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REVIEW ARTICLE

Systematic Review and Meta-analysis of Flibanserin's Effects and Adverse Events in Women with Hypoactive Sexual Desire Disorder

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Abstract: The efficacy and safety of flibanserin in the treatment of Hypoactive Sexual Desire Disorder (HSDD) is controversial. We reviewed existing evidence on the efficacy and safety of flibanserin in treating HSDD, and performed a meta-analysis of reported effects. Literature search was performed on PubMed, Scopus, and Cochrane library to find all trials on the efficacy of flibanserin in HSDD. Meta-analysis was performed using fixed- and random-effects models. Egger's test and "trim and fill" methods were used for the assessment of publication bias and imputation of potentially missing studies, respectively. Among 105 studies that were initially found, only ten related documents (six published and four non-published studies) were included in the final analysis, comprising 8345 subjects (6113 and 2232 subjects in the flibanserin and placebo groups, respectively). Incomplete outcome data bias was probable in the included studies. Most studies had an acceptable validity and quality. There was no significant difference between flibanserin and placebo groups in most of the HSDD-assessed indices. Our results showed that although SSE, DSDS, FSFID and FSFI are significantly improved with flibanserin, this change did not reach statistical significance compared with placebo. For FSDSR-item 13 score and FSDSR total score, no significant difference was observed between flibanserin and placebo. The most common side effect of flibanserin was somnolence. The most common causes of heterogeneity were black ethnicity, duration of therapy, age of participants and duration of marital relationship. In conclusion, the efficacy of flibanserin in women with HSDD was not found to be significantly different compared with placebo. Additional trials are required to clarify the efficacy of flibanserin for the treatment of HSDD.

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INTRODUCTION

Flibanserin is a 5-HT1A receptor agonist and 5-HT2A receptor antagonist that was first introduced as an antidepressant drug [1]. Few previous studies showed that flibanserin, as a non-hormonal drug, can be effective in treating Hypoactive Sexual Desire Disorder (HSDD). HSDD, as defined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, is a persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty [2]. HSDD is the most commonly reported type of sexual dysfunction in women [3]. According to a population-based survey conducted in 2006, about 1 in 10 women reported low sexual desire with associated distress, which may be considered as HSDD [4].

Several large clinical trials were conducted in the US, Canada and Europe to assess the effect of flibanserin on HSDD [5, 6]. Satisfying sexual events (SSE), eDiary sexual desire score (DSDS), FSFI desire domain score (FSFID), Female Sexual Function Index total score (FSFI), Female Sexual Distress Scale Revised (FSDSR) item 13 score and FSDSR total score are indicators of HSDD and frequently used in clinical trials [5, 7-11].

As mentioned, several studies have evaluated the efficacy of flibanserin in HSDD [8, 9, 11-14]. However, many of these studies failed to show a statistically significant improvement on the primary endpoints of sexual desire. Although according to some of the earlier studies, flibanserin is safe and effective in improving several indicators of HSDD such as SSE and FSFI, the efficacy of this drug in improving some dimensions of sexual dysfunction, particularly eDiary desire score, is still unknown and more evidence is needed to verify its efficacy and safety [15]. Recently, two systematic review and meta-analysis studies with controversial results have been published on this topic [16, 17]. One systematic review conducted by Zhenli Gao *et al.* in 2015 assessed the results of four published randomized clinical trials including 3414 patients, and concluded that flibanserin is an effective and safe treatment for women with HSDD [16]. Another systematic review was performed by Loes Jaspers and colleagues, and assessed the results of 5 published and 3 unpublished studies including 5914 patients. This latter study

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concluded that the existing evidence is not sufficient and could not support the efficacy and safety of flibanserin, particularly due to significant risk of some major adverse effects such as dizziness, somnolence, nausea and fatigue [17].

Given the results of previous systematic reviews, there is no firm evidence supporting the efficacy and safety of flibanserin. Since few studies were assessed in previous systematic reviews (5 studies were assessed by Zhenli Gao *et al.* and 4 studies by Loes Jaspers *et al.*), and on the other hand, recent systematic reviews did not provide the same results, we decided to conduct a new systematic review, considering all existing information using comprehensive search in different databases, in order to provide additional evidence to illustrate more aspects of the safety and efficacy of flibanserin. The main objective of the present study was to assess the efficacy and safety of flibanserin in the treatment of women with HSDD.

