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Permalink

<https://escholarship.org/uc/item/05x4w5kv>

Journal

Sexual medicine reviews, 10(1)

ISSN

2050-0513

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Publication Date

2022

DOI

10.1016/j.sxmr.2021.07.003

Peer reviewed

A Systematic Literature Review of Health-related Quality of Life Measures for Women with Hypoactive Sexual Desire Disorder and Female Sexual Interest/Arousal Disorder

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ABSTRACT

Introduction: Hypoactive Sexual Desire Disorder (HSDD) / Female Sexual Interest/Arousal Disorder (FSIAD) impacts health-related quality of life (HRQoL) of women and their partners, yet existing measures fail to adequately capture relevant concepts (ie, what is essential to measure including symptoms/impacts) important to women with HSDD/FSIAD.

Objectives: To identify HRQoL tools used to assess women with HSDD/FSIAD, and to evaluate their psychometric properties (ie, reliability, validity, and responsiveness).

Methods: We conducted searches in PubMed, Embase and PsychINFO from June 5, 1989 to September 30, 2020 for studies in women with HSDD/FSIAD and psychometric analyses (English only). Principles of the Preferred Reporting Items for Systematic reviews and Meta-Analyses, the CONsensus-based Standards for the selection of health Measurement INstruments Risk of Bias Checklist and other psychometric criteria were applied. Based on this search, 56 papers were evaluated including 15 randomized-controlled trials, 11 observational/single arm/open label studies, and 30 psychometric studies.

Results: Of the 18 measures identified, the Female Sexual Function Index (FSFI) and Female Sexual Distress Scale-Revised (FSDS-R) were included in most studies (> 50%). General HRQoL instruments were not used in any of the clinical trials; the SF-12, SF-36 and EQ-5D-5L were reported in two observational studies. No instruments achieved positive quality ratings across all psychometric criteria. The FSFI, FSDS-R, Sexual Event Diary (SED) and the Sexual Desire Relationship Distress Scale (SDRDS), were the only measures to receive a positive rating for content validity.

Conclusion: Reliable and valid HRQoL measures that include sexual desire and distress are needed to provide a more systematic and comprehensive assessment of HRQoL and treatment benefits in women with HSDD/FSIAD. While inferences about HRQoL are limited due to the lack of uniformity in concepts assessed and limited psychometric evaluation of these measures in women with HSDD/FSIAD, opportunities exist for the development of reliable and validated tools that comprehensively measure the most relevant and important concepts in women with HSDD/FSIAD. **Lim-Watson MZ, Hays RD, Kingsberg S, et al. A systematic literature review of health-related quality of life measures for women with Hypoactive Sexual Desire Disorder and Female Sexual Interest/Arousal Disorder. Sex Med Rev 2021;XX:XXX–XXX.**

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Key Words: Hypoactive Sexual Desire Disorder; Female Sexual Interest/Arousal Disorder; Patient-Reported Outcome; Health-Related Quality of Life; Psychometric

Received March 28, 2021. Accepted July 23, 2021.

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<https://doi.org/10.1016/j.sxmr.2021.07.003>

INTRODUCTION

Hypoactive sexual desire disorder (HSDD) is the most prevalent sexual dysfunction reported among women in the United States¹⁻⁸ and is diagnosed as an absence or deficiency of sexual fantasies and sexual desire that is associated with distress.^{7,9} HSDD affects approximately 1 in 10 premenopausal women¹ and has a prevalence higher than major depressive disorder ([MDD] 7.1%).⁹ HSDD has a neurobiological basis in the dysregulation of sex hormones and neurotransmitters⁴⁻⁷, and can result in significant psychological issues, sexual distress and impact on the mental and emotional well-being of women and their partners.^{6-8,10}

The impact of HSDD on the lives of women living with this condition has been characterized in only a few studies. Two observational studies demonstrated that women with HSDD experience substantial decrements to their physical health (eg, general health, physical functioning, bodily pain) and mental well-being (eg, social functioning, role-emotional, and mental health) as assessed by global health-related quality of life (HRQoL) measures: SF-36, SF-12 and EQ-5D-5L.^{11,12} Oberg and Fugl-Meyer found that women's sexual distress was related to low relationship satisfaction and the presence of a partner's sexual problems.¹³ Hendrickx and colleagues reported that women with not only impairment in sexual desire but also distress had lower mental well-being, were less satisfied with their relationship, had less dyadic sexual communication, had more severe impairment in sexual desire, and had more impairments in sexual functioning.¹⁴

The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) merged HSDD and female sexual arousal disorder (FSAD) into a single syndrome: female sexual interest/arousal disorder (FSIAD).¹⁵ FSIAD is defined in the DSM-5 as significantly reduced, sexual interest/arousal as manifested by any of the three of the following set characteristics for a minimum of six months:^{15,16}

1. absent/reduced interest in sexual activity;
2. absent/reduced sexual/erotic thoughts;
3. no/reduced initiation of sexual activity and unreceptive to partner's attempts to initiate;
4. absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (75-100%) sexual encounters;
5. absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (written, verbal, visual);
6. absent/reduced genital or nongenital sensations during sexual activity in almost all or all (75-100%) sexual encounters.

Several sexual health experts and medical consortiums have disagreed with the new definitions presented in the DSM-5 and the criteria required to be diagnosed with FSIAD.^{7,8,16,17}

As a result, the lack of medical consensus and the evolution of HSDD/FSIAD nomenclature and attempts made by regulatory

and medical communities to align HSDD/FSIAD to the paradigm of male sexual dysfunctions have challenged healthcare professionals in their abilities to accurately diagnose and effectively manage this condition.^{7,18,19} Furthermore, measurement developers need to accurately reflect the most relevant signs, symptoms and HRQoL impacts in women with this condition in a patient-reported outcome (PRO) tool that is reliable, validated and responsive to change¹⁹⁻²⁰; a task necessary to determine treatment benefit and long-term disease management.

The use of HRQoL instruments in clinical practice could facilitate physician-patient conversations about treatment selection, and overall disease management.^{21,22} Reliable and validated measures that are not overly burdensome and help healthcare practitioners accurately and consistently diagnose, manage, and treat women with HSDD/FSIAD represents a substantial unmet need.^{19,20}

To our knowledge, this is the first systematic literature review that specifically reports on the psychometric properties of HRQoL tools utilized to evaluate the relevant signs, symptoms and impacts in women with HSDD/FSIAD as well as the studies that utilized these measures. The objectives of this systematic literature review (SLR) were to identify HRQoL instruments most commonly used as outcome measures in studies of women with HSDD/FSIAD, and to evaluate the psychometric performance of these assessments using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement,²³ and the principles of Consensus-based Standards for the selection of health Measurement Instruments (COSMIN),²⁴ and other psychometric criteria.^{25,26}

METHODS

Systematic Literature Review (SLR) Methodology

A SLR was conducted using transparent and reproducible methods, in accordance with PRISMA.²³ A systematic search was conducted in Embase, PubMed and PsychINFO based on predefined inclusion/exclusion criteria (Table A.1. Study Eligibility Criteria) of research studies and psychometric analyses in women with HSDD/FSIAD. Two searches were performed in the same databases due to the volume of articles retrieved, and the time (> 12 months) from article screening to manuscript preparation: the first included articles published in English between June 5, 1989 and June 5, 2019, and the second search was conducted between January 1, 2018 and September 30, 2020. All selected studies were cross-checked to ensure that there were no duplicates. Search terms (Appendix A.1) included permutations of "health-related quality of life", "sexual function", "female", "hypoactive sexual desire disorder", "female sexual interest and arousal disorder". Reference lists were also searched using Google, Google Scholar and known HRQoL-based websites. This process ensured that relevant publications not identified in the searches would be included.

