Original Investigation

Efficacy and Safety of Flibanserin for the Treatment of Hypoactive Sexual Desire Disorder in Women
A Systematic Review and Meta-analysis

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IMPORTANCE In August 2015, the US Food and Drug Administration (FDA) approved flibanserin as a treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women, despite concern about suboptimal risk-benefit trade-offs.

OBJECTIVE To conduct a systematic review and meta-analysis of randomized clinical trials assessing efficacy and safety of flibanserin for the treatment of HSDD in women.

DATA SOURCES Medical databases (among others, Embase, Medline, Psycinfo) and trial registries were searched from inception to June 17, 2015. Reference lists of retrieved studies were searched for additional publications.

STUDY SELECTION Randomized clinical trials assessing treatment effects of flibanserin in premenopausal and postmenopausal women were eligible. No age, language, or date restrictions were applied. Abstract and full-text selection was done by 2 independent reviewers.

DATA EXTRACTION AND SYNTHESIS Data were extracted by one reviewer and checked by a second reviewer. Results were pooled using 2 approaches depending on the blinding risk of bias.

MAIN OUTCOMES AND MEASURES Primary efficacy outcomes included number of satisfying sexual events (SSEs), eDiary sexual desire, and Female Sexual Function Index (FSFI) desire. Safety outcomes included, among others, 4 common adverse events (AEs): dizziness, somnolence, nausea, and fatigue.

RESULTS Five published and 3 unpublished studies including 5914 women were included. Pooled mean differences for SSE change from baseline were 0.49 (95% CI, 0.32-0.67) between 100-mg flibanserin and placebo, 1.63 (95% CI, 0.45-2.82) for eDiary desire, and 0.27 (95% CI, 0.17-0.38) for FSFI desire. The risk ratio for study discontinuation due to AEs was 2.19 (95% CI, 1.50-3.20). The risk ratio for dizziness was 4.00 (95% CI, 2.56-6.27) in flibanserin vs placebo, 3.97 (95% CI, 3.01-5.24) for somnolence, 2.35 (95% CI, 1.85-2.98) for nausea, and 1.64 (95% CI, 1.27-2.13) for fatigue. Women's mean global impression of improvement scores indicated minimal improvement to no change.

CONCLUSIONS AND RELEVANCE Treatment with flibanserin, on average, resulted in one-half additional SSE per month while statistically and clinically significantly increasing the risk of dizziness, somnolence, nausea, and fatigue. Overall, the quality of the evidence was graded as very low. Before flibanserin can be recommended in guidelines and clinical practice, future studies should include women from diverse populations, particularly women with comorbidities, medication use, and surgical menopause.

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In August 2015, the US Food and Drug Administration (FDA) approved flibanserin as a medical treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women.[1] Flibanserin, a 5-HT1A agonist, a 5-HT2A antagonist, and a very weak partial agonist on dopamine D4 receptors, increases levels of dopamine and norepinephrine and decreases serotonin in animal brain areas.[2,3] Therefore, since dopamine and norepinephrine are thought to promote and serotonin is thought to inhibit sexual desire and arousal,[3,4] it was suggested that flibanserin enhances sexual desire in HSDD.

With prevalences from 10% to 40%, HSDD is defined as "persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity"[5(p541)] accompanied by "marked distress and interpersonal difficulty"[5(p541)] that is not accounted for by a nonsexual mental disorder, medication, severe relationship stress, or a general medical condition.[5,6] With the appearance of the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition), HSDD was replaced by female sexual interest/arousal disorder, merging arousal and desire disorders.

The approval of flibanserin at the intersection of science, policy, and advocacy received considerable attention in the public domain and was accompanied by debates among health institutions and stakeholders.[7] Some observed significant benefits without safety concerns,[8] whereas others expressed concern about medicalization of women's sexuality, questioned whether benefits outweighed risks, and expressed concern about the pharmaceutical industry influencing FDA's decisions.[9]

Several narrative reviews and commentaries have been published, providing a complete or partial overview of biomedical and integrative treatment options for HSDD.[8,10-17] To our knowledge, no studies have comprehensively summarized the evidence regarding the beneficial and harmful treatment effects of flibanserin for women with HSDD. Therefore, in view of these controversies and the availability of this new prescription drug, we aimed to assess efficacy and safety of flibanserin for the treatment of HSDD in women by performing a systematic review and meta-analysis of randomized clinical trials.

Key Points

Question: What is the efficacy and safety of flibanserin for the treatment of women with hypoactive sexual desire disorder?

Findings: This systematic review and meta-analysis of 5 published and 3 unpublished clinical trials found that treatment with flibanserin resulted in one-half additional satisfying sexual event per month while statistically and clinically significantly increasing the risk of dizziness, somnolence, nausea, and fatigue.

Meaning: The clinical benefits of flibanserin are marginal, with statistically and clinically significant adverse effects.

Methods

Search Strategy and Inclusion Criteria

We conducted a systematic search of 3 trial registries and 13 electronic databases (including Embase.com, Medline [Ovid], and Psycinfo) from inception to June 17, 2015, to identify all studies assessing efficacy and safety of flibanserin for the treatment of women with HSDD. The search strategy for each database was designed by an experienced medical information specialist (eMethods 1 in the Supplement).