METHODS

Search and Study Selection

In this systematic review, different combinations of keywords "flibanserin" and "hypoactive sexual desire" were searched on PubMed, Scopus and Cochrane library by November 23, 2014. We did not have any limitation for language, age or any other variable. Studies were judged to be eligible for selection if they had a controlled or single-arm design and conducted in women with hypoactive sexual desire, without considering age range or menopause status as inclusion criteria. There was no necessity for having a placebo arm.

Our primary outcomes were different indices of flibanserin efficacy including SSEs across 28 days, DSDS, FSFI, FSFID, FSDS-R item 13 score and FSDS-R total score, while the secondary outcomes were number of adverse events and causes of study withdrawal.

Variables

SSE is considered when a woman reported that a recorded sexual event was satisfying for her [8]. Sexual desire is assessed via the eDiary item "indicate the most intense level of sexual desire in the last 24 hours," with responses scored on a four-point scale of 0 (no desire), 1 (low desire), 2 (moderate desire), and 3 (strong desire) [8]. FSFI desire domain score and total score, and sexual distress and distress because of low desire were assessed using the FSDS-R total score and item 13 score, respectively. The FSFI is a self-administered questionnaire designed to assess key dimensions of female sexual function. It consists of 19 questions scored from 0 or 1 to 5 and includes six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI desire domain comprises two questions on sexual desire or interest: one on the frequency and one on the level. Both questions are rated from 1 to 5, and the weighted domain score ranges from 1.2 to 6 [8]. The FSDS-R is a 13-item self-administered questionnaire. Its 13 items are rated from 0 (never) to 4 (always); thus the total score ranges from 0 to 52, with lower scores indicating less distress. Item 13 of the FSDS-R specifically assesses distress because of low sexual desire [8].

In this meta-analysis, we also considered all causes of withdrawing the trials or any adverse effects mentioned in the included studies.

Data Collection Process

Two independent reviewers (MH and AK) evaluated all papers according to their titles/abstract and full texts in two separate phases (Fig. **1**). Related data of all selected papers were extracted based on a designed form. Collected data were demographic characteristics, study design specifications, participants, intervention characteristics, results and adverse events of the treatment.

Selected studies were assessed for their quality using CONSORT checklist. Quality scores between 40-70% of total possible score was considered moderate. Scores lower and higher than this range were considered as low and high, respectively. Risk of bias was also evaluated for all selected papers in terms of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting according to the Cochrane standard form.

Data Synthesis

Mean differences of all mentioned scores and indices were calculated as the primary outcome measure. Meta-analysis was done on these mean differences. Prevalence rates of zero were also analyzed using Bartlett's adjustment, 1/4n. We used this adjustment because we could not include zero in the analyses and excluding them disproportionately eliminates studies with the lowest proportions, which will bias our meta-analysis.

Data Analysis

We used fixed- and random-effects models based on the absence or presence of heterogeneity, respectively. Heterogeneity was assessed using Cochrane Q test and I^2 index. Egger's test was used for evaluating the presence of publication bias. Trim and fill method was used to overcome the publication bias. Meta-regression was used to find the most important independent factors in evaluating female sexual desire while omitting the confounding effect of other variables. Meta-regression was also used to find the most important sources of heterogeneity among studies. For meta-analysis of proportions (e.g. complications), we used a variance stabilizer (here arcsine transformation) because percentage of complications (proportions) were low and were dependent only on sample size and not the size of the proportion. We used sin (arcsine) to back-transform the values to the main proportion. Metaprop was used for the meta-analysis of side effects and causes of discontinuing the studies. Metainf was also used to evaluate the effect of omission of each single study on the outcomes. P-value of all statistical tests was considered significant at 0.05 except for the Cochrane Q, meta-regression and Egger's tests which were set to less than 0.1. All statistical tests were performed using the Stata 11.0 software (STATA Corp. LP).

RESULTS

Study Selection

From published papers 91 studies we initially found during database (except clinicaltrial.gov) search, and after deleting duplicates, 61 papers remained. After removing non-relevant papers, six related published papers (one with one treatment arm, 3 with two arms, one with three arms and one with four arms) were found to be eligible and included in our final analysis [8-11, 13, 14].