Table A1. Study eligibility criteria.

Category	Inclusion Criteria	Exclusion Criteria
Patient Population	<ul style="list-style-type: none"> Patients ≥ 18 years of age with a primary diagnosis of HSDD or FSIAD 	<ul style="list-style-type: none"> Pediatric populations (< 18 years of age) Surgically induced menopausal women
Intervention and Comparators	<ul style="list-style-type: none"> Nonpharmacologic (counseling, psychotherapy, sensate focus therapy, cognitive behavioral therapy) Pharmacologic (flibanserin, bremelanotide, estrogen, testosterone, bupropion, sildenafil, buspirone) Over the Counter/Homeopathic (Zestra, Alura, K-Y, Argin-Max, Avlimil, ProSensual) 	
Variables of Interest	<ul style="list-style-type: none"> Health-related quality of life including symptom burden (desire and distress) Instrument psychometrics 	
Study Design	<ul style="list-style-type: none"> Interventional studies: randomized or single-arm clinical trials Non-interventional studies <ul style="list-style-type: none"> Large-scale relevant prospective observational studies or retrospective studies Database analyses, registries PRO validation 	<ul style="list-style-type: none"> Case reports Case series (sample size < 5) Pre-clinical studies Notes/Comments/Letters Reviews/Meta-Analyses/Editorials Abstracts/Proceedings News/Newspaper articles Book chapters
Restrictions	<ul style="list-style-type: none"> English language 	<ul style="list-style-type: none"> Non-English language studies

Figure A1. PRISMA Flow Diagram.

Study Selection and Data Collection

The electronic database search yielded 10,047 records. After title and abstract screening, 5,865 articles were considered relevant for full-text review. Following full-text assessment and exclusion of non-relevant articles (ie, articles that did not include women with HSDD/FSIAD or HRQoL measures, were pre-clinical, non-English, other), 54 articles were selected for data extraction: 25 non-psychometric studies, and 29 psychometric studies (see below). The second search yielded one additional article, and another article was provided by author SK on October 20, 2020. Thus, a total of 56 publications (26 non-psychometric studies, and 30 psychometric studies) meeting all inclusion criteria were included in this study. (Fig. A1)

Five reviewers, including MLW, independently screened and assessed all publications (titles/abstracts, followed by full text) against the criteria. All publications selected for full-text review were indexed into two categories of studies, non-psychometric and psychometric studies, and retained for data extraction using Microsoft Excel (Office 365 Version). Data included study sample demographics, methodology, treatments evaluated, outcomes of HSDD and FSIAD (eg, desire and distress scores, HRQoL), development history and rationale, study population, translations, domains assessed, year of first use, reliability, validity, and responsiveness scores. Any discrepancies were resolved through mutual discussions among the reviewers as well as senior authors (SK, JDK, RDH, and IMW) who also acted as arbiters. A review protocol was developed, but the protocol was not published

because this review was not done to support a meta-analysis. Non-psychometric studies included randomized-controlled trials (RCTs), observational, retrospective, single-arm, and open-label studies where HRQoL was used to assess patient outcomes in women with HSDD/FSIAD with non-pharmacologic and pharmacologic agents. Domains and items used to evaluate improvements in HRQoL in women with HSDD/FSIAD were captured. Psychometric studies consisted of articles that reported on the psychometrics of HRQoL instruments.

Psychometric Assessment

The psychometric assessment of HRQoL measures was evaluated by one researcher and validated by a second researcher using principles from COSMIN and other criteria²⁴⁻²⁶ and guidance provided by the FDA Patient-Reported Outcome Measures Guidance for Industry.²⁷

Psychometric properties (ie, reliability, validity and responsiveness) for each HRQoL assessment were ranked as follows:²⁴⁻²⁶

- ‘± positive rating’ – all criteria and thresholds at or above acceptable values, clear descriptions of design or method;
- ‘? = indeterminate rating’ – lacking clear description of the description of the design or methods of the study, sample size smaller than 50 subjects, or any important methodological weakness in the design or execution of the study;
- ‘- = negative rating’ – despite adequate design and methods, values below acceptable thresholds; or
- ‘0 = no information available’.

RESULTS

Non-Psychometric Studies

Literature screening identified 15 RCTs reporting on pre and postmenopausal women with HSDD, FSAD, and FSIAD.²⁸⁻³⁹ Key characteristics of the identified studies are presented in Table B1. Across all RCTs reviewed, only one included desire and distress as a co-primary endpoint using the Female Sexual Function Index (FSFI)⁴³ and Female Sexual Distress Scale – Desire, Arousal, Orgasm (FSDS-DAO).^{31,37} The FSFI was utilized in 11 (73%) RCTs.^{28,31-35,37,38,40-42} The FSDS-DAO is a revision of the 13 item instrument, the Female Sexual Distress Scale–Revised (FSDS-R)⁴⁴, which was designed to evaluate various aspects of sexual distress over a 30 day recall period.^{31,37} The FSDS-DAO includes two additional questions – one concerns arousal, and one concerns orgasm.^{31,37} A publication on the psychometric evaluation of its measurement quality was not identified in the literature search. However, question 13 of the FSDS-DAO was included in the clinical trial program evaluating bremelanotide, a pharmacologic agent for the treatment of generalized, acquired HSDD in premenopausal women.^{31,37} Seven (47%) studies included either sexual satisfying events (SSEs) or number of sexual events as the primary or co-primary endpoint.^{31,32,34,38-41} One study used the Personal Experiences Questionnaire (PEQ) to assess arousal, desire, orgasm, enjoyment, and frequency of sexual relationships.²⁹ Only nine RCTs (60%) reported race, and of these studies, white, non-Hispanic women represented approximately 71-90% of the study population.^{31,32,34,35,37-41} None of the RCTs included measures evaluating impacts to HRQoL (eg, physical functioning, mental well-being, partner relationship, and life satisfaction).

A total of 11 retrospective, observational, single-arm, and open-label studies were also identified for inclusion in this literature review (Table B2).^{11,45-53} Only four (36%) of these studies^{11,12,45,49} assessed other HRQoL concepts beyond sexual functioning including: the Short-Form 36 (SF-36),⁵⁴ Short-Form 12 (SF-12),⁵⁵ Euro-Qual 5-Level (EQ-5D-5L),⁵⁶ and the Fugl-Meyer Life Satisfaction Checklist (FMLSC)⁵⁷ in pre and postmenopausal women.