A stepwise selection procedure was followed (eFigure 1 in the Supplement). Eligible studies included interventional studies assessing efficacy and safety of flibanserin in women with HSDD or sexual interest/arousal disorder (eMethods 2 in the Supplement). Studies in premenopausal and postmenopausal women were eligible, given the potential off-label use in postmenopausal women.[7] Studies assessing any outcome measure were eligible; outcome measures included, among others, change from baseline in number of satisfying sexual events (SSEs), sexual desire, and distress related to desire; adverse events (AEs) leading to study discontinuation; specific AEs including dizziness, somnolence, nausea, and fatigue and serious AEs. No age, language, or date restrictions were applied.

Study Selection

Two independent researchers reviewed all abstracts and registered trials and selected potentially eligible studies. Full texts of these studies were retrieved to assess fulfilment of the selection criteria. Disagreements were resolved through consensus or consultation of a third reviewer. The references of the retrieved studies were scanned to identify additional publications that were missed by the initial search.

Data Extraction

A data collection form was prepared to extract all relevant information from the included studies. Extracted data included period of surveillance, country, funding source, participant characteristics (age, menopausal status, duration of HSDD, and other characteristics), dose regimens, and participant flow. Furthermore, baseline and end of follow-up levels of the outcomes were extracted. A second researcher checked the extracted data.

In cases of missing data, the clinicaltrials.gov website and the Advisory Committee Briefing Documents were consulted.[18] In 5 cases, we contacted authors and in all cases the owner of flibanserin, Sprout Pharmaceuticals Inc.

Quality Evaluation

The quality of the evidence per outcome was graded according to the recommendations of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group, and included consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, imprecision, and risk of publication bias.[19] The within-study risk of bias was assessed by 2 researchers independently using the Cochrane Collaboration risk of bias tool.[19]

Since the number of eligible studies was smaller than 10, assessing publication bias with funnel plots was not feasible.[19]

Efficacy and Safety Outcomes

Primary efficacy outcomes included number of SSEs per month, monthly sexual desire intensity (eDiary desire; Invivodata Inc), and Female Sexual Function Index[20] desire

domain (FSFI desire). Five efficacy outcomes were labeled as secondary: FSFI total score, Female Sexual Distress Scale-Revised Item 13 and total score,[21] Patient's Global Impression of Improvement, and Patient Benefit Evaluation.

Safety outcomes included any AEs, investigator-defined drug-related AEs, AEs leading to study discontinuation, the 4 most common AEs (dizziness, somnolence, nausea, and fatigue), and severe and serious AEs.

Statistical Methods

Heterogeneity permitting, we sought to pool the results of women using 100-mg doses of flibanserin (100 mg once daily at bedtime or 50 mg twice daily) vs women using placebo via fixed and random effects models. Heterogeneity was assessed using Cochrane χ^2 and I^2 statistics. Random effects models were used in cases of clinical heterogeneity (differences in study inclusion criteria) or statistical heterogeneity ($I^2 \geq 40\%$ or a significant test for heterogeneity). In all other cases, fixed effects models were used.

Adequately blinded studies (eMethods 3 in the Supplement) were summarized using the inverse variance weighted mean difference and 95% CI for continuous outcomes, and the risk difference or risk ratio and 95% CI for dichotomous outcomes. For inadequately blinded studies, we presented outcomes for flibanserin and placebo groups separately.[22,23]

In cases of missing data for the number in analysis or standard error (SE), for efficacy outcomes the number of study completers and the largest outcome-specific SE from the other studies were imputed, respectively; a conservative approach given its modest effect on study size, weighting, and precision estimates. For safety outcomes, the number of study starters was used, given that dropout, among other reasons, was likely to be related to AEs.

We performed 3 subgroup analyses, one in premenopausal women only, a second for the FDA-approved dose of 100 mg once daily at bedtime, and a third comparing published and unpublished studies.

In sensitivity analyses, the smallest outcome-specific SE was taken, and the numbers of study completers and study starters were replaced by each other in efficacy and safety assessments, respectively. Furthermore, to detect the influence of a single study on the overall meta-analysis, the studies were omitted 1 by 1.

All statistical data analyses were performed using Stata Statistical Software: Release 12 (StataCorp LP).

Results

Of 592 references and registered trials initially identified, 8 studies were included in the qualitative assessment, and 4 to 7 studies were included in the quantitative synthesis, depending on how many studies reported each outcome (eFigure 1 in the Supplement). Three studies were unpublished trials conducted between 2006 and 2011: Alternate Dose Study (NCT00360243), EU Study (NCT00491829), and Terminated Study (NCT01057901) (eTable 1 in the Supplement). The remaining 5 studies were published between 2011 and 2014: DeRogatis et al[24] (NCT00360529), Goldfischer et al[25] (NCT00277914), Katz et al[26] (NCT00996164), Simon et al[27] (NCT00996372), and Thorp et al[28] (NCT00360555).

