

ORIGINAL RESEARCH—WOMEN'S SEXUAL HEALTH

Intended or Unintended Consequences? The Likely Implications of Raising the Bar for Sexual Dysfunction Diagnosis in the Proposed DSM-V Revisions: 1. For Women with Incomplete Loss of Desire or Sexual Receptivity

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ABSTRACT

Introduction. Combining female sexual desire and arousal disorders is proposed for the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). Brotto et al. challenged our findings that the proposed criteria could potentially exclude from diagnosis or treatment a large number of women with distressing loss of function or in sexual desire, because (i) our samples were insufficiently severe; (ii) we sought to retain the current diagnostic criteria, whereas they contend that “the bar should be raised”; and (iii) the current sexual function diagnostic criteria are unreliable.

Aim. Here we provide additional data to support our view suggesting that the proposed criteria would potentially exclude large numbers of women from diagnosis or treatment if they have moderate-to-marked (rather than severe) hypoactive sexual desire disorder (HSDD), or HSDD with incomplete loss of receptivity.

Methods. In nontreatment validation studies of 481 women in North America and Europe, 231 women diagnosed with HSDD only were compared to women with no female sexual desire.

Main Outcome Measures. Clinicians experienced in sexual medicine determined the severity of HSDD using the standard Clinical Global Impression of Severity. Rating scale data were also used, including the clinician-rated Sexual Desire and Interest Inventory-Female and the self-rated Female Sexual Function Index, Changes in Sexual Functioning Questionnaire, Female Sexual Distress Scale, and an e-Diary about desire during sexual events.

Results. The severity of the HSDD was rated by clinicians as generally moderate-to-marked, not mild. The women with HSDD scored as manifestly sexually dysfunctional and significantly sexually distressed, and reported markedly fewer satisfying sexual events compared to age-matched, non-dysfunctional controls, even for those with moderate or milder degrees of severity, providing compelling evidence that our sample of women with HSDD had clinically disordered sexual function. Yet the proposed criteria would apparently allow diagnosis (and therefore treatment) of only severe desire dysfunction.

Conclusion. It would be counterproductive to combine the two disorders, to make individual criteria for the disorders more stringent or to require more such criteria for a diagnosis because such disorders tend to be distinct in presentation, in treatability with currently available therapies, and in logical approaches to be tested to improve therapy. Clayton AH, DeRogatis LR, Rosen RC, and Pyke R. Intended or unintended consequences? The likely implications of raising the bar for sexual dysfunction diagnosis in the proposed DSM-V revisions: 1. For women with incomplete loss of desire or sexual receptivity. *J Sex Med* 2012;9:2027–2039.

Key Words. HSDD; HSD; DSM-V

Introduction

Brotto [1] have critiqued the existing *Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision* (DSM-IV-TR) [2] criteria for hypoactive sexual desire disorder (HSDD) and recommended that female sexual desire and arousal disorders be combined into one taxonomic category in the forthcoming revision (DSM-V). In a previous letter, we [3] provided evidence that premenopausal women with HSDD and with female sexual arousal disorder (FSAD) according to DSM-IV-TR criteria have distinct symptom patterns and that the majority of premenopausal women with HSDD are unlikely to meet the proposed new criteria for sexual interest/arousal disorder (SI/AD), although equally distressed by their disorder (based on Female Sexual Distress Scale-Revised [FSDS-R] scores).

More recently, Brotto et al. [4] have challenged our findings and conclusions on three grounds: (i) that our samples were insufficiently severe to warrant diagnosis or treatment; (ii) that we sought to retain the current diagnostic criteria, whereas they contend that “the bar should be raised”; and (iii) that the current sexual function diagnostic criteria are unreliable. Here we provide additional data to suggest that the new criteria proposed by Brotto et al. would potentially exclude large numbers of women from diagnosis or treatment if they have moderate-to-marked (rather than severe) HSDD or HSDD with incomplete loss of receptivity.

In the prior letter on this topic from our group [3], we reported on two North American (NA) observational studies funded by Boehringer Ingelheim (BI). Our letter addressed the issue of clinical presentation, namely the different symptom profiles in women with (DSM-IV-TR-diagnosed) HSDD vs. women with FSAD. One set of critiques by Brotto et al. [4] of our letter is based on this study. Brotto et al. claim that our data may not be “representative . . . of women with low desire who seek treatment.” As they note, we cited a conference presentation, not a peer-reviewed article, and thus recruitment strategy and inclusion criteria were missing. We seek to remedy this by citing broader data, overlapping with the data we presented before, including BI studies 511.73 of NA volunteers and 511.85 of European (EU) volunteers. Results from these studies are added here to verify the representativeness of the severity of the NA HSDD sample in particular.

Brotto et al. also took issue with the degree of HSDD severity in our samples based on their sexual behavior: “The fact that the mean number of sexual events reported by the HSDD group was 4.45 per month (approximately once a week) raises questions about the inclusion criteria used to recruit women with HSDD. It is not uncommon in clinical situations for women seeking treatment for HSDD to have only a few sexual episodes per year, and achieving 4.45 per month would typically be considered an excellent treatment outcome.”

Thus, we evaluated sexual behavior and the severity of sexual dysfunction as rated by an experienced clinician in these two studies, comparing women by diagnostic groups.

Brotto et al. [5] have recently published a case series of 110 consecutive women with low desire showing that non-receptive patients had more psychiatric history (current and past diagnoses of Axis I and II disorders, use of psychotropic medications, life stressors), more psychosexual history (sexual debut, past sexual experiences), and greater severity of HSDD than receptive patients. Thus, they make the case for using non-receptivity as a criterion potentially to be required for SI/AD [6] in DSM-V.

