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# Is 100mg Flibanserin Effective in Increasing the Number of Sexually Satisfying Events (SSE) in Women with Hypoactive Sexual Desire Disorder (HSDD)?

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# Is 100mg Flibanserin effective in increasing the number of sexually satisfying events (SSE) in women with Hypoactive Sexual Desire Disorder (HSDD)?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not 100mg Flibanserin is effective in increasing the number of sexually satisfying events in women with HSDD.

STUDY DESIGN: Review of three, placebo-controlled trials in which women ≥ 18 years old with HSDD were treated with either 100mg Flibanserin or a Placebo once daily qhs for 24 weeks

DATA SOURCES: Three randomized, placebo-controlled trials found via PubMed searches and published in English peer-reviewed journals between 2011-2014

OUTCOMES MEASURED: Outcomes measured were the number of SSE over 4 weeks and analyzed with Wilcoxon's rank-sum test.

RESULTS: In DeRogatis et al, 100mg Flibanserin led to increases in the mean (standard error) SSE 1.6 (0.23) vs 0.80 (0.20) and was proven to be statistically significant ($p<0.01$). AEs led to 6.8% of 100mg Flibanserin subjects vs. 3.4% of Placebo subjects to discontinue the study medication. In Katz et al, 100mg Flibanserin led to increases in the mean (standard deviation) SSE of 2.5(4.6) vs 1.5(4.5) with a p value $<0.001$. AEs led to 9.76% of Flibanserin subjects vs. 3.47% of subjects on Placebo to discontinue study medications. In Simon et al, 100mg Flibanserin led to increases in in the mean (standard error) SSE 1.0 (0.1) vs. 0.6 (0.1) and was statistically significant with $p=0.004$. 8.1% of Flibanserin subjects discontinued study medication due to AEs while on 3.1% of Placebo subjects.

CONCLUSIONS: Based on this review, 100mg Flibanserin taken once daily qhs is effective and well tolerated in treating those with HSDD in both pre- and postmenopausal women. The mean number of SSE was statistically significant vs. placebo in all three studies.

KEYWORDS: Flibanserin, Hypoactive Sexual Desire Disorder, Women

INTRODUCTION

Hypoactive Sexual Desire Disorder (HSDD) can be clinically characterized as a lack of sexual fantasies or desire for sexual activity that leads to marked distress and interpersonal relationship difficulties.[1] Women with HSDD have described feeling less physically and emotionally satisfied in a relationship as well as generally less happy.[1] This paper evaluates three randomized, double blind, placebo controlled studies that determined if 100mg Flibanserin was effective at increasing the number of sexually satisfying events (SSE) in women with HSDD.

It is estimated that nearly 10% of all premenopausal women aged 18-55 years old suffer from a sexual dysfunction disorder.[1,2] Women with HSDD are often underreported due to the difficult nature of diagnosing HSDD and the need to exclude other medical conditions or psychosocial history.[1,2] The exact cause of HSDD is unknown but it is thought that both biological and psychosocial factors play a role. Biologically, it is thought that there is an imbalance between the excitatory and inhibitory neurotransmitters thus decreased amounts of dopamine and norepinephrine and an increased amount of serotonin, which normally has an inhibitory effect of sexual functioning.[1]

HSDD is relevant to both patients and the PA practice in that it can impact women's quality of life, the amount of money spent on healthcare costs and the number of healthcare visits each year due to the disorder. Because of its multifactorial etiology, women suffering from HSDD generally need more outpatient visits, radiological services, laboratory work and prescription medications to determine its cause.[3] Though the exact number of healthcare visits and cost each year due to HSDD is unknown, one study estimated that women with HSDD spent 16.8% more on healthcare when compared to women without the disorder.[3]

Treatment of HSDD includes looking for underlying etiological causes such as depression or a psychiatric disorder, an arousal disorder, an orgasm disorder, cancer, uncontrolled hypertension or a side effect from a medication.[4] Treatment options vary for different etiological causes but generally include seeing a psychotherapist or a sex therapist.[4] Uncontrolled hypertension can easily be treated with medication and lifestyle changes while side effects due to a medication can be treated by discontinuing a medication and/or switching to a different type of medication. Psychotherapy or a sex therapist can help relieve psychological symptoms in patients with HSDD but oral Flibanserin is the first FDA approved medication shown to effectively increase the number of SSE in women suffering from HSDD.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not 100mg Flibanserin is effective in increasing the number of sexually satisfying events in women with HSDD.