General Characteristics of the Included Studies

All studies were randomized, double-blind, placebo-controlled trials performed in the United States and Canada, except for 1 study, which was performed in 13 European countries. All studies included premenopausal (6 studies) or postmenopausal women (2 studies) with generalized acquired HSDD according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) and for whom the diagnosis was ascertained by a trained clinician via a diagnostic interview (**Table 1**). No studies were found for women with sexual interest/arousal disorder. Furthermore, all women were in stable, heterosexual, monogamous relationships for at least 1 year. Most studies included a dosing regimen of 100 mg of flibanserin once daily at bedtime.

Overall, at least 7914 women were assigned to any treatment arm, and 5914 women completed the various trials. An overview of study participant flow and number of dropouts per reason is provided in eTable 2 in the Supplement.

General Characteristics of the Study Participants

Five studies reported characteristics of the study participants (eTable 3 in the Supplement). These characteristics did not differ between studies or treatment arms except for the mean (SD) age of 36.1 (6.7) years and 55.5 (5.4) years in premenopausal and postmenopausal women, respectively. Mean (SD) BMI was 26.9 (5.8), and nearly 90% of participants were white. No information was found on level of education and socioeconomic status. Study exclusion criteria specified an extensive list of diseases and medications.

Women's mean (SD) number of baseline SSEs per month was 2.5 (2.6) (eTable 4 in the Supplement). Baseline eDiary desire (scale 0-84) was 11.5 (9.3), and FSFI desire (scale 1.2-6.0) was 1.8 (0.7).

Quality Evaluation

Even though all studies were randomized clinical trials, the overall quality of the evidence for both efficacy and safety outcomes was very low (**Table 2**). The summary of the within-study risk of bias assessment can be found in eTables 5 through 7 in the Supplement.

Beneficial Treatment Effects

An overview of reported efficacy and safety outcomes is provided in **Table 3**. For all efficacy outcomes, it was feasible to pool the results except for Patient's Global Impression of Improvement (eTable 8 in the Supplement).

Given the presence of mostly unclear risk of bias in the blinding domains, we sought to pool the results of the efficacy outcomes as described in the Methods section. Pooled efficacy analyses included all available studies except Goldfischer et al[25] owing to its deviating "withdrawal" study design. The Alternate Dose Study (NCT00360243) compared a dosing regimen of 50 mg twice daily with placebo; all other included studies used the 100-mg, once-daily at bedtime dosing regimen.

Table 1. General Characteristics of the Included Randomized Clinical Trials[a]

Study	Trial No.	Surveillance Period	Study Arm, Participants Assigned/Completed[b]	Menopausal Status	Primary Efficacy Outcomes	Follow-up, wk
DeRogatis et al,[24] 2012 (US and Canada)	NCT00360529	2006-2008	100-mg F, 290/199 50-mg F, 295/230 Placebo, 295/234	Pre	SSE and eDiary desire	24
Thorp et al,[28] 2012 (US and Canada)	NCT00360555	2006-2008	100-mg F, 396/251 50-mg F, 393/259[c] 25-mg F, 396/274[c] Placebo, 399/287	Pre	SSE and eDiary desire	24
Katz et al,[26] 2013 (US)	NCT00996164	2009-2011	100-mg F, 543/408 Placebo, 547/446	Pre	SSE and FSFI desire	24
Simon et al,[27] 2014 (US)	NCT00996372	2009-2011	100-mg F, 468/365 Placebo, 481/397	Post	SSE and FSFI desire	24
Alternate Dose Study (US)	NCT00360243	2006-2008	50-mgF,NR/336[c] 50-mgF,NR/363 25-mgF,NR/337[c] Placebo,NR/349	Pre	SSE and eDiary desire	24
EU Study (Europe[d])	NCT00491829	2007-2009	100-mg F, 316/202 50-mg F, 311/216 Placebo, 318/243	Pre	SSE	24
Terminated Study[e] (US and Canada)	NCT01057901	2010-2011	100-mg F, 376/116 Placebo, 372/124	Post	SSE and FSFI desire	24
Goldfischer et al,[25] 2011 (US and Canada)	NCT00277914	2006-2007	All F, 163/132[f] Placebo, 170/146	Pre	SSE and eDiary desire	24/48[g]

Abbreviations: EU, European Union; F, flibanserin; FSFI, female sexual function index; NA, not applicable; NR, not reported; post, postmenopausal women; pre, premenopausal women; RCT, randomized clinical trial; SSE, satisfying sexual event using eDiary; US, United States.

[a] All analyses were performed by last observation carried forward; all studies were sponsored by Boehringer Ingelheim, who owned flibanserin at the time all studies were begun. Flibanserin was subsequently sold to Sprout Pharmaceuticals Inc and finally sold to Valeant Pharmaceuticals International Inc after US Food and Drug Administration approval.

[b] All doses are once daily at bedtime unless otherwise stated.

[c] These doses are twice daily.

[d] Participating European countries were Austria, Belgium, Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom.

[e] This study was terminated early by the study sponsor for commercial reasons and has no published peer-reviewed report or abstract, but results are reported at clinicaltrials.gov. The premature study termination could have resulted in inadequate power for analysis of the individual study.

[f] Data were provided only for 3 flibanserin arms combined: 100 mg once daily, 50 mg twice daily, and 50 mg once daily.

[g] 24 weeks of double-blind period was preceded by 24 weeks of open-label period.