Their case series was highly selective, lacked relevant controls, and was of limited size. With this observation in mind, we queried results relevant to receptivity in the two aforementioned BI studies, which included almost 500 women with HSDD, FSAD, or no sexual disorder and were conducted primarily to provide discriminant validity data on the Sexual Desire and Interest Inventory-Female (SIDI-F), as these trials also included a daily diary asking about receptive desire.

Methods

Study Design

Both studies were 4-week prospective multicenter trials designed to assess the reliability and validity of the SIDI-F in assessing the severity of HSDD symptoms, as previously described [7].

Subjects

BI observational study 511.73, including NA volunteers with HSDD, FSAD, or no sexual dysfunction, included not only the premenopausal data we included in our prior letter, but also peri- and postmenopausal women. BI observational study 511.85 of EU volunteers also included pre-, peri-,

and postmenopausal women with HSDD or no sexual dysfunction, although not a group with FSAD. The primary method of recruitment for the NA study was by advertisement in local media (newspapers and radio, plus a website). Women 18–65 years old were solicited in the United States: “If you are (■) in a monogamous heterosexual relationship for at least one year, and (■) are experiencing a lack of sexual interest and desire, (■) or are having difficulty becoming aroused, (■) or are having a typical sex life with no sexual dysfunction, you may be eligible to participate in a research study to check the reliability and validity of a new sexual desire questionnaire.”

Treatment was neither extended nor implied, although the importance of the study was noted at the end of the advertisement, “Remember, sexual health is an important part of a relationship.” The Canadian sites in the NA study, and the EU study sites, used similar advertising materials where permitted. Both studies also utilized referrals of subjects with sexual dysfunction of desire or arousal from local practitioners.

Women aged 18–65 years were eligible. Diagnostic requirements and methods and inclusion/exclusion criteria were given in the prior article by Clayton et al. [7] Both studies required that women be in a long-term, communicative, monogamous relationship. The relationship was assessed in a semi-structured diagnostic interview with probes to investigate the couple’s problem-solving, money-handling, decision-making, etc. Women with same-sex partners were excluded due to lack of validation of the diagnostic interview and study measures in these women. Male partners were required to be available at least half the time and have no sexual dysfunction at study baseline per subject report.

Assessments

Both studies included, at baseline and after 28 days of e-Diary entries, four measures of sexual dysfunction. One was the 13-item clinician-rated SIDI-F, a scale created to measure each of the dimensions of female HSDD found most relevant by experienced clinicians, using a 1-month recall [8]. The other three measures of sexual dysfunction were self-rated and had been extensively validated previously: the Female Sexual Function Index (FSFI) [9], the Changes in Sexual Functioning Questionnaire-Female (CSFQ-F [10]), and the FSDS ([11]).

Clinicians trained and highly experienced in sexual medicine clinical trials at 10 research sites in the United States or Canada, and 30 sites in 11 countries in EU, performed the diagnostic inter-

views and determined the severity of HSDD in a sample of 239 women with HSDD, using the standard Clinical Global Impression of Severity [12]. This widely used scale has seven categories: not at all ill, borderline ill, mildly ill, moderately ill, markedly ill, severely ill, and extremely severely ill. No severity criterion was required for acceptance to the study.

At baseline, all subjects were asked to complete an early version of the e-Diary for HSDD on their sexual activity and attitudes daily for the next 28 days. The diary asked five yes–no questions, whether subjects had had, in the prior 24 hours: (i) sexual thoughts, (ii) desire to have sex; (iii) a sexual event, and if an event; (iv) whether it was satisfying for her; and (v) whether she had an orgasm. Crucial to the issue of receptivity, the e-Diary also asked desire information about the sexual event: her *level of desire at the start* of the event and her *highest level of desire during* the event: no (0), low (1), moderate (2), or strong (3) desire.

Desire at the start of an event and the highest level during the event were analyzed in two ways: as the mean for each diagnostic grouping’s means and as a count per month of events with desire moderate or strong at the start, and with desire moderate or strong at the highest. Sexual thoughts and desire were analyzed as the proportion of entries answered as “yes.”

Statistical Analysis

All results are based on prespecified analyses; no post hoc analyses were performed for this article. Sample size calculations and most of the statistical methods were outlined previously [7]. In addition, to evaluate e-Diary results between diagnostic populations, the total monthly counts of successful and satisfying sexual encounters were compared using a nonparametric Wilcoxon rank sum test stratified by center and age categories using StatXact (Cytel, Cambridge, MA, USA). The 95% confidence interval around the median was determined using the Hodges-Lehmann procedure. To explore the relationship between the e-Diary and SIDI-F, the Pearson coefficients were calculated between e-Diary secondary end points and the planned day 28 SIDI-F total score.