Biddle and colleagues (2009) assessed health burden and HRQoL in postmenopausal women and reported substantial differences in HRQoL between women with and without HSDD on the SF-12 and EQ-5D-5L instruments.¹¹ In this study, women with HSDD reported worse health SF-12 summary and domain scores, with statistically significant differences observed for the mental health summary score ($P = .033$), bodily pain ($P = .025$), mental health ($P = .006$), vitality ($P = .004$), and social functioning ($P = .025$) scale scores.¹¹ In addition, women with HSDD reported worse EQ-5D-5L index scores than women without HSDD (0.76 vs 0.84, $P < .010$), and were more likely to report difficulties in each of the five dimensions with the pain/discomfort, anxiety and depression domains being

statistically different ($P = .017$ and $P < .001$) compared to women without HSDD.¹¹

The WISHeS (Women's International Study on Health and Sexuality) study¹² explored correlates of sexually related distress using both general HRQoL and disease-specific measures: the SF-36,⁵⁴ the Profile of Female Sexual Function (PFSF),⁵⁸ and the Personal Distress Scale (PDS)⁵⁹ to measure distress caused by low desire. Women with HSDD scored significantly worse than women without HSDD on 7 of 8 domains of the SF-36, with greater differences in mean scores on domains that measure aspects of mental health (vitality, social function, role limitations due to emotional problems, mental health, and general health perceptions) than on domains that measure physical function, role limitations due to physical health and bodily pain.¹²

A prospective, single-blind study evaluating bupropion in pre and postmenopausal women utilized not only the FSFI⁴⁴ and Relationship Questionnaire (Partnerschaftsfragebogen, PFB),⁶⁰ but also the FMLSC, which assessed general well-being of study participants.⁴⁵ The PFB consists of nine domains evaluating overall life, vocational situation, self-care ability, leisure situation, vocational situation, financial situation, sex life, partner relationship, family life and contacts with friends and acquaintances.⁶⁰ Study results demonstrated nonsignificant improvement of the sexual life domain and a significant (5% level) deterioration in the partner relationship domain as measured by the PFB in women with HSDD treated with bupropion.⁴⁵

Rosen and colleagues reported the initial results of a multicenter longitudinal registry of pre and postmenopausal women ($n = 1,574$) with HSDD.⁴⁹ Several measures were utilized to assess female sexual function (FSFI, FSDS-R, and sexual activity frequency), relationship status and satisfaction, and HRQoL (SF-36, Patient Health Questionnaire-9 [PHQ-9]).⁶⁰ Analysis of baseline data demonstrated that women had low overall sexual function scores (total FSFI score, 15.9 ± 7.1) with postmenopausal women scoring lower on the total FSFI (14.0 ± 7.5) than premenopausal women (16.7 ± 6.8).⁴⁹ Participants cited multiple factors as contributing to their HSDD including stress or fatigue, body image dissatisfaction, other sexual concerns (eg, lack of arousal, sexual pain) and dissatisfaction with the partner relationship or partner's lack of desire; menopausal women also reported menopausal symptoms as significant contributors of their HSDD. HRQoL results captured by SF-36 were not reported. The registry was supported by an investigator-initiated grant from Boehringer Ingelheim (BI) Pharmaceuticals, Inc., which was cancelled in 2010 after a negative opinion on the efficacy of flibanserin, a treatment for HSDD.⁶²

Psychometric Studies

A total of 30 articles reporting on the psychometric properties of 18 unique HRQoL measures developed for use in women with HSDD/FSIAD were identified.^{41,43,62-89} Measures ranged

Table B.1. Summary of Non-Psychometric Studies (randomized controlled trials)

Author, Year	Country	Treatment Evaluated	Population	Mean Dose per Patient (mg)	Treatment Arm Sample Size	Study Duration (Weeks)	Menopausal Status	Race / Ethnicity (%)	Primary Endpoint(s)	Instruments used to assess PROs
Akhtari et al, 2014	Iran	Tribulus terrestris	HSDD	7.5	30	56	Pre	Not Reported	Change from baseline in Desire and Total FSFI Score	FSFI
Caruso et al, 2004	Italy	Apomorphine SL	HSDD, FSAD	2.0 3.0	55	68	Pre	Not Reported	Change from baseline in PEQ (arousal, desire, orgasm, enjoyment and frequency in sexual relationships)	PEQ
Chudakov et al, 2007	Israel	TTG	HSDD	50	10	4	Pre	Not Reported	Change from baseline in Arizona Sexual Experiences Scale and Sexual Function Questionnaire	ASEX, SFQ V1
Clayton et al, 2016	USA, Canada	BMT	FSAD, HSDD or combination	0.75 1.25 1.75	100 98 98	64	Pre	White (71.0/66.0/71.0) Black (25.0/32.0/23.0) Other (4.0/2.0/5.0)	Change from baseline in Number of Satisfying Sexual Events per month	FSEP-R, FSFI, FSQS-DAO, SSEs
Derogatis et al, 2012	USA, Canada	Flibanserin	HSDD	50 100	230 199	28	Pre	White, non-Hispanic (80.3/79) White, Hispanic (8.8/6.6) Black, non-Hispanic (9.8/12.1) Black, Hispanic (0.3/0.3) Asian, non-Hispanic (0.7/1.4) Asian Hispanic (0.0/0.3) Missing (0.0/0.3)	Change from baseline in number of Satisfying Sexual Events and change from baseline in desire	FSFI, FSQS-R, PGI-I, PBE, SSEs (e-Diary)
De Souza et al, 2016	Brazil	Tribulus terrestris	HSDD	75	20	78	Post	Not Reported	Change from baseline in sexual function (desire, arousal, lubrication, satisfaction, orgasm and pain)	FSFI, QS-F
Goldfischer et al, 2011	USA, Canada	Flibanserin	HSDD	50 (qhs) 50 (bid) 100 (qhs)	901	48	Pre	White (89.8)	Change from baseline in Satisfying Sexual Events and desire	FSFI, FSQS-R, PGI-I, SSEs (e-Diary)
Katz et al, 2013	USA	Flibanserin	HSDD	100	542	24	Pre	White (73.2) White Hispanic (12.7) Black/African American (11.6) Asian (1.3) Other (1.2)	Change from baseline in desire to week 24 and number of Satisfying Sexual Events over 28 days	FSQS-R, FSFI, PGI-I, PBE
Kaviani et al, 2014	Iran	Education	HSDD	Weekly education	40	6	Pre	Not Reported	Change from baseline in desire	Hurlbert's sexual activity questionnaire
Kingsberg et al, 2019*	USA, Canada	BMT	HSDD	1.75 1.75	313 282	24	Pre	American Indian or Alaska native (0.8); Asian (1.1); Black / African American (11.6); White (85.5); Other (1.0) American Indian or Alaska native (0.8); Asian (1.1); Black / African American (11.6); White (85.5); Other (1.0)	Change from baseline in desire and distress	FSFI-D, FSQS-DAO, GAQ

(continued)