The pooled mean difference for change in mean SSEs from baseline was 0.49 (95% CI, 0.32-0.67) between 100-mg flibanserin and placebo (**Figure 1**A). In premenopausal women only, this was 0.65 (95% CI, 0.38-0.92) (eTable 9 in the Supplement), and in studies using the FDA-approved 100-mg once-daily dose, this was 0.54 (95% CI, 0.35-0.73) (eTable 10 in the Supplement). For published studies, the mean difference for SSEs was 0.58 (95% CI, 0.37-0.80), and for unpublished studies, this was 0.31 (95% CI, 0.00-0.62) (eTable 11 in the Supplement). The mean difference for eDiary desire score mean change from baseline, which was only measured in studies with premenopausal women, was 1.63 (95% CI, 0.45-2.82) (Figure 1B). For FSFI desire, this was 0.27 (95% CI, 0.17-0.38) in all women (Figure 1C). All primary and secondary efficacy outcomes (eFigure 2 in the Supplement) showed a statistically significant difference between 100-mg flibanserin vs placebo ($P < .001$) in main analyses. An overview of the meta-analysis results for the efficacy outcomes in flibanserin and placebo groups separately can be found in eTable 12 in the Supplement.

Harmful Treatment Effects

All except 2 safety outcomes were feasible to pool, and all studies assessed the effect of 100-mg flibanserin once daily vs placebo. The risk for any AEs, which also included non-drug-related AEs such as common cold, was 1.29 (95% CI, 1.15-1.45) times higher for flibanserin than for placebo (eFigure 3A in the Supplement). Investigator-defined drug-related AEs were reported by 2 studies and ranged from 29.9% to 36.5% for flibanserin and from 12.7% to 15.8% for placebo. The risk for study discontinuation owing to AEs was 2.19 (95% CI, 1.50-3.20) times higher for flibanserin than for placebo, but this outcome was only reported in 4 studies (eFigure 3B in the Supplement).

The risk for dizziness was 4.00 (95% CI, 2.56-6.27) times higher with flibanserin than with placebo; for somnolence, 3.97 (95% CI, 3.01-5.24) times higher with flibanserin; for nausea, 2.35 (95% CI, 1.85-2.98) times higher with flibanserin; and for fatigue, 1.64 (95% CI, 1.27-2.13) times higher with flibanserin (**Figure 2**). The overall risk ratio for the 4 most common AEs was 2.86 (95% CI, 2.32-3.52). *Severe AEs*, defined as being incapacitating or causing inability to work or undertake activity, such as syncope, hypotension, injury, and severe manifestations of AEs such as somnolence and dizziness, were reported by 2 studies; in flibanserin users, the percentages were 4.2% and 6.0%, and 3.5% in controls. *Serious AEs* were defined as those resulting in death, those that were immediately life-threatening, those that required longer-lasting hospitalization, or those were deemed serious for any other reason; these included, among others, appendicitis, cholelithiasis, and concussion.[29] The absolute number of serious AEs was small, and the risk ratio did not differ between flibanserin and placebo users (1.48 [95% CI, 0.91-2.41]) (eFigure 3C in the Supplement). All safety outcomes, except serious AEs, showed a

Table 2. Summary of the Evidence Quality Grading Using GRADE[a]

Characteristic	Efficacy	Safety
Quality rating, before downgrading	High. All studies were randomized clinical trials.	High. All studies were randomized clinical trials.
Within-study risk of bias	Serious limitation. The quality was downgraded because the risk of bias of the included studies was unclear or high (eTables 5, 6, and 7 in the Supplement). Of particular concern was the shift of primary end point from eDiary desire to FSFI desire. Furthermore, dropout rates were high, and it remained unclear how many responses were used to extrapolate the SSE to a 28-day period.	Serious limitation. The quality was downgraded because the risk of bias of the included studies was unclear or high (eTable 5, 6, and 7 in the Supplement). Of particular concern was that the investigator-defined drug-related and severe AEs were provided in only 2 studies and that dropout rates were high.
Indirectness evidence	Serious limitation. Women with a wide range of diseases and medication uses were excluded from study participation. Furthermore, women were, on average, overweight, and they might represent a higher functioning group given the base rate of 2.5 SSEs per month and their willingness to engage in sexual activity at least once per month. Finally, the dropout rate was higher in the flibanserin than the placebo arm.	Serious limitation. Women with a wide range of diseases and medication uses were excluded from study participation. Furthermore, women were, on average, overweight, and they might represent a higher functioning group given the base rate of 2.5 SSEs per month and their willingness to engage in sexual activity at least once per month. Finally, the dropout rate was higher in the flibanserin than the placebo arm.
Heterogeneity	No limitation.	No limitation. Moderate heterogeneity occurred for dizziness (I^2 = 58.3%, P = .04), which could be explained by menopausal status (I^2 = 32.2%, P = .22) in premenopausal women only. Substantial heterogeneity occurred for any AEs (I^2 = 79.9%, P < .001). Indeed, any AEs consisted of a very heterogenous group of AEs, including the 4 most common AEs, but also events like upper respiratory tract infection, which could vary seasonally.
Imprecision	No limitation.	Serious limitation. Both in the individual studies and to a lesser extent in the overall effect size for particularly dizziness, somnolence, and AEs leading to study discontinuation, the confidence intervals were wide.
Publication bias	Serious limitation. Three of 8 studies were results from unpublished trials, of which the primary completion year ranged from 2008 to 2011.	Serious limitation. Three of 8 studies were results from unpublished trials, of which the primary completion year ranged from 2008 to 2011.
Final judgement	Very low quality	Very low quality

Abbreviations: AEs, adverse events; FSFI, Female Sexual Function Index; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SSE, satisfying sexual event.