From Grey literature: searching clinicaltrials.gov with the search term "flibanserin" showed 14 studies which were all performed in women with HSDD. Eight of the studies had results. Among them, there were three studies which their full-texts were published and included in our search and remained as an eligible paper for data extraction. Five studies (from the abovementioned eight ones) [18-22] were not published. One of them was without any result [19]. Three other studies were single-arm [18, 23, 24] and one of them was a controlled trial which had some results about the efficacy or adverse effects of flibanserin [21]. We added these four unpublished studies to our meta-analysis as well. Their proposal and limited results about primary outcome and main side effects were extracted.

Finally, data of ten studies were extracted. There were six randomized controlled trials (RCTs) and four non-RCT studies among these ten studies. We considered all trials irrespective of their designs (RCT or non-RCT) because of our interest to do subgroup

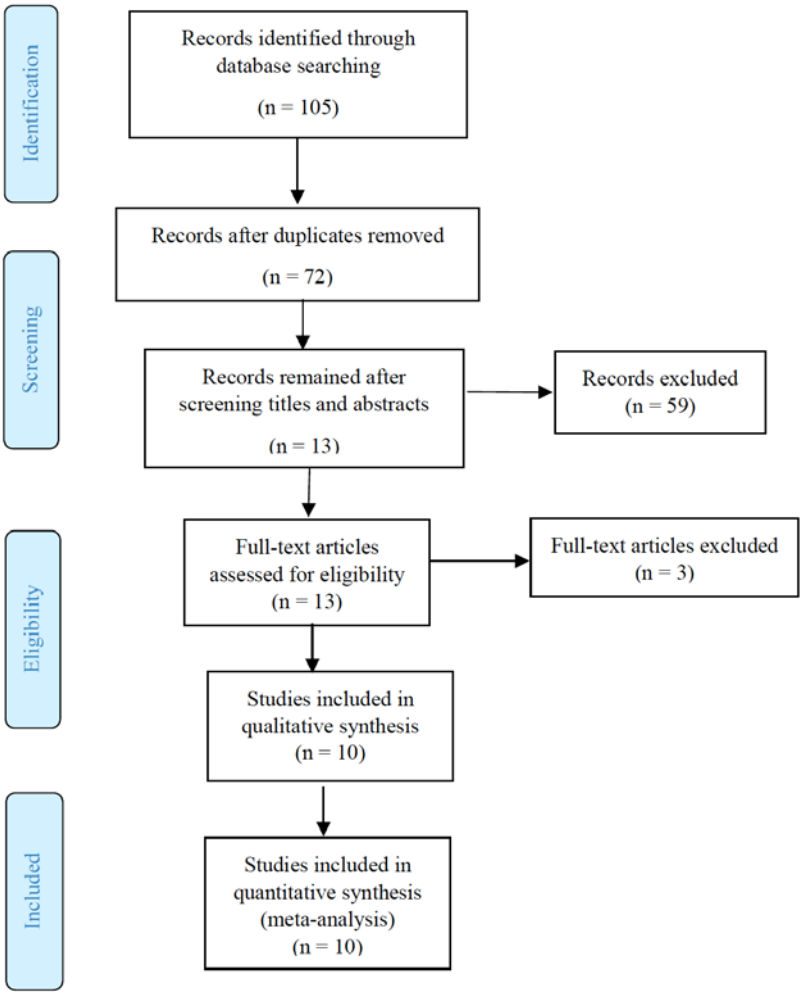

Fig. (1). Number of searched studies, related documents and studies which included in analysis of the effect of flibanserin on female with hypoactive sexual desire disorder.

analysis based on the type of study and evaluating the effect of design of study on the results.

Study Characteristics

Overall, 8345 cases from ten studies were evaluated. Of whom, 6113 patients were under treatment with flibanserin and 2232 cases received placebo. Table **1** shows important characteristics of all selected papers. Because of missing data in various variables, different numbers of studies were included in different analyses. Only one study had a quality lower than 70% (it was 68%). Hence, all studies had an acceptable quality. All six indices (SSE, DSDS, FSFID, FSFI, FSDSR-items 13, and FSDSR-total) had significant ($P<0.001$) heterogeneity with $I^2 > 95\%$ in all cases.