Portman et al, 2017	USA, Canada	Flibanserin	HSDD	100	376	24	Post	White (86.2) White Hispanic (4.8) Black (6.6) Other (2.4)	Change from baseline in Satisfying Sexual Events, desire, safety	FSFI, FSDD-R, PGI-I, PBE, SSEs
Rooji et al, 2013	Netherlands	T+PDE5i T+5-HT _{1A} Ra	HSDD, FSAD	0.05 + 5 0.05 + 10	26 28	26	Pre and Post	Caucasian (76.9/96.4) Black (11.5/0.0) Asian (7.7/0.0) Other (3.8/3.6)	Change in genital response, desire and number of sexual events	SARSAQ, Event diary, weekly diary, SEI, SEG
Simon et al, 2014	USA, Canada	Flibanserin	HSDD	100	468	24	Post	White (85.0) Black/African American (7.5) White Hispanic (6.0) Asian (0.9) Other (0.6)	Change from baseline in Satisfying Sexual Events over 28 days, and desire to week 24	FSDD-R, FSFI, PBE, PGI-I, SSEs
Thorp et al, 2012	USA, Canada	Flibanserin	HSDD	25 50 100	396 392 395	24	Pre	White (86.1/88.0/ 84.6) White Hispanic (4.0/4.1/6.1) Black non-Hispanic (8.3/6.9/7.3) Black Hispanic (0.3/0.0/0.0) Asian non-Hispanic (1.3/1.0/2.0)	Change from baseline in Satisfying Sexual Events and desire	SSEs (e-Diary), FSFI (e-Diary), FSDD-R, PGI-I, PBE
Vale et al, 2018	Brazil	Tribulus terrestris	HSDD	750	20	76	Pre	Not Reported	Change from baseline in sexual function (desire, arousal, lubrication, satisfaction, orgasm and pain) and testosterone levels	FSFI, QS-F

ASEX = Arizona Sexual Experiences Scale; BMT = Bremelanotide; DHEA = Dehydroepiandrosterone; FSAD = Female Sexual Arousal Disorder; FSDD-DAO = Female Sexual Distress Scale – Desire/Arousal/Orgasm; FSDD-R = Female Sexual Distress Scale-Revised; FSEP-R = Female Sexual Encounter Profile – Revised; FSFI = Female Sexual Function Index; FSFI-D = Female Sexual Function Index-Desire; GAQ = General Assessment Questionnaire; HRQoL=Health-related quality of life; HSDD = Hypoactive Sexual Desire Disorder; PBE = Patient Benefit Evaluation; PEQ = Personal Experiences Questionnaire; PGI-I = Patient Global Impression of Improvement; QS-F = Sexual Quotient Female Version; RCT = Randomized Controlled Trial; SARSAQ = Sexual Arousal Response Self-Assessment Questionnaire; SEG = Subjective Evaluation of Gain; SEI = Sexual Evaluation of Improvement; SFQ = Sexual Function Questionnaire; SSE = Satisfying Sexual Event; TTG = Transdermal Testosterone Gel; T +PDE5i = combination of testosterone (0.5mg) sublingually with cyclodextrin as carrier and sildenafil (50mg); T+5-HT_{1A}Ra = combination of testosterone (0.5mg) sublingually with cyclodextrin as carrier and buspirone (10mg); USA = United States of America.

*Integrated results of 2 identical RCTs evaluating efficacy and safety of BMT.

from 4 to 39 items, and include several sexual functioning concepts such as desire, distress, arousal (frequency, ease, continuation), interest, orgasm, lubrication, pain, sexual events, activity, satisfaction, pleasure, relationship concerns, responsiveness, self-image, affection, and initiation. Fourteen measures (78%) were developed before 2010.^{43,44,62,64,67,77-78,80,83,85,86,89} Completion time was not reported for any of the measures. A summary of instrument characteristics is presented in Table C1.

Of all the 18 HRQoL measures, none received a positive rating across all psychometric properties: validity (content validity, construct validity), reliability (internal consistency, reproducibility) and responsiveness based on pre-specified criteria.²⁴⁻²⁷ The spread of ratings among the four psychometric properties (+/-/0) for the 18 HRQoL measures was highly variable with several of the assessments (~50%) not reporting any information for a given psychometric property (ie, scoring “0” or “no information available”) (Table C2). Four studies (13%) evaluating FSFI,⁷³ FSDS-R,⁶⁸ SED (Sexual Event Diary),⁸¹ and SDRDS (Sexual Desire Relationship Distress Scale),⁷⁹ received positive ratings for content validity as clear descriptions of the target population, involvement of experts, and commonly used methods (eg, focus groups and cognitive interviews) to determine concepts most relevant and meaningful to women with HSDD/FSIAD were provided. Interestingly, of the four articles reporting on the psychometric properties of the FSFI (which has been used in 50% of non-psychometric studies) and is recommended by the FDA for inclusion in drug trials for treatments for low desire, two studies received an indeterminate rating for content validity and reliability, and 2 provided no information on these measurement properties (ie, receiving a rating of “0”).^{43,73-75}

Thirteen (43%) studies were given a positive rating for construct validity which is defined by the extent scores of an instrument are associated with other measures consistent with hypotheses about the concepts being measured.^{43,63-67,71,72,78,79,84,85,89} A positive rating for this measurement property indicates “specific hypotheses were formulated and at least 75% of the results are in accordance with these hypotheses”.²⁴⁻²⁷ Adequate internal consistency reliability (coefficient alpha $\geq$ 0.7) was found in 18 (60%) studies.^{43,62,63,66-69,71,72,74-76,78,79,82,84,87,89} Reliability was rated positive (ICC or weighted kappa $\geq$ 0.7) for 15 (50%) of the studies.^{43,62,63,67,69,71,72,76,79-82,84,87,89} Responsiveness quality, which is the ability of the measurement to detect clinically important changes over time, was assessed across all studies, and 10 (33%) studies were given a positive rating (AUC $\geq$ 0.7).^{66,67,69,72,76-78,82,87,89}

DISCUSSION

This SLR was designed to identify measures most commonly used to assess HRQoL in women with HSDD/FSIAD and to evaluate the psychometric properties of these tools using the principles of internationally accepted criteria²⁴⁻²⁶ and FDA

Guidance²⁷. Several measures examining sexual functioning were identified during the screening process but were not included due to insufficient evidence of their use in women with HSDD/FSIAD.

Of the 18 HRQoL measures for which psychometrics were reported, variable quality was identified across 30 different studies.^{41,43,62-89} Internal consistency reliability was the most commonly reported psychometric property assessed, with content validity and measurement error least commonly reported on. Content validity is considered by both COSMIN and the FDA as a critical measurement property to ensure concepts and items included in a questionnaire are relevant to a specific population,^{24,27} and under FDA guidance, “fit for purpose”.²⁷ Only four instruments scored positively in demonstrating adequate content validity.^{68,73,79,81} Furthermore, 14 instruments were developed before 2010,^{43,44,62,64,67,75-78,80,83,85,86,89} including the FSFI and FSDS which were developed almost two decades ago.^{43,67} Notably, all 18 assessments were evaluated in populations of mostly white, non-Hispanic women. Further studies are needed to evaluate the content validity of these instruments to ensure relevancy to women of today, particularly women of color.