[a] The GRADE Working Group grades of evidence are as follows: 1, high quality, further research is very unlikely to change the group's confidence in the estimate of effect; 2, moderate quality, further research is likely to have an important impact on the group's confidence in the estimate of effect and may change the estimate; 3, low quality, further research is very likely to have an important effect on the group's confidence in the estimate of effect and is likely to change the estimate; 4, very low quality, the group is very uncertain about the estimate.

statistically significant difference between 100-mg flibanserin vs placebo (P < .001) in main analyses.

None of the studies was found to be too influential on the overall effect size when omitted 1 by 1. The direction, size, and significance of the associations remained the same in the sensitivity analyses performed based on the assumptions made regarding the imputation process detailed in the Methods section (eTable 13 in the Supplement).

Discussion

This systematic review and meta-analysis summarizes 5 published and 3 unpublished studies investigating efficacy and safety of flibanserin for the treatment of HSDD in nearly 6000 women. Treatment with flibanserin, on average, resulted in one-half an additional SSE per month while statistically and clinically significantly increasing the risk of dizziness, somnolence, nausea, and fatigue. Overall, the quality of the evidence was graded as very low for efficacy and safety outcomes, particularly due to limitations in design, indirectness of evidence, and more favorable efficacy outcomes in published compared with unpublished studies.

To our knowledge, this is the first systematic review and meta-analysis addressing the impact of flibanserin treatment in women with HSDD. The most important question concerns the clinical relevance of the statistically significant efficacy outcomes,[30] particularly considering AEs that could worsen with concurrent alcohol intake or CYP3A4 inhibitors, including oral contraceptives and fluconazole.[7,31] Clinical significance was evaluated by assessing the magnitude of effect sizes and by patient-reported minimum relevant difference and self-perceived meaningful benefit.[30,32]

The data presented in this review suggest that the meaningful change caused by flibanserin is minimal. First, for the range of 0.5-1.0 increase in SSEs reported by the FDA,[33] frequently referenced by scientific articles and mass media, the difference in SSEs change per month in our review was at the lower end of this range in main, subgroup, and sensitivity analyses (eTables 9 through 11 and eTable 13 in the Supplement). Second, the perceived minimum important difference for the SSE eDiary in postmenopausal women ranged from 0.16-1.84 per

Table 3. Overview of Flibanserin[a] Efficacy and Safety Outcomes

Characteristic	DeRogatis et al,[24] 2012	Thorp et al,[28] 2012	Katz et al,[26] 2013	Simon et al,[27] 2014	Alternate Dose Study[b] (NCT00360243)	EU Study (NCT00491829)	Terminated Study[c] (NCT01057901)	Goldfischer et al,[25] 2011[d]
Efficacy, Difference in Mean (95% CI) Changes From Baseline for Flibanserin Compared With Placebo[e]								
SSE	0.80 (0.20 to 1.40)	0.80 (0.09 to 1.51)	1.00 (0.44 to 1.56)	0.40 (0.12 to 0.68)	0 (−0.62 to 0.62)	0.60 (0.02 to 1.18)	0.30 (−0.17 to 0.77)	0.90 (0.08 to 1.72)
eDiary desire	2.20 (−0.45 to 4.85)	1.70 (−0.51 to 3.91)	NA	NA	0.20 (−2.29 to 2.69)	2.30 (0.09 to 4.51)	NA	3.30 (0.24 to 6.36)
FSFI desire	0.40 (0.13 to 0.67)	0.30 (0.03 to 0.57)	0.30 (0.03 to 0.57)	0.30 (0.03 to 0.57)	0.20 (−0.07 to 0.47)	0.20 (−0.07 to 0.47)	0.20 (−0.07 to 0.47)	0.30 (0.03 to 0.57)
Safety Outcomes, Flibanserin/Placebo, %								
Any AEs	66.6/59.3	69.4/58.8	62.2/50.5	63.4/51.7	NA	81.3/50.0	33.0/21.1	32.5/32.4
Investigator defined drug-related AEs	NR	NR	36.5/15.8	29.9/12.7	NR	NR	NR	NR
AEs leading to study discontinuation	11.4/3.4	15.7/10.8	9.6/3.7	8.1/3.5	NA	NR	NR	1.2/2.4
Dizziness	9.0/1.7	12.2/2.0	10.3/1.1	9.9/3.1	NA	14.6/4.4	6.4/3.5	0.6/2.9
Somnolence	11.0/3.1	11.9/3.5	14.4/3.5	8.8/1.5	NA	5.1/0.9	6.9/2.2	NR
Nausea	11.4/4.1	11.9/4.0	7.6/2.2	7.5/3.5	NA	12.3/6.0	5.3/4.1	1.2/3.5
Fatigue	6.2/2.7	9.6/6.8	5.7/3.3	NR	NA	17.1/10.4	NR	0.6/1.8
Severe AEs	NR	NR	4.2/3.5	6.0/3.5	NR	NR	NR	0.6/3.5
Serious AEs	1.0/0.0	NR	0.7/0.4	1.7/0.8	NA	6.0/5.0	1.6/1.1	0.6/0.6

Abbreviations: AEs, adverse events; EU, European Union; FSFI, Female Sexual Function Index; NA, not applicable (measure was not listed as predefined outcome); NR, not reported (measure was listed as predefined outcome, but not reported); SSE, satisfying sexual event.