Risk of Bias Within Published Studies

Figure **2** shows details of risk of bias of published studies. Only the study by Jayne *et al.* had no reliable information among included studies in meta-analysis [9]. As Fig. (**2**) shows, some biases were more probable such as incomplete outcome data. Blinding of outcome assessment was unclear in all of the studies. Most studies had an acceptable validity (low risk of bias). It shows relatively high quality of these studies in most aspects. Moreover, omission of each single study, particularly that of Jayne *et al.* (which had the highest risk of bias and differed in design with other studies included in this meta-analysis) using metainf, did not show any significant change in any outcome. Therefore, we can rely on the pooled estimate of these studies and the generalizability of these studies seems logical.

Results of Individual Studies

SSE showed a significant change in different follow-up times because its 95% CI did not cover zero. However, this difference was not different from placebo. Placebo has no significant effect with respect to its effect on SSE. Effect of flibanserin on SSE increased from 4 to 8 weeks but after that, it reached to a plateau. A completely similar pattern was also observed for DSDS, FSFID and FSFI. Increase in each of the SSE, DSDS, FSFID and FSFI indices shows that flibanserin is effective.

Negative scores about FSDSR (item-13 or total) showed improvement. Hence, according to FSDSR, an improvement in HSDD cases was found which was not significant because the confidence intervals covered zero. Although this difference increased with follow-up duration, it was not significantly different from placebo (Table **2**). In all cases of Table **2**, there was a significant ($P<0.001$) heterogeneity amounting to >90% according to the I^2 index. The most common causes of discontinuing the studies were adverse events, withdrawal of consent and loss to follow-up in eleven, four and four percent of cases, respectively. These discontinuation rates were related to higher dosages and longer duration as well (Table **3**).

The most common side effects were somnolence for all dosages of the drug. Interestingly, in the placebo group, headache was the most common side effect. Table **4** shows the most common side effects according to different dosages.

Table 1. Basic characteristics of the studies included in this meta-analysis.

Author, (Reference)	Year	Group	Sample size	SSE mean, SD	DSDS mean, SD	FSFID mean, SD	FSFI mean, SD	FSDSR-items 13 mean, SD	FSDSR-total mean, SD
Goldfischer ER, (10)	2011	F, 100 mg/d, 24 weeks	163	6.9±5.9	34.2±16.2	3.6±1.1	28.8±4.9	1.8±1.2	15.2±10.4
Goldfischer ER, (10)	2011	P, 24 weeks	170	7.2±5.9	35.5±16.6	3.6±1.1	28.6±4.8	1.9±1.1	17.1±11.3
Jayne C, (11)	2012	F, 25 or 50 mg/d, 52 weeks	1723	-	-	2±0.9	20.1±7.6	3±0.9	27.5±11.2
Katz M, (12)	2013	F, 100 mg/d, 24 weeks	542	2.5±2.5	-	1.9±0.7	19±6	3.4±0.7	32.8±9
Katz M, (12)	2013	P, 24 weeks	545	2.7±2.9	-	1.9±0.7	19±6.1	3.4±0.7	32.5±8.7
Thorp J, (13)	2012	F, 100 mg/d, 24 weeks	395	2.6±2.9	12±9.8	1.8±0.7	19.1±6	3.3±0.7	30.6±9.3
Thorp J, (13)	2012	F, 50 mg twice daily, 24 weeks	392	2.9±2.7	11.8±9.5	1.8±0.7	19.8±6.4	3.3±0.8	31.6±8.9
Thorp J, (13)	2012	F, 25 mg twice daily, 24 weeks	396	3±2.7	11.4±9.1	1.8±0.6	19.8±6.3	3.2±0.8	30.3±10.1
Thorp J, (13)	2012	P, 24 weeks	398	2.7±2.8	10.2±8.8	1.8±0.7	19.5±6.3	3.2±0.8	30.2±9.9
DeRogatis LR, (9)	2012	F, 100 mg/d, 24 weeks	290	3±2.8	12.9±10.5	1.9±0.7	19.5±6.6	3.2±0.9	30.7±10
DeRogatis LR, (9)	2012	F, 50 mg/d, 24 weeks	295	2.7±2.6	11±8.9	1.8±0.7	18.7±6.5	3.2±0.8	30.8±9.6
DeRogatis LR, (9)	2012	P, 24 weeks	295	2.7±2.8	11.8±9.6	1.9±0.7	19.8±7	3.2±0.8	30.1±9.9
Simon JA, (16)	2014	F, 100 mg/d, 24 weeks	468	2±2	-	1.8±0.7	15.9±6.6	3.3±0.8	30.5±9.3
Simon JA, (16)	2014	P, 24 weeks	481	2±2.4	-	1.8±0.7	15.9±6.4	3.3±0.7	31.2±9.1
Sprout Pharmaceuticals, (17)	2010	F, 100 mg/d, 1.1 weeks	22	-	-	-	-	-	-
Barbour K, (19)	2010	F, 100 mg/d, 28 weeks	596	-	-	-	-	-	-
Sprout Pharmaceuticals, (20)	2010	F, 100 mg/d, 24 weeks	351	0	-	0	-	-	-
Sprout Pharmaceuticals, (20)	2010	P, 24 weeks	343	0	-	0	-	-	-
Barbour K, (21)	2008	F, 50 mg/d, 28 weeks	480	-	-	-	-	-	-