Fifteen instruments received positive ratings for reliability, and 10 earned a positive rating for responsiveness. Despite what is described in the literature as signs, symptoms and impacts of HSDD/FSIAD, none of the instruments identified in this SLR fully account for other relevant and important concepts such as disease severity, other clinical manifestations of low desire and associated distress, mental well-being, physical functioning, and life satisfaction. The Elements of Desire Questionnaire (EDQ),^{66,90} was developed recently to specifically assess additional dimensions of desire with both monthly and daily recall. The EDQ is a positive step forward for use in future clinical trials and clinical practice but warrants further evaluation, given some of its psychometric limitations (ie, poor test-retest reliability, and the reported high rates of missing data from the daily recall version possibly impacting its reliability, construct validity and ability to detect change)^{66,90} and lack of HRQoL concepts beyond desire.

Three measures, SSE, FSFI and FSDS-R are most frequently utilized in clinical trials, possibly because of the 2016 FDA guidance on the clinical development of drug trials for low sexual interest, desire/arousal in women.^{27,91} Four clinical endpoints for inclusion into clinical development programs were recommended: satisfying sexual events (SSEs), change from baseline in level of sexual interest or desire (FSFI Q1-Q2), change from baseline in level of sexual arousal (FSFI Q3-Q6), and change from baseline in level of distress (FSDS-R Q 13).^{27,91} However, the FDA has publicly expressed concerns with the psychometric properties of the FSFI (specifically content validity),^{27,91} and sexual health experts have criticized the use of SSEs given its lack of alignment to the DSM-IV-TR definition of HSDD.^{19,20}

Table B2. Summary of Non-Psychometric Studies (Retrospective, observational, single-arm, and open-label).

Author, Year	Country	Study Type	Treatment Evaluated (mg)	Population	Total Sample	Study Duration (Weeks)	Menopausal Status	Race / Ethnicity (%)	Study Objective(s)	Instruments used to assess PROs
Biddle et al, 2009	USA	Cross-sectional survey	Not Applicable	HSDD	1,189	24	Post	White (87.0) Black (6.4) Hispanic (4.4) Other (2.3)	To describe the health-related quality of life (HRQOL) implications of hypoactive sexual desire disorder	PFSF, PDS, SF-12, EQ-SD-5L
Hartmann et al, 2012	Germany	Prospective, single blind, single arm, single center	Bupropion (150 mg)	HSDD	15	26	Pre and Post	Not Reported	Change from baseline in sexual thoughts and fantasies, desire and activity, handling of possible changes, and partner's reaction to changes	FSFI, PFB, Fugl-Meyer
Hurlbert DF, 1993	USA	Prospective, observational, single center	Orgasm consistency training	HSDD	11	24	Pre	White (72.7) Black (18.2) Hispanic (9.1)	Changes in sexual behavior	DAS, Relationship checklist, HISD, ISS, SAI, HISA
Jayne et al, 2012	USA, Canada	Open-label extension study	Flibanserin	HSDD	1,723	52	Pre	White non-Hispanic (86.6) White Hispanic (4.9) Black non-Hispanic (6.9) Black Hispanic (0.3) Asian (1.2)	To assess safety and tolerability of flibanserin	FSDS-R, FSFI, CGI-I, PBE
Leiblum et al, 2006	USA results reported only; France, Germany, Italy and UK not reported	Prospective, observational, single center study	Not applicable	HSDD	952	16	Pre and Post	White (87.7) Black (5.0) Hispanic (8.0) Other (2.0)	In post-menopausal women, the prevalence of low sexual desire, distress and association of sexual desire and female sexual response (arousal, pleasure, orgasm and frequency of sexual activity)	SF-36, PFSF, PDS
Pyke et al, 2019	USA	Phase 2, dose finding, multicenter, open-label, active-control, 1-way, crossover study	Low-dose Trazodone (TRZ) + Bupropion Moderate dose Trazodone (TRZ) + Bupropion	HSDD	30	15	Pre	White (93.3)	Efficacy of TRZ compared to BUP alone; dose relationship of lorexys (LOR)	FSFI, FSDS-R, PGI-C, ESS, Columbia Suicide Severity Rating Scale, PHQ-9
Rosen et al, 2010	USA	Prospective, observational, multicenter registry	Not applicable	HSDD	209	34	Pre and Post	White (76.0) Black (13.0) Hispanic (8.0) Asian (1.0) Other (2.0)	Patient-based global impression of change in HSDD	DSDS, FSFI, FSDS, SDDQ, PHQ-9, SF-36, SF-12, SAQ-study specific items
Simon et al, 2018	USA, Canada	Open-label extension study	Flibanserin (100mg)	HSDD	595	28	Pre and Post	White (79.3) White Hispanic (8.9) Black / African American (8.9) Black / African American Hispanic (0.2) Asian (1.2) Other (1.5)	Adverse events; change from baseline of FSDS-R total score and Q13, FSFI total score, PBE and CGI-S/E	FSDS-R, FSFI, PBE, CGI-S, CGI-E

(continued)

Simon et al, 2019*	USA, Canada	Open-label extension study	Study 301: Bremelanotide (1.75mg)	HSDDS	363	52	Pre	Race White (84.0) Black / African American (12.7) Asian (1.1) Other (1.6) Ethnicity Hispanic/Latina (9.1) Not Hispanic/Latina (90.9)	Changes in FSFI-D, FSDS-DAO and GAQ scores; safety	FSFI-D, FSDS-DAO, GAQ
			Study 302: Bremelanotide (1.75mg)	HSDD	321			Race White (89.7) Black / African American (7.8) Asian (0.9) Other (1.5) Ethnicity Hispanic/Latina (4.7) Not Hispanic/Latina (95.3)		
Van Anders et al, 2005	Canada	Prospective, single center	Testosterone (100 mg)	HSDD	37	12	Pre and Post	Not Reported	Change from baseline in sexual desire and bioavailable Testosterone	SDI
Warnock et al, 2006	USA	Prospective, observational, multi-center study	Combined Oral Contraceptives	HSDD	106	Not reported	Pre	Not Reported	Measures of free testosterone, total testosterone, and sex hormone-binding globulin (SHBG)	None used

CGI-E = Clinical Global Impression of Efficacy Index (Side Effects Component); CGI-I = Clinical Global Impression of Efficacy Index (Therapeutic Effect); CGI-S = Clinical Global Impression of Severity; DAS = Dyadic Adjustment Scale; DSDS = Decreased Sexual Desire Screener; ESS = Epworth Sleepiness Scale; EuroQoL-5D = EQ-5D-5L; FSFI = Female Sexual Function Index; FSFI-D = Female Sexual Function Index-Desire; FSDS-DAO = Female Sexual Distress Scale – Desire/Arousal/Orgasm; FSDS = Female Sexual Distress Scale; FSDS-R = Female Sexual Distress Scale – Revised; Fugl-Meyer = Fugl-Meyer Life Satisfaction Checklist; GAQ = General Assessment Questionnaire; HRQoL = Health-related quality of life; HISA = Hurlbert Index of Sexual Assertiveness; HISS = Hurlbert Index of Sexual Desire; ISS = Index of Sexual Satisfaction; PBE = Patient Benefit Index; PDS = Personal Distress Scale; PFB = Partnerschaftsfragebogen (Relationship Questionnaire); PFSF = Profile of Female Sexual Function; PGI-C = Patient Global Impression of Change; PHQ-9 = Patient-Health Questionnaire-9; SAI = Sexual Arousal Inventory; SAQ = Self-Administered Questionnaire; SDDQ = Sexual Desire and Distress Questionnaire; SDI = Sexual Disorder Inventory; SF-12 = Short-Form 12; SF-36 = Short-Form 36; UK = United Kingdom; USA = United States of America.