[a] Unless otherwise indicated, flibanserin was administered in a single 100-mg dose at bedtime.

[b] This study used flibanserin, 50 mg, twice daily.

[c] This study was terminated early by the study sponsor for commercial reasons and has no published peer-reviewed report or abstract, but results are reported at clinicaltrials.gov. The premature study termination could have resulted in inadequate power for analysis of the individual study.

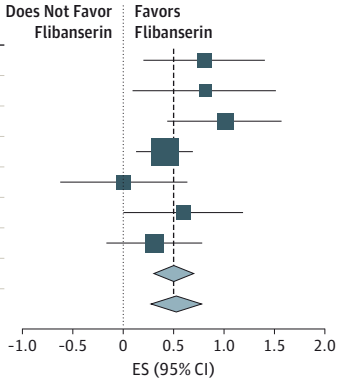
[d] This study started with a 24-week open-label period, after which only women who showed a predefined improvement were randomized to a 24-week double-blind period. Data were provided only for 3 flibanserin dose arms combined: 100 mg once daily, 50 mg twice daily, and 50 mg once daily.

[e] Scales of efficacy outcomes: SSE, number per 4 weeks; eDiary desire, score per 4 weeks (scale, 0-84); and FSFI desire, score per 4 weeks (scale, 1.2-6.0).

Figure 1. Mean Differences in 3 Measures of Sexual Desire, 100-mg Flibanserin vs Placebo

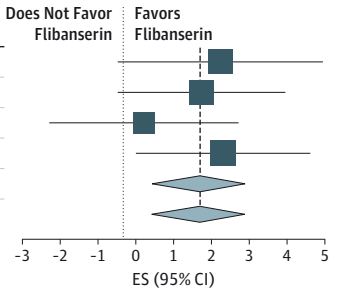
A Monthly SSEs

Study	Menopausal Status	No. of Patients		ES (95% CI)	P Value	Weight (I-V), %
		Intervention	Control			
DeRogatis et al,[24] 2012	1	199	234	0.80 (0.20 to 1.40)	.002	8.96
Thorp et al,[28] 2012	1	251	287	0.80 (0.09 to 1.51)	.008	6.40
Katz et al,[26] 2013	1	506	525	1.00 (0.44 to 1.56)	<.001	10.35
Simon et al,[27] 2014	0	429	462	0.40 (0.12 to 0.68)	.004	41.60
Alternate Dose Study (NCT00360243)	1	291	325	0.00 (-0.62 to 0.62)	.25	8.41
EU Study (NCT00491829)	1	299	307	0.60 (0.02 to 1.18)	.14	9.58
Terminated Study (NCT01057901)	0	346	335	0.30 (-0.17 to 0.77)	NR	14.71
Fixed effects model overall (I^2 = 30.4%; P = .20)				0.49 (0.32 to 0.67)		100.00
Random effects model overall				0.52 (0.29 to 0.75)		



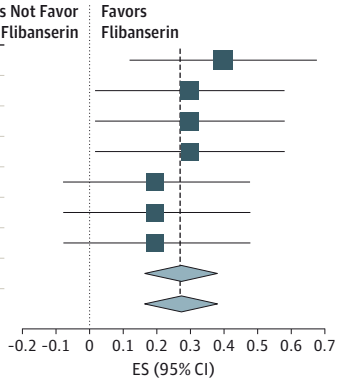
B eDiary desire

Study	Menopausal Status	No. of Patients		ES (95% CI)	P Value	Weight (I-V), %
		Intervention	Control			
DeRogatis et al,[24] 2012	1	199	234	2.20 (-0.45 to 4.85)	.07	20.06
Thorp et al,[28] 2012	1	251	287	1.70 (-0.51 to 3.91)	.11	28.63
Alternate Dose Study (NCT00360243)	1	291	325	0.20 (-2.29 to 2.69)	.86	22.67
EU Study (NCT00491829)	1	299	307	2.30 (0.09 to 4.51)	.02	28.63
Fixed effects model overall (I^2 = 0.0%; P = .62)				1.63 (0.45 to 2.82)		100.00
Random effects model overall				1.63 (0.45 to 2.82)		