DSDS: eDiary sexual desire score, FSFI: Female Sexual Function Index total score, F: Flibanserin, FSFID: FSFI desire domain score (FSFID), FSDSR: Female Sexual Distress Scale Revised, P: Placebo, SSE: satisfying sexual events

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Simon JA, 2014[10]	+	+	+	?	-	+
DeRogatis LR, 2012[13]	+	+	+	?	-	+
Thorp J, 2012[11]	+	+	+	?	-	+
Katz M, 2013[14]	+	+	+	?	-	+
Jayne C, 2012[9]	-	-	-	?	-	+
Goldfischer ER, 2011[8]	?	?	+	?	-	+

+ : Low probability of bias

- : High probability of bias

? : Unclear

Fig. (2). Risk of bias in all six published studies included in meta-analysis.

Table 2. Efficacy of flibanserin in comparison with placebo at different follow-up durations.*

Outcomes		4th weeks, No. of studies	8th weeks, No. of studies	12th weeks, No. of studies	16th weeks, No. of studies	20th weeks, No. of studies	24th weeks, No. of studies
SSE	F	0.91 (0.51, 1.31), 6	1.27 (0.77, 1.77), 5	1.23 (0.71, 1.76), 5	1.28 (0.72, 1.83), 5	1.20 (0.63, 1.78), 5	1.24 (0.65, 1.83), 5
	P	0.44 (-0.12, 0.99), 6	0.44 (-0.49, 1.37), 5	0.51 (-0.23, 1.26), 5	0.45 (-0.43, 1.32), 5	0.41 (-0.38, 1.20), 5	0.35 (-0.55, 1.25), 5
DSDS	F	4.25 (1.58, 6.92), 3	5.91 (1.96, 9.85), 3	6.15 (2.32, 9.99), 3	6.19 (2.86, 9.52), 3	6.20 (2.86, 9.55), 3	6.35 (2.96, 9.74), 3
	P	1.65 (-3.40, 6.69), 3	1.70 (-6.30, 9.69), 3	1.82 (-6.31, 9.94), 3	1.51 (-7.28, 10.31), 3	1.65 (-7.54, 10.84), 3	1.91 (-7.22, 11.05), 3
FSFID	F	0.53 (0.34, 0.72), 6	0.65 (0.35, 0.95), 5	0.64 (0.29, 0.98), 5	0.66 (0.33, 0.99), 5	0.66 (0.33, 0.98), 5	0.68 (0.34, 1.01), 5
	P	0.28 (0.01, 0.56), 6	0.32 (-0.14, 0.78), 5	0.28 (-0.20, 0.76), 5	0.26 (-0.27, 0.79), 5	0.25 (-0.27, 0.77), 5	0.28 (-0.26, 0.82), 5
FSFI	F	2.25 (0.61, 3.90), 6	2.53 (0.32, 4.75), 6	3.51 (2.34, 4.67), 5	2.62 (0.19, 5.05), 6	3.57 (2.33, 4.76), 5	3.57 (2.39, 4.74), 5
	P	1.65 (-0.21, 3.51), 5	1.67 (-0.61, 3.94), 5	1.60(-0.47, 3.68),5	1.63 (-0.79, 4.04), 5	1.54 (-0.65, 3.74), 5	1.46 (-0.67, 3.59), 5
FSDSR-items 13	F	-1.00 (-2.32, 0.32), 5	-0.52 (-0.75, -0.30), 5	-0.55 (-0.81, -0.22), 5	-0.60 (-0.84, -0.36), 5	-0.61 (-0.86, -0.37), 5	-0.47 (-1.02, 0.09), 5
	P	-0.24 (-0.46, -0.02), 5	-0.30 (-0.60, -0.00), 5	-0.32 (-0.63, -0.01), 5	-0.32 (-0.68, 0.04), 5	-0.35 (-0.72, -0.03), 5	-0.36 (-0.79, 0.07), 5
FSDSR-total	F	-3.19 (-5.48, -0.91), 6	-4.32 (-7.67, -0.97), 6	-5.71 (-7.95, -3.47), 5	-4.84 (-8.82, -0.86), 6	-6.40 (-8.43, -4.37), 5	-6.61 (-8.67, -4.56), 5
	P	-2.41 (-4.95, 0.13), 5	-3.03 (-6.63, 0.57), 5	-3.42 (-6.51, 0.03), 5	-3.35 (-6.48, -0.23), 5	-3.45 (-6.80, -0.10), 5	-3.63 (-7.21, -0.06), 5

