctions, the failure to meet personal expectations, the lack of persistent motivation to be sexual and to continue the sexual part of the relationship, the absence of perceived changes in the quality of emotional intimacy (in spite of a perceived increase in desire), and changes in the personal evaluation of sexual worthiness.

The ROC approach to establishing a minimal clinically important change (in this instance, defining a responder threshold) is relatively commonplace, and has been used in several health care applications.[19-23] It may be combined with an integrated anchor-based and distribution-based approach to establishing an MID.[24] In ROC analyses, the AUC reflects the ability of a measuring instrument to distinguish between two groups.[25] In this case, it measures the likelihood that a patient selected at random who experienced a meaningful treatment benefit will have an increase in the outcome measure (i.e., satisfying activity, sexual desire, or personal distress) of greater magnitude than a randomly selected patient with no meaningful treatment benefit. Hosmer and Lemeshow indicate that AUC values greater than or equal to 0.7, 0.8, and 0.9 represent acceptable, excellent, and outstanding discrimination, respectively.[26] By this measure, the thresholds defined in this study are generally between acceptable and, in some instances, excellent.

For optimal threshold criteria, a large proportion of women who experienced a meaningful benefit should have changes exceeding the cutoff value (sensitivity) while a large proportion of women who did not experience a meaningful benefit

should have changes smaller than these values (specificity). The thresholds we've identified provide a good balance of sensitivity and specificity.

The MID defined for the measurement of satisfying sexual activity (>1 per 4-weeks) may seem small. Clearly, though, women in our studies found change of this magnitude to be meaningful. Our finding is consistent with a recently published work by another group of researchers who used anchor-based and distribution-based methods and found that an increase approximately of 0.2 satisfying sexual events per week in postmenopausal women with HSDD was a minimum important difference. More contemporary approaches to defining an MID have taken to reporting an MID "range of values"; however, while a range of values is a reasonable approach, the data from our trials was very consistent and allows us to be confident that our MID estimates are reliable.[13]

Based upon input from the women themselves, this study shows that the magnitude of treatment effects seen with the testosterone transdermal patch were meaningful to postmenopausal women with HSDD in clinical trials. The MIDs defined in this study may provide useful perspective for clinicians when evaluating a patient's response to treatment.

Conclusions

The changes in sexual desire, SSA, and personal distress that can be seen with transdermal testosterone patch treatment in surgically menopausal women with HSDD were clinically significant and were associated with a meaningful treatment benefit.

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Table 1. Patient characteristics in the large Phase III studies (SM1 and SM2) and in the sub-population enrolled in the follow-up study to evaluate clinical relevance.

	SM1 Study N=562	SM2 Study N=532	Clinical Relevance Study N=132
Age, years	49.0 (7.5)	48.9 (7.5)	48.0 (7.9)
Time since oophorectomy, years	8.5 (6.8)	9.0 (7.3)	8.6 (7.2)
Caucasian, %	89	90	94
Baseline frequency of satisfying sexual activity (SAL), events/month	2.9 (2.9)	3.1 (3.7)	2.7 (2.7)
Baseline sexual desire score (PFSF)	20.3 (13.3)	22.3 (13.5)	19.0 (12.0)
Baseline score on Personal Distress Scale	63.6 (25.1)	66.5 (24.8)	65.4 (26.2)

Values are mean (SD) unless otherwise indicated.

Table 2. Sensitivity, Specificity, and Correct Classification Rates of Potential Threshold Criterion

Criteria	Sensitivity	Specificity	Correct Classification
Satisfying Sexual Activity (AUC = 0.77)			
> 0.3	80%	57%	68%
> 0.5	74%	66%	70%
> 0.7	74%	68%	71%
> 1.0	69%	73%	71%
> 1.1	69%	74%	71%
> 1.2	67%	74%	70%
> 1.5	61%	79%	70%
Sexual Desire (AUC = 0.77)			
≥ 4.4	81%	54%	68%
≥ 6.7	74%	65%	70%
≥ 8.9	70%	72%	71%
≥ 11.1	65%	74%	70%
≥ 13.3	63%	83%	73%
Personal Distress Scale (AUC = 0.78)			
≤ -28.6	57%	85%	71%
≤ -25.7	61%	82%	72%
≤ -22.9	63%	78%	71%
≤ -20.0	72%	74%	73%
≤ -17.1	72%	63%	68%

Correct classification is the average of correct classification of women who did and did not experience a meaningful benefit; hence equal weight is given to both true negative classifications and true positive classifications. Negative values for personal distress scale indicate a decrease in distress.