*Consisted of 2 identical open-label extension studies of bremelanotide (1.75mg).

Table C1. Summary of HSDD/FSIAD Instrument Characteristics Identified*.

Instrument	Acronym	Mode of Administration	Country/ Language	Purpose of Measurement	Domains	Year of Development and Validation in Women with HSDD / FSAD	Target Population	Number of Items	Scoring Method	Recall Period	Completion Time
Brief-Profile of Female Sexual Function ⁶²	B-PFSF	Self-administered	English	To diagnose HSDD in postmenopausal women	Sexual Desire, Distress, Arousal, Sexual Concerns, Orgasm	2007	Postmenopausal Women with HSDD	7	Total Score	Not Reported	Not Reported
Daily Log of Sexual Activities ⁶³	DLSA	Self-administered	English	To provide an outcome measure of the number of sexual events, the number of satisfactory sexual events, and the magnitude of sexual interest or desire	Sexual Events	2010	Postmenopausal Women with HSDD	9	Total Score	24 hours	Not Reported
Decreased Sexual Desire Screener ⁶⁴	DSDS	Self-administered and Clinician-administered	English	To diagnose HSDD	Sexual Desire, Distress	2009	Women with HSDD	5	Total Score	Not Reported	Not Reported
Elements of Desire Questionnaire ⁶⁶	EDQ	Self-administered	English	To measure attributes of desire	Sexual Desire, Intensity, Thoughts/fantasies about Sex, and Receptivity to Sexual Requests	2020	PreMenopausal Women with HSDD with and without Decreased Arousal	9	Mean Total Score	24 hours and 4 weeks	Not Reported
Female Sexual Distress Scale ⁶⁷	FSDS	Self-administered	English	To measure sexually related personal distress in women	Distress	2002	Women with Sexual Dysfunction	12	Total Score	Not Reported	Not Reported
Female Sexual Distress Scale – Revised ⁴⁴	FSDS-R	Self-administered	English	To measure sexually related personal distress in women with HSDD	Distress	2008	Women with HSDD	13	Total Score	7 and 30 days	Not Reported
Female Sexual Function Index ⁴³	FSFI	Self-administered	English, Iranian, Turkish	To assess domains of sexual functioning	Sexual Desire, Arousal, Lubrication, Orgasm, Satisfaction and Pain	2000	Women with FSAD	19	Domain Score and Total Score	4 weeks	Not Reported
HSDD Screener ⁷⁶	HSDD Screener	Self-administered and Clinician-administered	English	To diagnose with HSDD in post-menopausal women	Sexual Pleasure, Sexual Relationship	2006	Post-menopausal Women with HSDD	4	Total Score	3 months	Not Reported
Personal Distress Scale ^{77,1}	PDS	Self-administered	English	To measure personal distress in menopausal women with HSDD	Distress	2004	Post-menopausal Women with HSDD	Not Reported	Not Reported	Not Reported	Not Reported
Profile of Female Sexual Function ⁷⁸	PFSF	Self-administered	English, Dutch for the Netherlands English (Australia, UK, USA), French (Canada, France), German (Germany), Italian (Italy), Spanish German for Germany Italian for Italy Spanish (USA)	To measure sexual desire and associated symptoms in women with HSDD following menopause	Sexual desire, Arousal, Orgasm, Sexual Pleasure, Sexual Concerns, Sexual Responsiveness, Sexual Self-Image, and one item on Sexual Satisfaction	2004	Post-menopausal Women with HSDD	37	Total Score	Not Reported	Not Reported
Sexual Activity Log ^{77,1}	SAL	Self-administered	English	To record frequency of sexual activity, orgasm and satisfying sexual activity	Sexual Activity	2004	Surgically Postmenopausal Women with HSDD	Not Reported	Total Score	7 days	Not Reported

(continued)

Sexual Desire Relationship Distress Scale ⁷⁹	SDRDS	Self-administered	English	To measure sexual distress in women with HSDD	Personal Distress, Distress Related to Relationship with Partner	2012	Women with HSDD	17	Total Score	14 days	Not Reported
Sexual Event Diary ⁸⁰	SED	Self-administered	English	To assess weekly satisfactory sexual events	Sexual Events	2007	Women with HSDD	11	Total Score and Sexual Function Score	24 hours	Not Reported
Sexual Function Questionnaire ⁸³	SFQ	Self-administered	English	To assess efficacy in female sexual dysfunction (FSD) clinical trials	Desire, Arousal—sensation, Arousal—lubrication, Subjective arousal, Enjoyment, Orgasm, Pain, and Partner Relationship	2002	Women with FSAD, HSDD with associated arousal disorder, FOD with associated arousal disorder or superficial/ introital dyspareunia due solely to lack of lubrication	34	Domains Score and Total Score	4 weeks	Not Reported
Sexual Function Questionnaire-28 ⁸⁴	SFQ-28	Self-administered	English	To assess female sexual function	Desire, Arousal (sensation), Arousal (lubrication), Arousal (cognitive), Orgasm, Pain, Enjoyment, Partner	2012	Women with FSAD and HSDD	28	Domain Score and Total Score	Not Reported	Not Reported
Sexual Interest and Desire Inventory – Female ⁸⁵	SIDI-F	Clinician-administered	English	To quantify severity of symptoms in women with HSDD	Relationship-Sexual, Receptivity, Initiation, Desire-Frequency, Affection, Desire-Satisfaction, Desire Distress, Thoughts-Positive, Erotica, Arousal-Frequency, Arousal-Ease, Arousal-Continuation, Orgasm	2005	Women with HSDD	13	Total Score	1 month	Not Reported
Women's Sexual Interest Diagnostic Interview ⁹⁹	WSID	Clinician-administered	English	To diagnose women with FSDs, including HSDD	Sexual Desire, Interest, Sexual Activity, Partner Relationship	2008	Women with FSDs, including HSDD (standardized)	39	Domain Score and Total Score	6 months	Not Reported
Women's Sexual Interest Diagnostic Interview - Short Form ⁶³	WSID-SF	Self-administered	English	To diagnose postmenopausal women with HSDD	Sexual Desire, Interest, Sexual Activity	2010	Postmenopausal Women with HSDD	9	Total Score	3 months	Not Reported

FOD = Female Orgasmic Disorder; FSAD = Female Arousal Disorder; FSD = Female Sexual Dysfunction; HSDD = Hypoactive Sexual Desire Disorder; UK = United Kingdom; USA = United States of America.