*: All variables are mean differences from baseline, values are expressed as mean difference (95% confidence interval)
DSDS: eDiary sexual desire score, FSFI: Female Sexual Function Index total score, F: Flibanserin, FSFID: FSFI desire domain score (FSFID), FSDSR: Female Sexual Distress Scale Revised, P: Placebo, SSE: satisfying sexual events

Table 3. Prevalence of women discontinuing flibanserin treatment according to different dosages irrespective of duration or type of administration (dividing dosing or once daily dosing).

Cause of discontinuing the studies	Prevalence (95% confidence interval)			
	100 mg/d	50 mg/d	25 or 50 mg/d	Placebo
Adverse events	0.11 (0.06, 0.15)	0.08 (0.06, 0.10)	0.1 (0.09, 0.12)	0.05 (0.03, 0.07)
withdrew consent	0.04 (0.02, 0.07)	0.07 (0.02, 0.12)	0.07 (0.06, 0.09)	0.04 (0.02, 0.07)
Lost to follow-up	0.04 (0.03, 0.06)	0.04 (0.03, 0.06)	0.07 (0.05, 0.08)	0.04 (0.02, 0.05)
Due to lack of efficacy	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.12 (0.10, 0.14)	0.02 (0.01, 0.03)
Due to non-compliance	0.02 (0.02, 0.03)	0.02 (0, 0.05)	0.04 (0.03, 0.05)	0.02 (0.01, 0.03)
Due to other reasons	0.03 (0.02, 0.05)	0.03 (0.02, 0.04)	0.04 (0.03, 0.05)	0.03 (0.01, 0.04)

Table 4. Prevalence of different side effects in studies of administering flibanserin according to different dosages irrespective of duration or type of administration (dividing dosing or once daily dosing).