Results

Study Subjects

Of the 516 subjects screened, 481 subjects entered the studies, about half in NA and half in EU. Roughly equal numbers were 50 or younger and

Table 1 Questionnaire means (sexual desire) in North American women with HSDD only, FSAD only, or no sexual diagnosis at baseline in study 511.73

Diagnosis	Statistic	SIDI-F total	FSFI total	CSFQ-F total	FSDS total
HSDD	N	113	113	113	113
	Mean (sexual desire)	20.3 (7.1)	21.6 (6.5)	42.5 (6.7)	24.1 (11.2)
FSAD	N	49	49	49	49
	Mean (sexual desire)	26.7 (8.4)	19.7 (6.2)	41.8 (8.0)	25.0 (10.3)
No FSD	N	61	61	61	61
	Mean (sexual desire)	42.1 (5.2)	31.4 (3.8)	55.5 (6.2)	4.7 (5.5)
HSDD—No FSD	<i>P</i> value	<0.0001	<0.0001	<0.0001	<0.0001
HSDD—FSAD	<i>P</i> value	<0.0001	0.0675	0.6033	0.3157
FSAD—No FSD	<i>P</i> value	<0.0001	<0.0001	<0.0001	<0.0001
HSDD—No FSD	95% CI	(-23.9, -19.5)	(-11.5, -8.0)	(-14.5, -10.4)	(16.2, 22.2)
HSDD—FSAD	95% CI	(-8.6, -3.8)	(-0.1, 3.6)	(-1.6, 2.8)	(-4.9, 1.6)
FSAD—No FSD	95% CI	(-18.2, -12.8)	(-13.6, -9.4)	(-15.5, -10.5)	(17.2, 24.5)

The desire-oriented SIDI-F scale showed more severity in North American women with HSDD than in those with FSAD; the arousal/lubrication-weighted FSFI showed more severity in those with FSAD, while the general female sexual dysfunction (FSD) scales CSFQ-F and FSDS showed equal severity. All four scales showed marked dysfunction in women with HSDD or FSAD compared to women with no FSD. SIDI-F = Sexual Interest and Desire Inventory-Female (range 0 [worst]–51 [best], cutoff for FSD vs. no FSD, 33; [7]); FSFI = Female Sexual Function Index (range 2 [worst]–36 [best], cutoff 26.55; Wiegel et al. [9]); CSFQ-F = Changes in Sexual Functioning Questionnaire-Female (range 14 [worst]–70 [best], cutoff 47; Keller et al. [10]); FSDS = Female Sexual Distress Scale (range 0 [best]–48 [worst], cutoff 15; Derogatis et al. [11]); CI = confidence interval

more than 50 years old. The demographics of both sets of volunteers have been set forth previously [7].

Women with Moderate to Marked HSDD

Tables 1–3 show the questionnaire results for each diagnostic group in each study. For the SIDI-F, FSFI, and CSFQ-F, a higher score indicates greater functionality; for the FSDS, a higher score indicates more distress. The scores on the SIDI-F are representative of women with HSDD compared to other publications cited by Brotto et al. [4] In the HSDD patients in NA study 511.73, one finds slightly lower FSFI mean total scores for FSAD patients (19.7) than for HSDD patients (21.6) although the difference between the two groups did not reach significance ($P = 0.067$; see Table 1). The other measure of general sexual function, the CSFQ-F, also showed the HSDD

and FSAD groups to not be statistically different from one another ($P = 0.60$).

In contrast, the SIDI-F, concentrating as it does on constructs most relevant to HSDD, showed the HSDD patients more severely affected than the FSAD subjects (mean 20.3 vs. 26.7, $P < 0.0001$). Also, the *symptom patterns* within the FSFI scores (the domain scores) were different for women with these two diagnoses: Table 2 shows these substantial differences in desire, arousal, lubrication, and orgasm between women with HSDD and FSAD, each in the expected direction. (As anticipated, scores on the other two domains, pain and satisfaction, did not differ by diagnosis.)

The similar questionnaire validation study of EU women (Table 3) verified the NA study (Table 3) in the level of severity in women with HSDD (Table 3).

Table 2 FSFI domain scores in North American study 511.73 by diagnosis

Diagnosis	Statistic	Total	Arousal	Desire	Lubrication	Orgasm
HSDD	N	113	113	113	113	113
	Mean (sexual desire)	21.6 (6.5)	3.4 (1.5)	1.9 (0.8)	4.2 (1.9)	3.9 (1.8)
FSAD	N	49	49	49	49	49
	Mean (sexual desire)	19.7 (6.2)	2.8 (1.3)	3.3 (1.3)	3.0 (1.6)	2.7 (1.5)
No FSD	N	61	61	61	61	61
	Mean (sexual desire)	31.4 (3.8)	5.2 (0.8)	4.6 (1.0)	5.4 (1.0)	5.2 (1.0)
HSDD—No FSD	<i>P</i> value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
HSDD—FSAD	<i>P</i> value	0.0675	0.0058	<0.0001	<0.0001	<0.0001
FSAD—No FSD	<i>P</i> value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
HSDD—No FSD	95% CI	(-11.5, -8.0)	(-2.1, -1.3)	(-2.9, -2.3)	(-1.7, -0.8)	(-1.7, -0.8)
HSDD—FSAD	95% CI	(-0.1, 3.6)	(0.2, 1.0)	(-1.7, -1.0)	(0.5, 1.5)	(0.6, 1.6)
FSAD—No FSD	95% CI	(-13.6, -9.4)	(-2.8, -1.8)	(-1.6, -0.9)	(-2.9, -1.7)	(-3.0, -1.9)

The domains of the FSFI specific to each dimension of sexual function showed more impairment of lubrication, arousal, and orgasm in those with FSAD than in those with HSDD, and more impairment of desire in those with HSDD, and marked impairment of both groups compared to women with no FSD. FSFI = Female Sexual Function Index (range 2 [worst]–36 [best], cutoff, 26.55); CI = confidence interval

Table 3 Severity of HSDD in North American (NA) vs. in European (EU) Women. BI trials 511.73 and 511.85, baseline values