C FSFI desire

Study	Menopausal Status	No. of Patients		ES (95% CI)	P Value	Weight (I-V), %
		Intervention	Control			
DeRogatis et al,[24] 2012	1	199	234	0.40 (0.13 to 0.67)	<.001	14.29
Thorp et al,[28] 2012	1	251	287	0.30 (0.03 to 0.57)	<.001	14.29
Katz et al,[26] 2013	1	506	525	0.30 (0.03 to 0.57)	<.001	14.29
Simon et al,[27] 2014	0	432	463	0.30 (0.03 to 0.57)	<.001	14.29
Alternate Dose Study (NCT00360243)	1	315	335	0.20 (-0.07 to 0.47)	.04	14.29
EU Study (NCT00491829)	1	308	313	0.20 (-0.07 to 0.47)	.08	14.29
Terminated Study (NCT01057901)	0	351	343	0.20 (-0.07 to 0.47)	NR	14.29
Fixed effects model overall (I^2 = 0.0%; P = .94)				0.27 (0.17 to 0.38)		100.00
Random effects model overall				0.27 (0.17 to 0.38)		



A, Monthly number of sexually satisfying events (SSEs). B, eDiary desire (scale, 0-84). C, Female Sexual Function Index (FSFI) desire (scale, 1.2-6.0).[20] Menopausal status, 1 indicates premenopause; 0, postmenopause. ES indicates effect size; I-V, inverse-variance; NR, not reported.

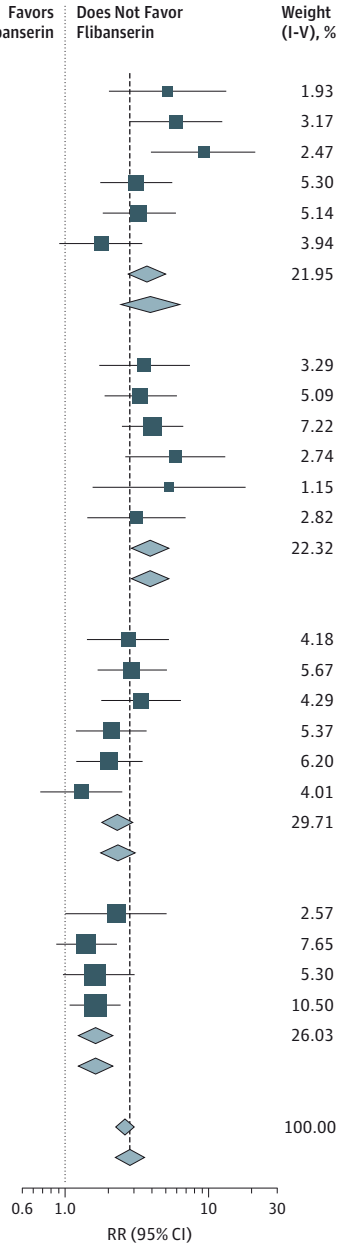
month.[34] Hence, the mean difference for change in SSE per month in this study was also at the lower end of this spectrum (Figure 1A). Patient Benefit Evaluation and Patient's Global Impression of Improvement measured overall subjectively experienced improvement. The difference in experienced meaningful benefit between flibanserin users and controls was small, ranging from minimal improvement to no change (eTable 8 and eFigure 2D in the Supplement).

The most common reported AEs were of mild and moderate intensity, and serious AEs were equally low in flibanserin and placebo users. This reflects positively on flibanserin' s safety, but the conclusion that flibanserin is safe is premature. Investigator-defined drug-related AEs and severe AEs were underreported (2 studies each). Severe AEs included, among others, syncope and hypotension. Both can occur with flibanserin use alone but are amplified with concurrent alcohol use and were labeled by the FDA as serious safety concerns.[33] In an open-label extension study including 1723 women with a median follow-up of 1 year, 723 participants (43%) reported investigator-defined drug-related AEs, and 143 (8.3%) reported severe AEs.[35] The continued safety (and efficacy) of flibanserin with long-term use remains to be established.

The strengths and limitations of our work merit careful consideration. The systematic search for eligible studies in numerous medical databases, trial registries, and reference lists

Figure 2. Risk Ratios (RRs) for the 4 Most Common Adverse Events, for 100-mg Flibanserin vs Placebo