*PDS First presented at the International Society for the Study of Women's Sexual Health (ISSWSH) Annual Meeting 2004, Atlanta, Georgia, USA, October 28–31; publication in 2009

†SAL First presented at the International Society for the Study of Women's Sexual Health (ISSWSH) Annual Meeting 2004, Atlanta, Georgia, USA, October 28–31; publication in 2009

‡The focus of this SLR was to identify patient-reported outcome (PRO) measures, however, two clinician-reported (ClinRO) measures were identified and are listed in this table given that ClinROs are developed based on patient interviews. The two ClinROs include: WSID and HSDD screener. The HSDD screener consists of five items: four are patient-reported, one is clinician-reported.

Table C2. Psychometric assessment of identified HSDD/FSIAD instruments

Measure	Publication	Country of Study Sample Included in Instrument Validation	Internal Consistency	Reliability	Measurement Error	Content Validity	Construct Validity	Responsiveness
Brief-Profile of Female Sexual Function (B-PFSF)	Rust J, <i>et al.</i> 2007	United Kingdom	+	+	0	0	?	0
Decreased Sexual Desire Screener (DSDS)	Clayton A, <i>et al.</i> 2009	United States, Canada	0	0	0	0	+	0
	Clayton A, <i>et al.</i> 2013	United States, Canada, Austria, Belgium, Czech Republic, France, Germany, Hungary, Italy, The Netherlands, Spain, Sweden, United Kingdom	0	0	0	0	+	0
Elements of Desire Questionnaire (EDQ)	Revicki D, <i>et al.</i> 2020	United States, Canada	+	-	+	?	+	+
Female Sexual Dysfunction Scale (FSDS)	DeRogatis L, <i>et al.</i> 2002	Not Specified	+	+	?	?	+	+
e-Diary (Distress Item) & Female Sexual Distress Scale (FSDS)	DeRogatis L, <i>et al.</i> 2011	United States	+	?	?	0	?	?
Female Sexual Dysfunction Scale – Revised (FSDS-R)	Aydin S, <i>et al.</i> 2016	Turkey	+	+	+	0	?	+
	DeRogatis L, <i>et al.</i> 2008	Not Specified	+	+	+	?	+	+
	DeRogatis L, <i>et al.</i> 2011	United States	0	0	0	+	0	0
	Nekoo EA, <i>et al.</i> 2014	Iran	+	+	+	0	+	0
	Nowosielski K, <i>et al.</i> 2013	Poland	+	+	0	0	+	+
Female Sexual Function Index (FSFI)	Revicki D, <i>et al.</i> 2011	United States	?	?	?	+	?	?
	Rosen R, <i>et al.</i> 2000	United States	+	+	?	?	+	?
	Ryding E, <i>et al.</i> 2015	Sweden	+	0	?	0	0	0
	Wiegel M, <i>et al.</i> 2005	Not Specified	+	0	0	0	?	0
HSDD Screener	Leiblum S, <i>et al.</i> 2006	United States	+	+	0	0	0	+
Profile of Female Sexual Function (PFSF)	Derogatis L, <i>et al.</i> 2004	United States, Canada	+	?	0	0	+	+
Profile of Female Sexual Function, Sexual Activity Log, and Personal Distress Scale (PFSF, SAL, and PDS)	Derogatis L, <i>et al.</i> 2009	United States, Canada, Australia	0	0	0	0	0	+
Sexual Desire Relationship Distress Scale (SDRDS)	Revicki D, <i>et al.</i> 2012	United States	+	+	0	+	+	0
Sexual Event Diary (SED)	Symonds T, <i>et al.</i> 2007	Europe, United States, Australia, Canada	0	+	0	0	0	0
	van Nes Y <i>et al.</i> 2017	The Netherlands	-	+	?	+	-	-
	van Nes Y, <i>et al.</i> 2018	The Netherlands	+	+	0	0	-	+
Sexual Function Questionnaire (SFQ)	Quirk F, <i>et al.</i> 2005	United Kingdom, United States, Australia, the Netherlands, Denmark, France, Italy	0	0	0	0	?	?
Sexual Function Questionnaire-28 (SFQ-28)	Symonds T, <i>et al.</i> 2012	United States, Germany, Spain	+	+	0	?	+	0
Sexual Interest and Desire Inventory – Female (SIDI-F)	Clayton A, <i>et al.</i> 2006	United States	?	?	0	0	?	0
	Clayton A, <i>et al.</i> 2010	United States, Canada, Austria, Belgium, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, United Kingdom	0	0	0	0	0	+
	Clayton A, <i>et al.</i> 2010	United States, Canada, Austria, Belgium, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, United Kingdom	+	+	0	0	?	0
	Sills T, <i>et al.</i> 2005	Not Specified	0	0	0	?	+	0
Women's Sexual Interest Diagnostic Interview (WSID)	DeRogatis L, <i>et al.</i> 2008	Not Specified	0	-	0	0	0	0
Women's Sexual Interest Diagnostic Interview Short-Form and Daily Log of Sexual Activities (WSID-SF and DLSA)	DeRogatis L, <i>et al.</i> 2010	United States	+	+	?	0	+	0

Psychometric properties for each instrument were ranked as '+ = positive rating' '? = indeterminate rating', '- = negative rating', and '0 = no information available'.

Interestingly, despite there being multiple assessments to evaluate sexual function in women with HSDD/FSIAD, and studies demonstrating that women with HSDD/FSIAD report more HRQoL impairment than healthy population norms^{11,12,92}, HRQoL assessments evaluating concepts beyond sexual functioning were not included in any interventional trial and are only described in two published observational studies.^{11,12} Postmenopausal women with HSDD/FSIAD have also reported significant HRQoL decrements to mental health, vitality, social function, and bodily pain on the SF-12.^{11,12} In addition, premenopausal women indicate greater overall HSDD symptom burden than postmenopausal women, stating interference in their relationship with their partner, mental and emotional well-being, and household and personal activities (identified as taking care of their partner/spouse, pursuing hobbies, exercising, and enjoying time with friends and family, and others) as the largest contributors to overall burden of HSDD/FSIAD.⁹² This overall burden was also associated with lower mental composite scores of the SF-12.⁹² Furthermore, women with HSDD/FSIAD also report missing some work due to their symptoms,⁹² furthering highlighting the breadth of disease impact.

The literature that was reviewed here provides evidence to support our hypothesis that women with HSDD/FSIAD experience significant impacts to their sexual behavior, day-to-day functioning, and HRQoL, and that their condition involves a complex interaction of biological, psychological, sociocultural and interpersonal aspects.⁹³ This review reveals that physical functioning and mental well-being are inadequately assessed in this population, despite the supportive evidence that already exists demonstrating decrements in these domains. A recent review further highlights this gap,⁹⁴ noting, for example, that sexual performance anxiety (SPA) was strongly associated with sexual dysfunction in women. Roughly 6% to 16% of women in the United States are affected by SPA,⁹⁴ yet current scales such as the Sexual Excitation and Inhibition Scales⁹⁵ and the FSDS-R⁴⁴ are limited by the paucity of items that measure this common sexual complaint. In addition, the limited representation of women of color also brings into question the validity of these instruments, with white women accounting for the vast majority of the study populations described in [Tables B1](#) and [2](#). This lack of diversity in clinical trials has been recently acknowledged by the FDA in a guidance document entitled “Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation” whereby the FDA recommended translations and inclusion of limited English-speaking participants in trials in PRO development.⁹⁶ As such, the FDA Guidance for industry on developing treatments for low desire should also be updated to reflect these recent recommendations as well as endpoints that reflect signs, symptoms and impacts that are most relevant to women with HSDD/FSIAD.