Diagnosis	Statistic	SIDI-F Total		FSFI Total		CSFQ-F Total		FSDS Total	
		NA	EU	NA	EU	NA	EU	NA	EU
HSDD	N	113	126	113	126	113	125	113	128
	Mean	20.3	20.1	21.6	20.4	42.5	39.7	24.1	24.3
	sexual desire	7.1	8.4	6.5	7.4	6.7	7.1	11.2	10.5
No FSD	N	61	124	61	123	61	121	61	122
	Mean	42.1	41.8	31.4	32.0	55.5	54.4	4.7	3.3
	sexual desire	5.2	5.2	3.8	2.9	6.2	5.8	5.5	4.0
HSDD-No FSD	P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	95% CI	(-23.9, -19.5)	(-23.5, -20.2)	(-11.5, -8.0)	(-13.2, -10.4)	(-14.5, -10.4)	(-16.5, -13.4)	(16.2, 22.2)	(19.1, 22.9)

All four FSD scales showed similar severity in European and North American women with HSDD and marked dysfunction compared to women with no FSD. SIDI-F = Sexual Interest and Desire Inventory-Female (range 0–51, cutoff for FSD vs. no FSD 33); FSFI = Female Sexual Function Index (range 2–36, cutoff 26.55); CSFQ-F = Changes in Sexual Functioning Questionnaire-Female (range 14–70, cutoff 47); FSDS = Female Sexual Distress Scale (range 0–48, cutoff 15)

Our samples reported markedly fewer satisfying sexual events (SSEs) compared to age-matched, non-dysfunctional controls. This was true not only for those women with severe HSDD, but also for those with moderate or milder degrees of severity. The severity of the HSDD was rated (See Table 4 and Figure 1) by clinicians in the study as generally in the moderate-to-marked severity category. The women with marked HSDD reported, on average, about 25% of the number of SSEs compared to non-dysfunctional controls, those with moderate HSDD reported almost 1/3 as many SSEs as controls, and those with mild HSDD reported less than half as many SSEs as controls.

The results for the SIDI-F erotica item show that the women with HSDD had markedly impaired self-reported/clinician-rated responses to sexual stimuli compared to women without HSDD. In the NA validation study (see reference 14's table 1 and its footnote), not only was the mean difference between women with and without

HSDD on the erotica item highly significant, ($P < 0.0001$), but overlap of the Q1–Q3 distributions was negligible (not shown).

Women with HSDD with Incomplete Loss of Receptivity

Table 5 shows that women with HSDD, although not selected for non-receptivity, were significantly less receptive than women with no FSD, and were less interested in sex during sexual events. In the NA sample, women with HSDD were less receptive than those with FSAD, who in turn were less receptive than women with no FSD. Women with HSDD were significantly more dysfunctional than women with FSAD in frequency of sexual thoughts and in frequency of desire for sex. Level of desire at the start of sexual activity was lowest for women with HSDD, and was significantly higher but still subnormal for women with FSAD, compared to women with no FSD. Highest level of desire during sexual events showed the same

Table 4 HSDD severity in women unselected for severity: statistics on SSE at Day 28 (last day of collection of SSE data) and SIDI-F (baseline and Day 28) by Clinical Global Impression of Severity

	SIDI-F total score*				Satisfying sexual events (SSE)/28 days			
	NA		EU		NA		EU	
	N	Mean (sexual desire)	N	Mean (sexual desire)	N	Median (Q1, Q3)	N	Median (Q1, Q3)
Subjects without FSD	117	42.1 (5.0)	246	41.7 (5.1)	55	7.2 (3.8, 12.0)	120	9.3 (6.5, 12.6)
HSDD patients (CGI of Severity)								
Borderline	1	38.0	1	35.0	1	2.4	1	5.0
Mild	23	24.7 (5.9)	59	28.6 (6.0)	13	3.4 (2.6, 4.7)	32	3.2 (1.2, 4.5)
Moderate	107	22.3 (7.5)	83	21.7 (7.2)	48	2.7 (1.6, 5.9)	43	2.6 (1.0, 4.7)
Marked	67	20.3 (7.1)	76	17.4 (7.7)	32	1.8 (0.9, 4.6)	31	1.5 (0.0, 2.9)
Severe	23	13.8 (5.4)	26	15.2 (6.7)	9	0.0 (0.0, 2.2)	13	1.0 (0.0, 1.9)
Extreme	2	18.5 (2.1)	8	10.1 (7.7)	1	1.9	6	0.0 (0.0, 1.0)

North American and European women with HSDD, though not selected for the study based on any severity criterion for sexual activity, reported markedly fewer SSE compared to women with no FSD. This was true not only for those women with severe HSDD but also for those with moderate or mild degrees of severity. *Rated twice, at the beginning and the end of the 28 days of e-Diary participation



Figure 1 The distribution of Clinical Global Impression of Severity of HSDD in the North American and European samples of women with DSM-IV-TR-diagnosed HSDD shows a classic normal distribution, with most in the "moderate" or "marked" categories.

pattern, as did the number of events with desire moderate or strong at the start of an event and at the highest during the event. NA results for women with HSDD and those with no FSD were extremely similar to those in EU.

How closely was receptivity related to overall severity of HSDD? Table 6 shows internal consistency for the SIDI-F as assessed using Cronbach's alpha, and individual SIDI-F item-to-total correlations analyzed for the women with HSDD and for all women at baseline in the two studies using the unadjusted item deletion method. This paradigm for calculating item-total correlations with outcomes instruments involves correlating the item in question with an adjusted total score, the adjustment consisting of the score from the item in question being deleted or removed from the total. Correlation values for receptivity were high, rivaled only by desire frequency, desire satisfaction, and positive (sexual) thoughts frequency, impairments of which are hallmarks of desire disorder.