Table 3. Proportion of Patients Reaching Threshold Criteria on Individual Endpoints

Study	Placebo Group	TTP Group	OR (95% CI)	p-value
Increase of more than 1 in satisfying sexual activities/4 weeks				
SM2	64/255 (25%)	109/258 (42%)	2.2 (1.5, 3.2)	<0.0001
SM1	95/273 (35%)	126/276 (46%)	1.6 (1.1, 2.2)	0.0103
Pooled	159/528 (30%)	235/534 (44%)	1.8 (1.4, 2.3)	<0.0001
Increase in sexual desire domain of 8.9 or greater				
SM2	87/257 (34%)	124/252 (49%)	1.9 (1.3, 2.7)	0.0005
SM1	93/269 (35%)	138/269 (51%)	2.0 (1.4, 2.8)	0.0001
Pooled	180/526 (34%)	262/521 (50%)	1.9 (1.5, 2.5)	<0.0001
Decrease of 20 or more in personal distress scale				
SM2	101/258 (39%)	131/254 (52%)	1.6 (1.2, 2.3)	0.0056
SM1	104/266 (39%)	134/268 (50%)	1.6 (1.1, 2,2)	0.0117
Pooled	205/524 (39%)	265/522 (51%)	1.6 (1.3, 2.0)	0.0002

Odds ratios and p-values obtained from a logistic regression model adjusted by route of administration of concomitant estrogen for individual study analyses and adjusted by estrogen route and study for pooled analysis.
TTP: Transdermal Testosterone Patch

(figure 1)