Furthermore, no single instrument received a positive rating for meeting all psychometric properties: reliability (internal

consistency, test-retest), validity (criterion, construct) and responsiveness per internationally recognized criteria²⁴⁻²⁶. All 18 instruments also failed to capture the breadth of signs, symptoms and HRQoL impacts deemed most relevant to women with HSDD/FSIAD. Tools that reliably and accurately assess burden in women, regardless of menopausal status, are important particularly when women with HSDD/FSIAD require a “biopsychosocial” approach⁹³ to their medical care. This is necessary for patients, advocates, and professional caregivers who are developing new and innovative solutions (eg, treatments, educational programs, and supportive systems) that address the real needs and issues for improving women’s sexual health and addressing the sexual health care disparities that exist in this important area of health.

The application of COSMIN²⁴ principles and other internationally recognized criteria^{25,26} is a strength of this study; however, there are limitations associated with these recommendations. First, scoring of each item in the checklist is reliant on author judgment and therefore can be subjective. Second, the checklist is extensive and establishes a “gold standard” for evaluation but could potentially be difficult to apply for individuals unfamiliar with instrument development. While this assessment provides some reassurance when using principles of COSMIN,²⁴ it is possible that another review team may score items differently. Another strength of this systematic review is the use of the PRISMA guidelines²³ that were used to conduct a broad search strategy to identify all relevant studies demonstrating use of HRQoL measures in women with HSDD/FSIAD. However, this could also be a limitation, as studies that did not include women with HSDD/FSIAD were excluded, thus resulting in potentially missed HRQoL tools and psychometric analyses which might be useful and relevant to this SLR. In addition, despite searching multiple bibliographic databases, and other bibliographies and literature sources manually, it is possible articles may have been missed that otherwise should have been included.

There are several factors at play that contribute to the challenges of assessing and managing HSDD/FSIAD. The use of HRQoL instruments in routine clinical practice could lead to an improvement in patient management and treatment selection.^{21,22} Identifying low desire and associated distress is critical to HSDD/FSIAD diagnosis and management, but patients are reluctant to disclose and discuss sexual concerns to their healthcare provider.^{7,8} To advance the conversation around HSDD/FSIAD and ensure the appropriate treatment strategy to support improvements in all facets of HRQoL, including sexual functioning, it is important that deficiencies in studies, and the instruments themselves, are addressed. Furthermore, additional items and new instruments, developed with feedback from, and evaluated, particularly in women of color, may be necessary to address the most relevant and important signs, symptoms and HRQoL impacts of HSDD/FSIAD. Ultimately, through reliable and validated measures, healthcare practitioners can enhance

how they engage with patients to establish treatment goals and support the successful resolution of disease burden experienced by women suffering from HSDD/FSIAD.

CONCLUSION

HRQoL measures are limited in both their psychometric performance, and the concepts they include to evaluate signs, symptoms, and disease impact in women with HSDD/FSIAD. Among the instruments reviewed, all included concepts of sexual functioning, yet none contained constructs (eg, physical functioning, mental well-being, and life satisfaction) that have also been identified by women with HSDD/FSIAD as relevant and important. Further research is needed to develop reliable, valid, and comprehensive HRQoL measures that can assess the broad multifactorial nature of this condition and its impact in women with HSDD/FSIAD and their partners. The findings from this SLR may help to inform future instrument development and endpoint strategies for clinical trials evaluating effective treatments for women with HSDD/FSIAD.

ACKNOWLEDGMENTS

The authors wish to thank Joanne Doucette, Yuzhi Tang, Bhargavi Mahadik, and Mihaela Musat for their assistance with search strategies, article screening and data extraction for this SLR.

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Conflict of Interest: Michelle Z. Lim-Watson: No conflict, Ron D. Hays: No conflict, Sheryl Kingsberg, PhD: member of scientific advisory board and has been a consultant for AMAG Pharmaceuticals, Inc., Astellas, Dare, Duchesnay, Ovoca, Field Trip, Palatin Technologies, Pfizer, Materna, Maddora, TherapeuticsMD, Strategic Science Technologies, and Lupin. She has stock options in Vieve, Materna and Field Trip, Joel D. Kallich: No conflict, Irene Murimi-Worstell: No conflict.

Funding: Financial support for the study was provided by the International Society for the Study of Women's Sexual Health (ISSWSH). ISSWSH was not involved in the conceptualization, conduct, analysis and reporting of this work.

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APPENDIX A.1 SEARCH TERMS

Literature Search Terms: PubMed

("Quality of Life"[Mesh] OR quality of life[tw] OR life qualit*[tw] OR HRQOL[tw] OR HRQL*[tw] OR HQL[tw] OR QOL[tw] OR QOLs[tw] OR "patient preference"[MeSH] OR patient preference*[tw] OR "patient reported outcome measures"[MESH] OR patient reported outcome*[tw] OR PROM[tw] OR PRO[tw] OR "Patient Satisfaction"[MESH] OR Patient Satisfaction[tw]) AND (sexual function[tw] OR sexual dysfunction[tw] OR sexual problem*[tw]) AND (female[tw]

OR woman[tw] OR women[tw]) OR (hypoactive sexual desire disorder[tw] OR HSDD[tw] OR "female sexual interest/arousal disorder"[tw] OR FSIAD[tw])

Literature Search Terms: Embase

(exp "quality of life"/ OR patient preference/ OR patient-reported outcome/ OR patient satisfaction/ OR (quality of life or life qualit* or HRQOL or HRQL* or HQL or QOL or QOLs or patient preference* or patient reported outcome* or PROM or PRO or Patient Satisfaction).tw.) AND (sexual function or sexual dysfunction or sexual problem*).tw. AND (female OR woman OR women).tw. OR hypoactive sexual desire disorder/

OR (hypoactive sexual desire disorder or HSDD or "female sexual interest/arousal disorder" or FSIAD).tw.

Literature Search Terms: PsychINFO

("quality of life"/ OR exp client attitudes/ OR client satisfaction/ OR (quality of life or life qualit* or HRQOL or HRQL* or HQL or QOL or QOLs or patient preference* or patient reported outcome* or PROM or PRO or Patient Satisfaction).tw.) AND (sexual function or sexual dysfunction or sexual problem*).tw. AND (female OR woman OR women).tw. OR inhibited sexual desire/ OR (hypoactive sexual desire disorder or HSDD or "female sexual interest/arousal disorder" or FSIAD).tw.