Discussion

Women with Moderate to Marked HSDD

Symptom Patterns Shown in Questionnaires

In our prior letter [3] and in the current, expanded sample, the *symptom patterns* within the FSFI scores (the domain scores) were different for women with HSDD and FSAD. Brotto et al. argued that the samples we cited previously were insufficiently severe to be representative of women with HSDD, yet the SIDI-F scores on the total sample (adding to premenopausal the peri- and postmenopausal samples) in these two studies are representative of women with HSDD compared to

other publications cited by Brotto et al. And the present (NA) sample also shows SIDI-F scores lower in women with HSDD than in women with FSAD.

Brotto et al. also suggested that our findings are unrepresentative in the low correlations reported between FSFI desire and arousal domains ($r = 0.30$ for women with HSDD and $r = 0.57$ for women with FSAD). They cited r values between 0.5 and 0.76 in other publications. These values are sufficiently large to suggest a close relation between desire and arousal problems in these women; possibly that low desire in some cases may lead to arousal difficulties, or vice versa, or that some common diathesis may produce both, but they certainly are not high enough to suggest identity, i.e., that arousal and desire problems are one and the same, as identity is a very strict criterion which implies not only covariation in values, but actual "agreement" in scores or values. As the square of the correlation coefficient (the coefficient of determination) provides a measure of shared variation, a correlation of 0.95 (i.e., 90% shared variation) would be required to make two entities "identical." Moderate correlations such as these do not imply that the two constructs represent one disorder. This is a key element of our rejoinder, based on results of multiple studies including those cited previously.

Brotto et al. (2011) have claimed that the degree of comorbidity of HSDD and FSAD in women favors combining the disorders. But both disorders were present in only a modest minority, 21% and 27.6%, respectively, in the largest samples yet published of women actually seeking treatment, i.e., the summary article on almost 800 women in trials of sildenafil for FSAD [13] and the briefing document of BI on the phase 3 studies of almost

Table 5 Sexual Thoughts and Sexual Desire: daily diary measures, mean (sexual desire) for 28 days of entries

Diagnosis	Did you have (% "yes")		Level of desire		Number of events with desire moderate or strong	
	Sexual thoughts	Desire for sex	At start of event	Highest during event	At start of event	Highest during event
North American study						
HSDD (N = 105)	18.2 (17.0)*	16.3 (13.1)*	1.1 (0.7)*	1.7 (0.7)*	1.7 (1.9)*	3.0 (2.5)*
FSAD (N = 44)	35.4 (28.0) [†]	29.7 (22.5) [†]	1.5 (0.7) [†]	1.9 (0.7) [†]	4.3 (5.2) [†]	5.5 (5.1) [†]
No FSD (N = 59)	49.0 (25.9) [‡]	48.6 (22.8) [‡]	2.0 (0.5) [‡]	2.5 (0.4) [‡]	9.4 (11.6) [‡]	10.6 (11.6) [‡]
European study						
HSDD (N = 126)	17.8 (16.1)	16.2 (13.1)	1.3 (0.7)	1.9 (0.7)	1.5 (1.7)	2.5 (2.5)
No FSD (N = 120)	46.7 (25.9)	46.2 (20.3)	2.1 (0.5)	2.6 (0.4)	8.6 (5.1)	9.9 (5.0)
HSDD—No FSD (<i>P</i> value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
95% CI	(-34.4, -24.1)	(-34.5, -26.2)	(-1.0, -0.7)	(-0.8, -0.5)	(-7.3, -5.4)	(-7.8, -6.1)

*, †, and ‡Values with different superscripts in a column were statistically significantly different, $P < 0.05$.

Women with HSDD had sexual thoughts or a desire for sex significantly less often than women with FSAD. The level of desire at the start of sexual activity was lowest for women with HSDD, and was significantly higher but still subnormal for women with FSAD, compared to women with no FSD. The highest level of desire during sexual events showed the same pattern, as did the number of events with desire moderate or strong at the start of an event and at the highest during the event. North American results for women with HSDD and those with no FSD were extremely similar to those in Europe (FSAD not included in the EU study).

8,000 women in trials of flibanserin for HSDD [14].

Severity and Sexual Behavior

Broto et al. have also questioned the severity of HSDD in our sample given that a relatively high proportion of sexual events were categorized as satisfying (about 70%). We see no close connection between SSE and diagnostic criteria, as noted previously regarding the relationship between the frequency of sexual activity and diagnostic criteria [15]. Nevertheless, our samples reported markedly fewer SSEs compared to age-matched, non-dysfunctional controls. This was true not only for those women with severe HSDD but also for those with moderate or milder degrees of severity.

The two BI studies required that women be in a long-term, communicative monogamous relationship. Because male partners are frequently the initiators of sexual activity in long-term relationships and these couples are highly motivated to improve their sexual relationship, the frequency of sexual activity (not necessarily intercourse) should not be seen as surprising.

Reports of women with HSDD in a recent qualitative study found that women with HSDD frequently have sex to appease their partners or to maintain stability in the relationship [16]. That these women acquiesced to some form of sexual interaction with their partners on a weekly basis may indicate differences between the clinical trial population and specialized sex therapy referral settings; however, it is unclear which population is more representative of the larger population of women with HSDD in the general population. Women seen by Broto et al. in highly specialized, tertiary referral clinics may represent one end of the spectrum of women with the most chronic or intractable sexual dysfunction problems, compared to the larger number of women who seek help in a general practice setting, many of whom may have more moderate or milder degrees of dysfunction, but nonetheless deserving of intervention.