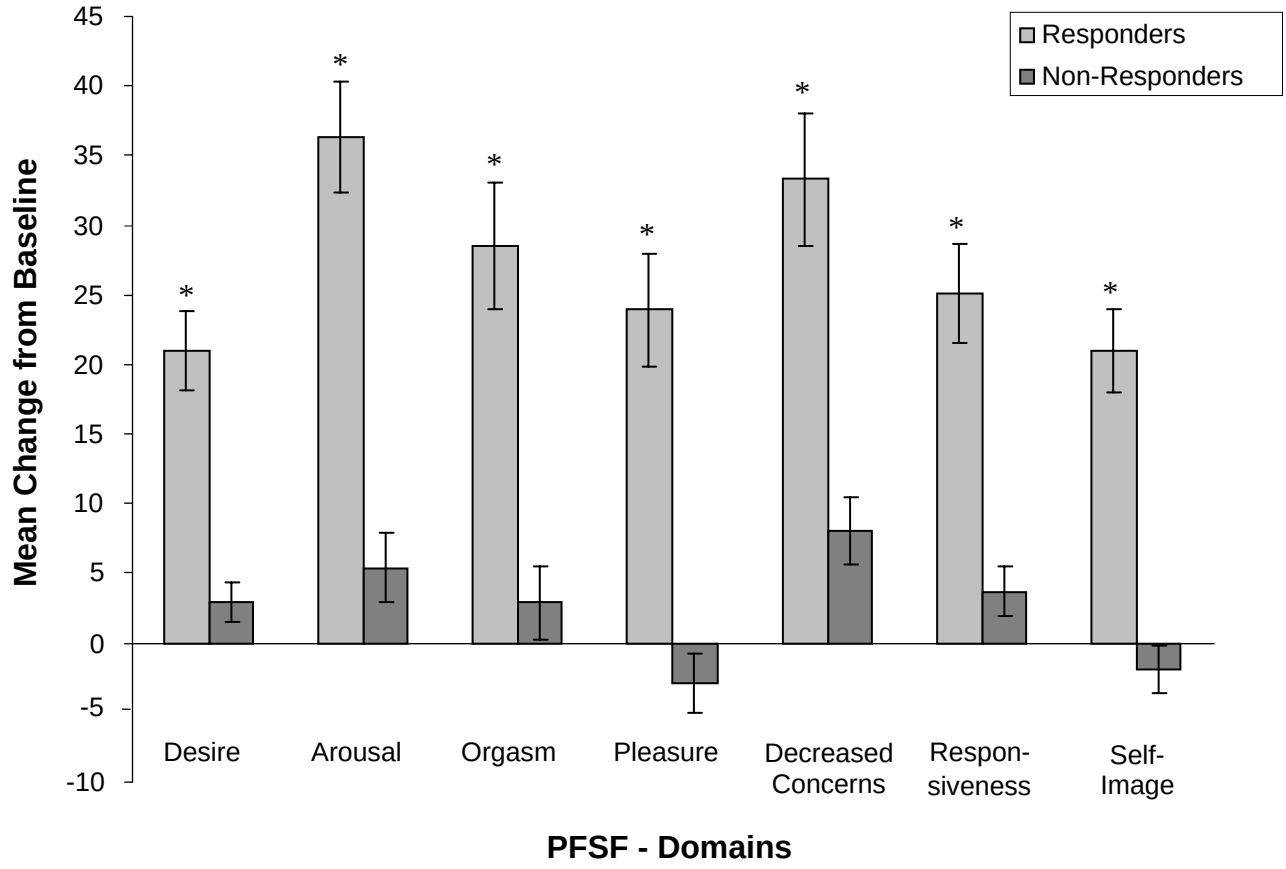

Figure 1. Mean Change (+/- SE) from Baseline in PFSF Domains in Women Who Answered Yes (Responders) or No (Non-Responders) to the Question of Whether They Received an Overall Meaningful Benefit from Study Patches.
* p <0.001 based on ANCOVA adjusted for interviewer method and study

(figure 2)