METHODS

All three studies used in this review required a population of adult females over the age of 18 years old who had been diagnosed with generalized HSDD. The intervention was the implementation of 100mg Flibanserin tablets once daily at bedtime. Comparisons were made between those taking 100mg Flibanserin tablets and those taking a placebo pill once daily before bedtime. The outcomes measured were the change in the number of sexually satisfying events that women reported. All three studies were randomized control trials, double blind and placebo controlled studies that compared 100mg Flibanserin PO qhs to Placebo PO qhs.

Keywords used when searching for articles included Flibanserin, Hypoactive Sexual Desire Disorder, and women. All three articles were published in English in peer-reviewed

journals. Articles were obtained through searching keywords in PubMed and were selected based on the relevance to the clinical question, being a randomized controlled trial and determining if the outcomes mattered to patients. Inclusion criteria for the articles included women over the age of 18 with generalized HSDD $\geq$ 24 weeks, a stable, communicative, monogamous and heterosexual relationships for $\geq$ 1 year with a sexually functional partner who was able to be present > 50% of every month and women who were willing to engage in sexual activity at least once per month. The three chosen articles had extensive exclusion criteria but the articles generally excluded those with a Major Depressive Disorder in the past 6 months, any history of a suicide attempt, those with other sexual dysfunction or gynecological disorders that could interfere with the study, a history of substance abuse in the past year or taking medications that could interfere with sexual dysfunction or cause a drug interaction while taking Flibanserin. Additional exclusion criteria includes see a psychotherapist in the past year, history of cancer in the past 10 years, a women who is pregnant or breastfeeding or a partner with HSDD. The statistics that were utilized and reported in all three studies were mean changes from baseline and p-values. Table 1 displays the demographics and characteristics of the included studies.

Table 1: Demographics of Characteristics of included studies

| Study | Type | # Pts | Age | Inclusion | Exclusion | w/d | Intervention |
|---|---|---|---|---|---|---|---|
| Derogatis (2011) | Double Blind, Placebo Controlled RCT | 880 | Premenopausal over 18 years old | Premenopausal women >18 years of age w/ HSDD ≥ 24 weeks in a stable monogamous heterosexual relationship >1 year and is willing to engage in sexual activity at least once a month | Other sexual dysfunctions or gynecological disorders, MDD in the last 6 months or hx of suicide attempt. Substance abuse in the past year or taking medications that could interfere with sexual dysfunction. Seeing a psychotherapist in past year. Hx of cancer in the past 10 years, Pregnant or breastfeeding women or a partner w/ HSDD | 217 | 50mg or 100mg Flibanserin qhs |
| Katz (2013) | Double Blind, Placebo Controlled RCT | 1090 | Premenopausal over 18 years old | Premenopausal women >18 years of age w/ HSDD ≥ 24 weeks in a stable monogamous heterosexual relationship >1 year and is willing to engage in sexual activity at least once a month activity at least once a month | Other sexual dysfunctions or gynecological disorders, MDD in the last 6 months or hx of suicide attempt. Substance abuse in the past year or taking medications that could interfere with sexual dysfunction. Seeing a psychotherapist in past year. Hx of cancer in the past 10 years, Pregnant or breastfeeding women or a partner w/ HSDD | 233 | 100mg Flibanserin qhs |
| Simon (2014) | Double Blind, Placebo Controlled RCT | 949 | Postmenopausal women of any age w/ at least one ovary | Naturally postmenopausal women of any age with HSDD lasting 6 months or more and those in a stable monogamous relationship >1 year | Beck Inventory Depression score of >14 or suicidal attempts, other sexual dysfunctions or gynecological disorders or taking medications that could interfere with sexual dysfunction or cause drug interactions | 185 | Flibanserin 100mg qhs |