Desire Induced by Any Competent Stimulus or Sexual/Erotic Cue

Broto et al. comment also that in our previously presented data, we failed to address whether our women with HSDD were affected severely enough as to lack desire induced by any competent stimulus: "At present, there are no validated instruments that assess this symptom, so it is understandable that DeRogatis et al. would find this difficult to assess. Nonetheless, we consider this a key symptom in our proposed diagnostic criteria and

Table 6 Correlation of SIDI-F items to total SIDI-F score in North American and European women with HSDD and in all subjects tested

Continent	Measure	SIDI-F item(s)	NA		EU	
			All	HSDD	All	HSDD
Cronbach's alpha	Correlation with total	Overall	0.8967	0.7705	0.9247	0.8105
		Relationship—sexual	0.7235	0.4441	0.7372	0.3888
		Receptivity	0.7808	0.5842	0.7892	0.5355
		Encouraged initiation	0.6444	0.4427	0.6514	0.3163
		Desire frequency	0.7927	0.5638	0.8562	0.6148
		Affection intensity	0.3103	0.2364	0.4041	0.2489
		Desire satisfaction	0.7632	0.2884	0.7868	0.3368
		Desire distress	0.6295	0.2024	0.6203	0.2519
		Positive thought	0.7521	0.5482	0.8179	0.5813
		Frequency erotica	0.5137	0.4502	0.4061	0.2927
		Arousal frequency	0.3417	0.3568	0.6771	0.6242
		Arousal ease	0.5298	0.2933	0.7780	0.6198
		Arousal—continuation	0.5359	0.4112	0.5932	0.5769
		Orgasm frequency	0.4160	0.3794	0.6362	0.5289

Internal consistency for the SIDI-F was assessed using Cronbach's alpha and individual SIDI-F item-to-total correlations were assessed using the unadjusted item deletion method, for the women with HSDD and for all women at baseline in the two studies. Receptivity was one of the items most closely related to overall severity of HSDD. Desire frequency, desire satisfaction, and positive (sexual) thoughts frequency were also consistently well correlated with the total score. Such impairments are hallmarks of desire disorder. Arousal items correlated well with the total in EU but not in NA.

NA = North American women; EU = European women.

one which reflects a key tenet of the Incentive Motivation Model, i.e., that an inability to become sexually excited in response to 'effective' or 'competent' stimuli denotes a problem."

Since then, the proposal for DSM-5 criteria (criterion A5) has been changed to, "absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g., written, verbal, visual, etc.)" [17]. We will not comment here on the feasibility of trying to impose either proposed criterion when there is no known or validated way to assess it. However, in considering what data are available, our results for the SIDI-F erotica item show that the women with HSDD whom we included in our trials had markedly impaired self-reported responses to sexual stimuli compared to women without HSDD. In the NA validation study, not only was the mean difference between women with and without HSDD on the erotica item highly significant ($P < 0.0001$) but overlap of the Q1–Q3 distributions was negligible [18]. Thus, these women with HSDD were clearly abnormally low in sexual desire in response to environmental stimuli. Given the heavy emphasis in NA mass media of erotic suggestion and imagery, this argues against the contention by Brotto et al. that women recruited for the clinical trials of BI were unevaluable in regard to criterion A5.

Whose Data Are Representative?

Brotto et al. argue, moreover, that their clinical experience is with more severe patients than those in the BI observational studies and that treatment

should be reserved for these patients only: "we were deliberately trying to 'raise the bar' for what qualifies as a disorder, given the extremely high rates of dysfunction reported in many epidemiological studies. . . ." Conversely, we question how representative are patients seen in *highly specialized sex therapy clinics*, as suggested by Brotto et al. of the general population of women with HSDD. We would strongly counter their assertion and point out, in response, that a highly specialized, tertiary referral service or sex therapy clinic is likely to attract men and women with long-lasting or intractable sexual problems, compared to more typical complaints likely to be seen by general practitioners or gynecologists. In the absence of approved medical therapies, it is difficult to ascertain the representativeness of the very small and select group of patients who receive psychological or sex therapy treatment for their disorder.

The representativeness of the BI observational study populations is further supported by recent data from the HSDD Registry for Women [19,20]. A national patient registry cohort was recruited for this study from pre- and postmenopausal women presenting at 34 clinical sites nationally with complaints of low sexual desire. The sites included a combination of sexual medicine clinics, gynecology and women's health practices, and general practice offices. All women in the study ($N = 1,571$) received a positive HSDD diagnosis from an experienced clinician using current DSM-IV criteria, and supported by a standardized evaluation using a validated diagnostic tool [21]. The

levels of overall sexual function (total FSFI scores) and FSFI sexual desire domain scores in the HSDD Registry population were not dissimilar from the levels observed in the studies described previously. Moreover, similar levels of distress and perceived HSDD severity were seen across the study populations. Of note, only 6.2% of the premenopausal participants in the Registry and fewer than 10% of postmenopausal women with HSDD reported seeking sex therapy or counseling for their problem. Clearly, the majority of women diagnosed with HSDD in ob-gyn or general practice settings are not drawn from the same population as those seen in specialized sex therapy clinics. Other comparisons by age, health and relationship status, and broader psychosocial measures indicate large areas of similarity in the populations. Finally, combined arousal and desire problems were observed in approximately half of the HSDD Registry participants, although approximately equal numbers of premenopausal women with diagnosed HSDD did *not* report arousal or lubrication difficulties, as assessed by the FSFI [20].

Unlike Brotto et al., we found in our NA and EU validation trial populations only a minority of patients with HSDD who had a complete absence of SSE. Of note, these women were generally rated as “severely” or “extremely ill” by clinicians, but represented a small percentage of the total group, approximately 10% (24/230 across both continents), of the population of women with HSDD in the BI observational studies.