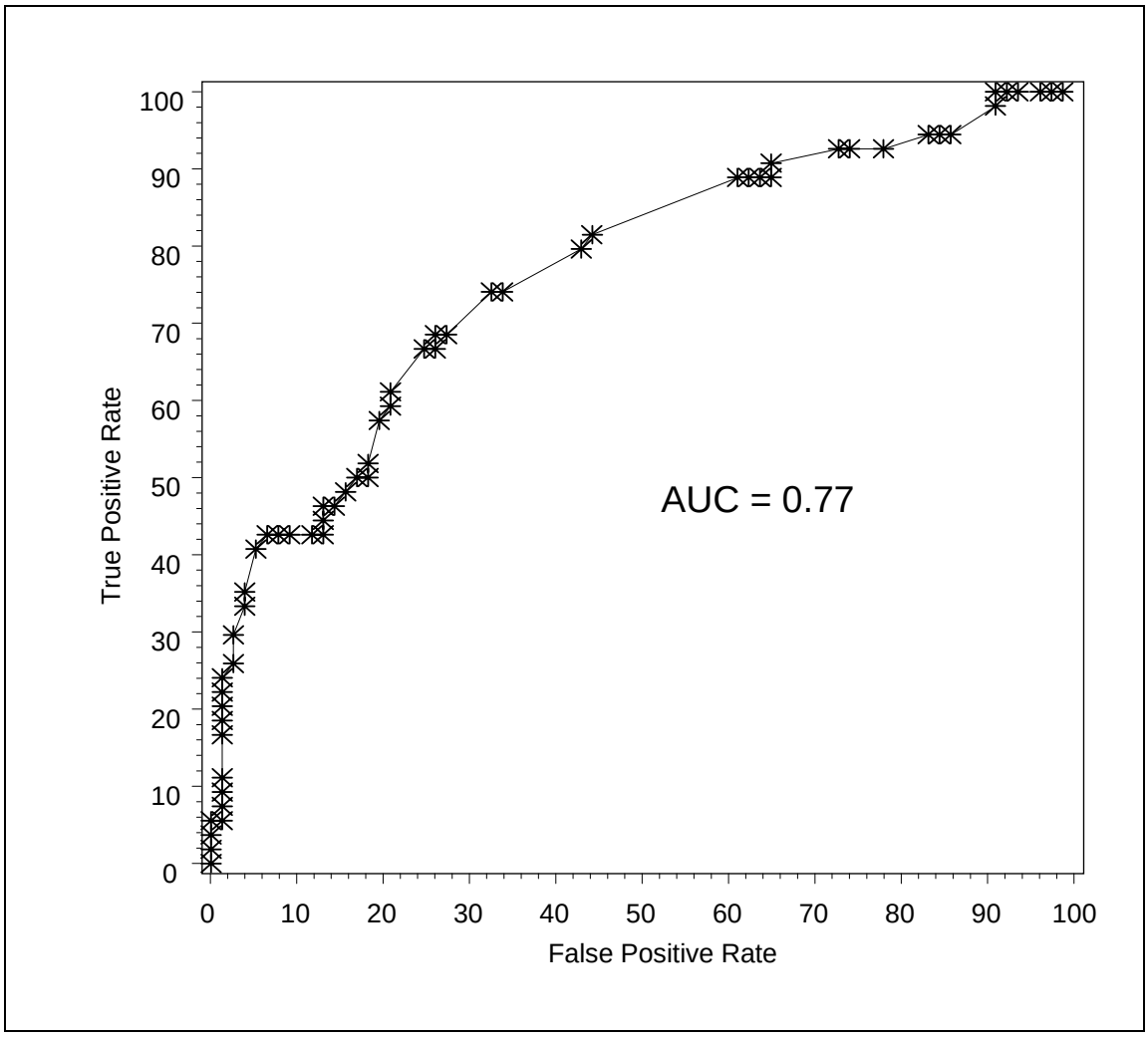

Figure 2. Frequency of Satisfying Sexual Activity ROC Curve.

(figure 3)

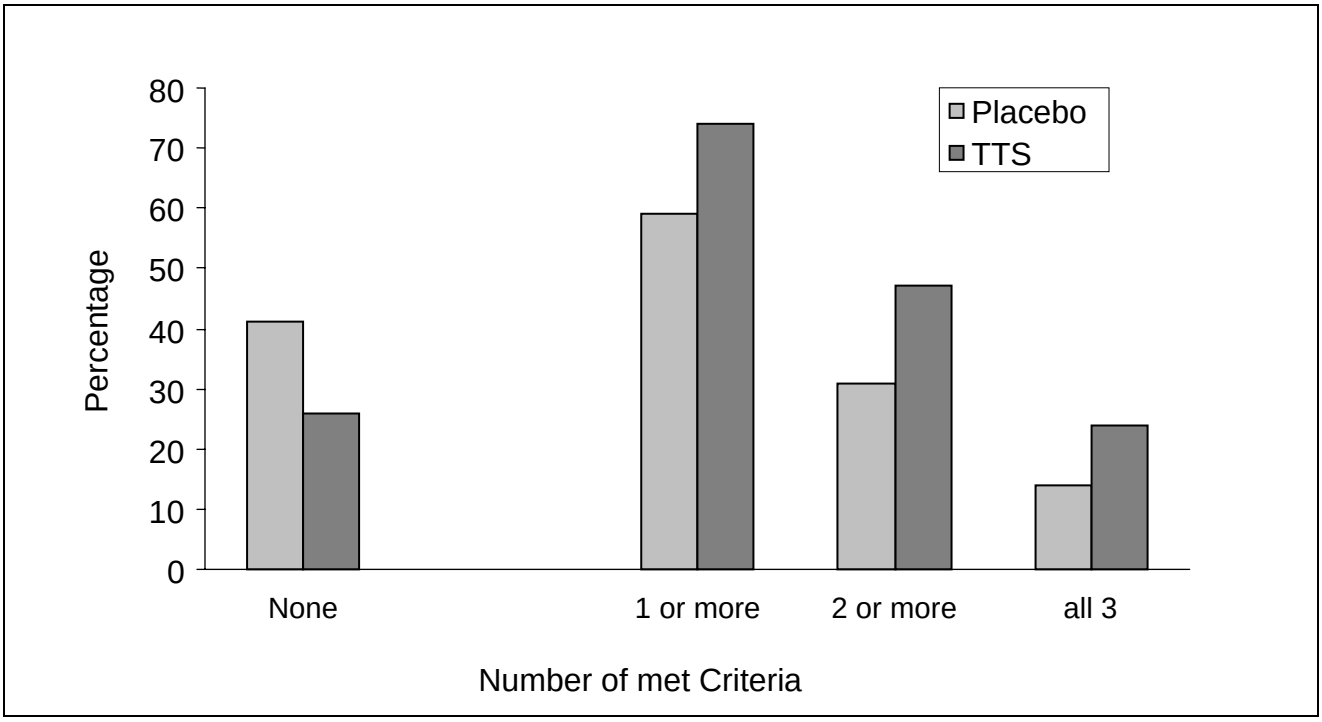

Figure 3. Percentage of Women who Met None, At least One, At least Two, or All Three of the HSDD Endpoint Responder Criteria. These criteria are an increase in satisfying activity greater than 1, an increase in sexual desire score of at least 8.9, and a decrease in personal distress score 20 or more.