Side effects	Percentage (95% confidence interval)			
	100 mg/d	50 mg/d	25 or 50 mg/d	Placebo
Any adverse events	0.61 (0.53, 0.70)	0.63 (0.59, 0.66)	0.74 (0.72, 0.76)	0.51 (0.43, 0.58)
Serious adverse events	0.010 (0.004, 0.016)	-	0.012 (0.007, 0.017)	0.005 (0.001, 0.009)
Severe adverse events	0.05 (0.04, 0.06)	-	0.08 (0.07, 0.1)	0.04 (0.02, 0.05)
Somnolence	0.12 (0.10, 0.15)	0.08 (0.06, 0.10)	0.16 (0.14, 0.18)	0.03 (0.02, 0.04)
Fatigue	0.07 (0.03, 0.12)	0.05 (0.02, 0.07)	0.08 (0.06, 0.09)	0.04 (0.02, 0.05)
Nasopharyngitis	0.05 (0.03, 0.06)	0.07 (0.03, 0.10)	0.07 (0.06, 0.09)	0.05 (0, 0.10)
Upper respiratory tract infection	0.05 (0.04, 0.06)	0.07 (0.05, 0.08)	0.07 (0.06, 0.08)	0.04 (0.02, 0.06)
Dizziness	0.09 (0.04, 0.14)	0.05 (0.04, 0.07)	0.07 (0.06, 0.08)	0.02 (0.01, 0.02)
Headache	0.07 (0.04, 0.10)	0.07 (0.05, 0.09)	0.07 (0.05, 0.08)	0.06 (0.03, 0.09)
Nausea	0.08 (0.04, 0.12)	0.06 (0.04, 0.08)	0.06 (0.05, 0.08)	0.03 (0.02, 0.04)
Sinusitis	0.06 (0.03, 0.09)	0.02 (0.01, 0.04)	0.046 (0.037, 0.054)	0.03 (0.01, 0.05)

Publication Bias

For evaluation of the publication bias, we checked clinicaltrials.gov for any unpublished data. Results of unpublished studies were compared with published ones for evaluating publication bias considering only flibanserin arm of studies. It was possible to test this hypothesis only for two variables: SSE and FSFID at the 4th week of treatment. Published studies showed 0.7 (0.31, 1.08) while non-published studies showed 0.83 (0.60, 1.07) improvement in SSE. These values were 0.42 (0.21, 0.63) and 0.50 (0.30, 0.70) for FSFID at the 4th week, respectively. Therefore, it appears that there is no significant publication bias between the results of published and non-published studies.

The result of the Egger's test did not show any publication bias in SSE as our main outcome. However, there were significant publication biases in the analyses of DSDS, FSFID, FSFI, FSDSR-item 13, and FSDSR-total scores in most follow-ups. Correcting this bias with metatrim command showed no significant change in 95% CI of these indices; albeit it changed the effect sizes minimally in some examples (Data not shown).

Additional Analyses

Subgroup Analysis

Effect of 50 mg daily dose of flibanserin was better than 100 mg daily in improving SSE, DSDS, FSFID, and FSFI in all follow-up durations from 4 to 24 weeks. The effect on FSDSR-total was similar to the abovementioned pattern except for the week 8. FSDSR-item 13 in all follow-ups and FSDSR-total only in the 8th week of follow-up had more improvement with 100 mg than 50 mg dose. Placebo was less effective compared with either 50 or 100 mg daily dosage of flibanserin in all follow-ups and for all outcomes. None of these differences were statistically significant.

Higher weekly dosage of flibanserin was slightly less effective in improving SSE, DSDS, FSFID and FSFI in all follow-ups and FSDSR-total at the 4th and 24th weeks of follow-up in comparison with lower dosages. On the contrary, FSDSR-item 13 during all follow ups and FSDSR-total score at the 8th, 12th, 16th, and 20th weeks of follow-up had better improvement with higher weekly dosage of flibanserin apart from some follow-ups with similar effect. Again, these differences were not statistically significant.

There were limited data about duration of using flibanserin, showing FSFI, FSDSR-item 13 and FSDSR-total score have significantly better improvements at the 24th week versus 52nd week of treatment.

Type of analysis was only significantly better for the effect on DSDS when using intention-to-treat analysis in comparison with per-protocol analysis. SSE, FSFID, FSFI and FSDSR-total in all follow-ups, and FSDSR-item 13 in all follow ups except the 4th week had better improvement with intention-to-treat analysis in comparison with per protocol analysis.

Studies with RCT design showed significantly better improvement in FSFI at weeks 4, 8, 16, and 24, FSDSR-item 13 at week 24, and FSDSR-total at weeks 4, 8, and 16 of flibanserin treatment compared with non-RCT studies. There were not sufficient studies to compare other indices between RCT and non-RCT studies.

Meta-Regression

We assessed the role of each potential source of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting), percentage of different ethnicities (white, white Hispanic, black, and others), population size, mean age, mean duration (year) of present marital relationship, mean duration (year) of history of HSDD, and duration (week) of treatment with flibanserin on the effect size. Among the, random sequence generation, allocation concealment, blinding of participants and personnel, black/white/white Hispanic ethnicity, sample size, duration of therapy, age of participants, and duration of present marital relationship were the main sources of heterogeneity in univariate analysis of meta-regression.