Distress as a Criterion for Diagnosis

In other settings, practitioners have been shown to underestimate the severity of women’s sexual desire problems. This may be true not only for sex therapists or sexual medicine specialists but also for primary care/gynecology practitioners. In the only study published on comparisons of practitioners and patients in rating sexual distress, the physician practitioners markedly underestimated the severity of women’s distress from their sexual desire problems [22]. In this study, 51 of 75 patients with distressing low desire (68%) rated themselves as “moderately” or “very distressed” about this problem; 30 of the patients (40%) were so rated by the 28 interviewing physicians. In the 17 patients (23%) who rated themselves as “very distressed,” physicians underestimated distress even more dramatically, rating 82% of them as “moderately” to “not” distressed.

In keeping with DSM-IV criteria and current regulatory guidelines, we have opted to focus on

validated measures of sexually related distress as the clearest marker or most reliable measure of clinical impact of a sexual dysfunction. In the two BI validation studies, using the originally validated version of the FSDS [23], Tables 1 and 3 show that, even when non-receptivity was not required, mean sexual distress scores in women with HSDD were at least 50% of the maximum possible score (>24 vs. 48), and over five times those in women with no sexual dysfunction (>24 vs. <5). We contend that high subjective distress scores such as these indicate strongly that these patients are seeking and deserve treatment.

We acknowledge that lowering bars to diagnosis could stigmatize a greater number of people, may overload practitioners, and can be costly for third-party payers. Conversely, raising the bar inevitably makes treatment potentially less available to men and women who may need it greatly. What evidence is there of the clinical need? BI sponsored three independent studies on this topic. Interviews in the United States, Germany, and France with 95 women with HSDD—as already defined—and with 137 practitioners who treat such patients found that HSDD affects patients in at least five ways: *low self-esteem* (inferiority, insecurity, shame, etc.); *frustrated* (confused, guilty, regretful, etc.); *anxious* (worried, angry, stressed, etc.); *depressed* (withdrawn, lonely, lacking energy, etc.); *defective* (damaged, deficient, incomplete, etc.); and *flat* (empty, unworthy, abnormal, etc.). Clinicians also stated that HSDD in their practice led to depression, anxiety, and a frequent concern for the health and stability of their partner relationships. Of the clinicians, 62% were primary care practitioners (45) or gynecologists (40), 19 urologists, 25 psychiatrists, and 8 sexologists were also included [24].

A study of 36 women with DSM-IV-TR HSDD or self-reported desire problems in five focus groups found that participants reported similar feelings about their decreased sexual desire. Reported impact on relationships included issues with trust, changes in intimacy, and having sex to appease partners. Women perceived the impact on their partners as inducing feelings of rejection and frustration [16].

Likewise, a survey that included over 5,000 EU women meeting the four simple yes/no Decreased Sexual Desire Screener (DSDS) criteria for bothersome loss of desire (satisfying level of desire in past, decrease in it, bothered about that, and would like level to increase) showed that the frequency of experiencing negative emotions is directly correlated with both frequency and level of desire expe-

rienced over the previous 12 months. Reports of negative emotions experienced frequently or always over the last 3 months included: unhappy about your sexual relationship (28.7%), guilty about sexual difficulties (36.0%), frustrated by your sexual problems (28.5%), stressed about sex (21.6%), feeling inferior because of sexual problems (18.1%), regrets about your sexuality (24.7%), dissatisfied with your sex life (36.3%), angry about your sex life (23%), and distressed about your sex life (32.8%). Women's reports of their frequency of sexual desire and level of sexual desire over the last 12 months were significantly correlated ($P < 0.01$) with reports of their level of distress about their low sexual desire and with each of these negative emotional responses. These findings emerged despite the potential dilution of morbidity by the way in which the sample was recruited, i.e., a population representative subgroup of 65,129 women from France, Germany, Italy, Spain, and the United Kingdom participating in a demographically representative research panel rather than complaining of a sexual problem to a practitioner, although the subjects with decreased desire were not required to meet any severity criterion for inclusion [25].

Diagnostic Reliability and Construct Validity

Brotto's final critique of our support of current DSM-IV diagnoses is that "The basic prerequisites for any clinical category include demonstrations of diagnostic reliability and construct validity. In fact, there are no published reliability studies for either HSDD or FSAD. We doubt that either diagnosis could withstand a serious reliability check." Regarding HSDD, a high degree of diagnostic accuracy (85% overall, with 84% sensitivity and 88% specificity) has been established between two clinicians blinded to each other diagnosing (or not diagnosing) the disorder based on a structured clinical interview vs. the DSDS [21] in a sample of over 260 patients in NA. Even higher concordance was found in two follow-up clinical trials of women with desire problems recruited by referrals and advertising, of 921 patients at 63 sites in NA and in 639 patients in 55 sites in EU [26].

We recommend that tests of diagnostic reliability should also include how well clinical diagnosis relates to a validated rating scale for that disorder. A publication on the SIDI cutoff score for HSDD showed, in the same two populations on two continents as shown in the current studies (511.73 and 511.85), that diagnosis or non-diagnosis of HSDD related closely to a cutoff score for the SIDI-F. In

the NA study, a SIDI-F cutoff score of 33 minimized the difference between sensitivity (94.7%) and specificity (93.4%). In the EU study, SIDI-F cutoff scores of both 33 and 34 minimized the difference between sensitivity (95.2%) and specificity (94.4%) [27].