Study	Menopausal Status	Intervention Group Adverse Events	Intervention Group Participants	Control Group Adverse Events	Control Group Participants	RR (95% CI)	Weight (I-V), %
Dizziness							
DeRogatis et al,[24] 2012	1	26	290	5	295	5.29 (2.06-13.59)	1.93
Thorp et al,[28] 2012	1	48	395	8	398	6.05 (2.90-12.61)	3.17
Katz et al,[26] 2013	1	56	542	6	545	9.38 (4.08-21.60)	2.47
Simon et al,[27] 2014	0	46	467	15	480	3.15 (1.78-5.57)	5.30
EU Study (NCT00491829)	1	46	316	14	318	3.31 (1.86-5.89)	5.14
Terminated Study (NCT01057901)	0	24	376	13	369	1.81 (0.94-3.50)	3.94
Fixed effects model overall (I^2 = 58.3%; P = .04)						3.75 (2.84-4.96)	21.95
Random effects model overall						4.00 (2.56-6.27)	
Somnolence							
DeRogatis et al,[24] 2012	1	32	290	9	295	3.62 (1.76-7.44)	3.29
Thorp et al,[28] 2012	1	47	395	14	398	3.38 (1.89-6.04)	5.09
Katz et al,[26] 2013	1	78	542	19	545	4.13 (2.54-6.72)	7.22
Simon et al,[27] 2014	0	41	467	7	480	6.02 (2.73-13.28)	2.74
EU Study (NCT00491829)	1	16	316	3	318	5.37 (1.58-18.24)	1.15
Terminated Study (NCT01057901)	0	26	376	8	369	3.19 (1.46-6.95)	2.82
Fixed effects model overall (I^2 = 0.0%; P = .85)						3.97 (3.01-5.24)	22.32
Random effects model overall						3.97 (3.01-5.24)	
Nausea							
DeRogatis et al,[24] 2012	1	33	290	12	295	2.80 (1.47-5.31)	4.18
Thorp et al,[28] 2012	1	47	395	16	398	2.96 (1.71-5.13)	5.67
Katz et al,[26] 2013	1	41	542	12	545	3.44 (1.83-6.46)	4.29
Simon et al,[27] 2014	0	35	467	17	480	2.12 (1.20-3.72)	5.37
EU Study (NCT00491829)	1	39	316	19	318	2.07 (1.22-3.49)	6.20
Terminated Study (NCT01057901)	0	20	376	15	369	1.31 (0.68-2.52)	4.01
Fixed effects model overall (I^2 = 13.6%; P = .33)						2.35 (1.85-2.98)	29.71
Random effects model overall						2.35 (1.81-3.04)	
Fatigue							
DeRogatis et al,[24] 2012	1	18	290	8	295	2.29 (1.01-5.18)	2.57
Thorp et al,[28] 2012	1	38	395	27	398	1.42 (0.88-2.28)	7.65
Katz et al,[26] 2013	1	31	542	18	545	1.73 (0.98-3.06)	5.30
EU Study (NCT00491829)	1	54	316	33	318	1.65 (1.10-2.47)	10.50
Fixed effects model overall (I^2 = 0.0%; P = .79)						1.64 (1.27-2.13)	26.03
Random effects model overall						1.64 (1.27-2.13)	
Heterogeneity between groups, P < .001							
Fixed effects model overall (I^2 = 57.3%; P < .001)						2.67 (2.34-3.04)	100.00
Random effects model overall						2.86 (2.32-3.52)	



Menopausal status, 1 indicates premenopause; 0, postmenopause. I-V indicates inverse-variance.

using broad search terms, and the inclusion of published and unpublished work, allowed us to provide a comprehensive overview of the evidence for the efficacy and safety of flibanserin for the treatment of women with HSDD. The inclusion of studies focusing on postmenopausal women took into account the potential off-label use. Furthermore, the extensive quality evaluation may facilitate the discussion of not only efficacy and safety of flibanserin, but also of reliability of the evidence put forward by the studies included in this review.

A limitation was the fact that the studies were light on details. This affected the accuracy of the quality evaluation (many within-study risk of bias domains remained with unclear risk) and the completeness of the meta-analyses (some outcomes were not feasible to meta-analyze and some meta-analyses did not include all studies). Therefore, some caution is required when interpreting the results of these assessments. The most important lacking data included blinding ascertainment, number in analyses, and completeness (effect and precision estimate) of every outcome. Contacting study investigators and study sponsor did not generate additional information. Therefore, given the unclear risk of bias for blinding, results were pooled via 2 different approaches and yielded comparable find-

ings with each, which generates confidence with regard to the reliability of the findings. Also, missing values were imputed to limit introduction of bias and proved robust in sensitivity analyses.

As women with a wide range of medication uses, diseases (including psychological comorbidities), and women not in a stable, communicative, heterosexual relationship were excluded from participation, the generalizability of the findings may be limited.[36] Because overall, study participants were overweight, results may not be generalizable to women in other BMI categories. In addition, it is unclear to what extent they represent typical women with HSDD, given that they had a baseline of 2.5 SSEs per month and had to be willing to engage in sexual activity once a month to be eligible to participate. Because the actual base rate of SSEs in women with HSDD is unknown, it is possible that the included women represent a higher functioning group, and conclusions may not be valid for all women with HSDD.[22]

Conclusions

With nearly 90% of American physicians indicating that they would prescribe an approved HSDD pharmacological product over available nonpharmacological treatments,[37] the need for sound evidence on the efficacy and safety profile of flibanserin is evident. The findings of this review suggest that the benefits of flibanserin treatment are marginal, particularly when taking into account the concurrent occurrence of AEs. It has been suggested that women with HSDD would benefit most from an integrative approach, including, medical, psychiatric, psychological, couple-relationship, and sociocultural domains: the biopsychosocial model.[11,17] Before flibanserin can be recommended in guidelines and clinical practice, future studies should include women from diverse populations, particularly women with (a history of) somatic and psychological comorbidities, medication use, and surgical menopause.

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Study concept and design: Jaspers, Feys, Leusink, Laan.
Acquisition, analysis, or interpretation of data: Jaspers, Feys, Bramer, Franco, Laan.
Drafting of the manuscript: Jaspers, Franco, Leusink.
Critical revision of the manuscript for important intellectual content: Jaspers, Feys, Bramer, Franco, Leusink, Laan.
Statistical analysis: Jaspers, Feys.
Administrative, technical, or material support: Bramer.
Study supervision: Feys, Franco, Leusink, Laan.

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