In multivariable meta-regression, black ethnicity, duration of therapy were the main sources of heterogeneity for all outcomes except FSDSR-item 13 which age of participants and duration of present marital relationship were main sources of heterogeneity of the outcome.

Because of absence of extreme value or a study causing more than 50% of the overall Q, there was not any need to repeat the analyses without outliers.

DISCUSSION

In this systematic review, we evaluated all existing evidence (published and unpublished), comprising 6 RCTs and 4 non-RCT studies, on the effects of flibanserin in the treatment of HSDD in women. Our results showed that flibanserin increases each of the 4 main indices including SSE, DSDS, FSFID, and FSFI; however, scores of FSDSR (item-13 or total) as another index did not show a statistically significant change with flibanserin treatment. In spite of increases in SSE, DSDS, FSFID and FSFI in the flibanserin group, these increases were not statistically significant compared with placebo. For FSDSR-item 13 score and FSDSR total score, we did not find statistically significant differences neither in the flibanserin nor in the placebo group.

The results showed that the most important causes of discontinuing the studies were adverse events, consent withdrawal and loss to follow-up. Moreover, among all side effects reported in the flibanserin group, somnolence for all dosages of the drug was the most frequent one. In one of the past systematic reviews, it was concluded that the efficacy of flibanserin despite the one-half additional SSE per month is still questionable because of the increasing risk of dizziness, somnolence, nausea and fatigue [17].

In subgroup analysis, we noticed that lower daily dosage (50 vs. 100 mg), and shorter duration of therapy (24 vs. 52 weeks) have better results despite what clinicians may believe. This finding may be due to the increased rate of adverse events that is a main problem when considering flibanserin's efficacy and safety [25].

In multivariable meta-regression, black ethnicity, duration of therapy, age of participants and duration of the present marital relationship were found to be the main sources of heterogeneity for all outcomes. With respect to publication bias, published and unpublished studies were compared. Such a comparison is the main concept of publication bias which is not usually possible due to unavailability of the results of unpublished studies. Here, although publication bias was present, it did not change the results significantly.

According to the obtained results in the present analysis, overall sexual function, desire and satisfaction were improved significantly with flibanserin, though this difference was not significantly different from placebo. Hence, there is not strong evidence to support the use of flibanserin in the treatment of HSDD. This drug has been recently approved by the FDA, but in letters wrote to the FDA Reproductive Health Advisory Committee, two reasons were mentioned by researchers for not approving flibanserin: 1) the questionable condition this drug is being considered for, and 2) what is known publicly thus far about the drug's effects [26]. In addition, if we rely on the results of recent systematic reviews, we do not reach a definite conclusion for using this drug. In one systematic review, Gao *et al*. indicated that flibanserin is an effective and safe treatment for HSDD in women while a relatively small number of patients were analyzed (n=3414). In addition, lack of assessing drug's safety was a potential limitations for the mentioned meta-analysis. In the second systematic review done by Jaspers *et al*., more patients were included compared with the study by Gao *et al*., and it was indicated that the quality of evidence is low and risk of adverse effects with flibanserin is the most important barrier against flibanserin's use. The results of our systematic review and meta-analysis in 8345 patients confirmed the results of Jaspers' study and showed that a definite conclusion about the efficacy and safety of flibanserin cannot be drawn because of adverse events and lack of significant differences in investigated indicators (SSI, DSDS, FSFID, and FSFI) between treatment and placebo groups.

Besides efficacy, the safety of flibanserin treatment needs to be taken into accurate consideration owing to the reported adverse events [12, 27]. According to the present results, somnolence was the main adverse event. In one of the previous systematic reviews, several adverse events such as dizziness, somnolence, nausea and fatigue were reported as most important challenges for the safety of flibanserin. Considering the results of all RCT and non-RCT studies, adverse effects were one of the most common causes of discontinuing the studies.

In conclusion, the present results showed that there is no statistically significant difference between flibanserin and placebo in terms of improving HSDD in premenopausal women. Nevertheless, more studies are still required to allow a larger size analysis and a more definite conclusion on the efficacy and safety of flibanserin.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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