In summary, regarding the applicability of a diagnosis of HSDD to women who meet current DSM-IV-TR criteria for HSDD and would be categorized as moderate to marked in severity, we believe that there is compelling evidence of dysfunction and distress in these women, i.e., that the current criteria identify a significant disorder. Yet the proposed criteria for SI/AD would apparently include only those clinically assigned as having severe to extreme symptoms, and thus, many or most women with HSDD would potentially be excluded from treatment. Thus, we find it unwarranted to "raise the bar" for severity required for a diagnosis of a disorder of sexual desire that already is currently reliably diagnosed, causes significant distress, and warrants treatment.

Given that the sample was primarily in the moderate-to-marked HSDD category, with mild and severe subgroups approximately balanced (approximating a bell-shaped normal distribution), we propose that the HSDD severity criterion required for diagnosis should not be elevated, because as shown in our results, following DSM-IV-TR criteria alone was sufficient to identify a population of women whose sexual behavior was markedly impacted, and who reported significant levels of sexually related distress in association with their reduced desire.

Women with HSDD with Incomplete Loss of Receptivity

Our data show that women with DSM-IV-TR-diagnosed HSDD had significant impairment in receptivity to sex compared to women with FSAD or women with no sexual dysfunction. Their responsive desire was markedly impaired in level and in frequency. Their sexual distress scores were clearly dysfunctional, as dysfunctional as for women with FSAD and far more than in samples of sexually functional women. Also, their (lack of) receptivity was highly correlated with the severity of their HSDD, as measured by the SIDI-F total. Yet none of the women with HSDD were required by study entry requirements to lack sexual receptivity. Thus, the use of DSM-IV-TR criteria for HSDD was adequate to show clear impairment in desire and receptivity with associated sexual distress. Therefore, it seems superfluous to require

non-receptivity for a diagnosis of a manifest sexual desire disorder of sufficient severity to merit treatment.

On the other hand, the women with HSDD in these two studies did not lack receptivity completely. The e-Diary data did not show a complete absence of desire (means near zero) at the start of sexual activity; the means were slightly greater than 1 (low), i.e., 1.1 in NA and 1.3 in EU, and rose to peaks of almost 2 (moderate), i.e., 1.7 in NA and 1.9 in EU. If women were required to lack receptivity completely in order to meet a diagnostic criterion, virtually none of these women would meet the criterion: for peak desire, those means of 1.7 and 1.9, the standard deviation (SD) was 0.7. Thus, zero values would be more than two SD below the mean values, i.e., would apply to less than 8% of women with HSDD.

The DSM-V committee has recently softened its proposed requirement A(3) from no receptivity and initiations to "Absence or reduced frequency of initiation of sexual activity and is typically unresponsive to a partner's attempts to initiate." [17] This corresponds better to the data on our populations of women with HSDD, but it does not alter the fact that the requirement appears, from our data, to be superfluous and interferes with clinical treatment.

Thus, we believe that there is compelling evidence of dysfunction and distress in affected women meeting the current DSM-IV-TR criteria for HSDD, i.e., the current criteria already identify significant loss of receptivity simply by requiring loss of desire. Yet the proposed criteria for SI/AD ostensibly applicable to such patients are unlikely to allow them to be diagnosed, and thus, they are likely to be excluded from treatment. Such an omission seems to be problematic in the exclusion of significant numbers of women who currently meet criteria for HSDD. In the United States, the standard model of medical, psychological, and sexual care is fee for service. If U.S. women with distressing loss of sexual desire are not diagnosed with a sexual disorder, then insurers will not cover care, and thus, the women may not receive treatment. Care is extraordinarily expensive in the U.S. compared to other developed nations, so many women would be unable to afford to self-pay for care. Yet HSDD is chronic, and sexual incompatibility is a major source of relationship conflict. So, raising the bar to diagnosis may not only impact women, but could potentially leave many untreated and ultimately impact the partnered relationships of these women.

As we noted in our prior letter, caution should always be exercised when considering fundamental changes to medical or psychiatric nomenclatures. Any such changes should be based on confirmed data—preferably from multiple clinical trials or large observational studies. We recommend that diagnostic field trials be done, and the proposed questionnaire set for DSM-V add the modifications suggested here, because they appear relevant to provide clear-cut evidence that will be applicable to real-world patients and thus determine whether diagnostic criteria should be changed.

Our overall conclusion is that it would be most unfortunate if the American Psychiatric Association rejected the valid, reliable diagnostic entity of HSDD and adopted instead the currently proposed "SI/AD" without extensive field-testing, especially as a recent study has shown that when 95 women with sexual difficulty were recruited to test the feasibility of empirically distinguishing sexual desire and arousal, divergence between the two was indicated by correlational and principal components analyses, and it was concluded that the two disorders are differentiable on the basis of both recruitment and self-identification. Three quarters of the sample, although having a desire or arousal problem at least 75% of the time for at least 6 months and feeling it causes significant distress or interpersonal interference, could not be diagnosed by DSM-IV-TR criteria [28]. Indeed, an inescapable conclusion from the latter data is that the current criteria for sexual desire or arousal disorders are too stringent rather than too lax. We conclude from our data that it would be counterproductive to combine the two disorders, to make individual criteria for the disorders more stringent, or to require more such criteria for a diagnosis (all of which the proposed DSM-V criteria would do) because such disorders are often, and perhaps usually, distinct in presentation, in treatability with currently available therapies [29], and in logical approaches to be tested to improve therapy. We find that the proposed criteria would allow diagnosis (and therefore treatment) of only severe desire dysfunction combined with lack of arousal, and would ignore or deny treatment to women with mild, moderate, or even marked symptomatology.

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