OUTCOMES MEASURED

A SSE is defined as "sexual intercourse, oral sex, masturbation, or genital stimulation by a partner."[1] For all three studies, women were required to keep an eDiary and record their sexual activity and whether this activity was satisfying.[1] If women had sexual activity she would respond to whether or not it was satisfying by responding yes or no. All three studies used a Wilcoxon's rank-sum test for analyzing whether sexual activity was considered a SSE.

RESULTS

All three studies compared the use of 100mg Flibanserin with placebo for the symptomatic treatment of HSDD. Two trials were in women ≥ 18 years and older who were premenopausal while the third study used women ≥ 18 years old who were postmenopausal. All three studies were randomized control trials in which the data was continuous and not converted into dichotomous data.

The DeRogatis et al study used pre menopausal women ≥18 years old and had a very large list of exclusion criteria (Table 1) that excluded a variety of women with relationship problems, gynecological disorders other than HSDD, exclusion of a variety of medications that could interfere with the study drug and any pregnancy or mental health concerns. Due to HSDD's multifactorial etiology, researchers felt that many factors had to be excluded that could affect any aspect of low libido, other than HSDD, such as hormonal changes, and any interactions with the study drug and/or mental health concerns. In this study the subjects were randomly selected to be in one of three groups: 50mg Flibanserin, 100mg Flibanserin or Placebo all taken qhs, but this paper will solely focus on the 100mg Flibanserin group for consistency across all three studies. Results showed that 100mg Flibanserin taken qhs for 24 weeks increased the number of SSE in women when compared with the Placebo control group and the results can

be found in Table 2.[1] The number of SSE was greater in the 100mg Flibanserin group at 3.0±2.8 when compared to the Placebo group at 2.7±2.8 over a 4 week time period. In Table 3, the mean change from baseline of SSE was determined to be 0.8 for the Placebo group and 1.6 for the 100mg Flibanserin group with a p value <0.01, showing statistical significance. The number of women who reported an Adverse Event (AE) from taking the study medication is displayed in Table 4. 59.3% of women in the Placebo group reported an AE with 3.4% of these women discontinuing the medication while nearly 66.6% of women in the 100mg Flibanserin group reported an AE and 11.4% discontinued the study drug due to these events.

Table 2: Number of SSE in DeRogatis et al Study[1]

| **Type of Treatment** | **# of SSE over 4 weeks** |
|---|---|
| 100mg Flibanserin | 3.0±2.8 |
| Placebo | 2.7±2.8 |

Table 3: Mean change from Baseline of SSE[1]

| **Type of Treatment** | **Mean Change from Baseline (Standard Error)** | **P value** |
|---|---|---|
| 100mg Flibanserin | 1.6 (0.23) | P<0.01 |
| Placebo | 0.8 (0.20) | P<0.01 |

Table 4: AE analysis[1]

| **Type of Treatment** | **Percent of AE reported** | **Percent who discontinued due to AE** |
|---|---|---|
| 100mg Flibanserin | 66.6% | 3.4% |
| Placebo | 59.3% | 11.4% |

The Katz et al study also studied women ≥ 18 years old who were premenopausal, diagnosed with HSDD and included identical inclusion and exclusion criteria to the DeRogatis et al study. In this study, subjects were also randomized to a 100mg Flibanserin group or a Placebo group and took the study medication qhs for 24 weeks. Results showed that the number of SSE was similar in both the Placebo group and the 100mg Flibanserin group as shown in Table 5. The

Placebo group had 2.7 SSE while the Flibanserin group had 2.5 SSE over a 4 week time period. The mean change from baseline of the number of SSE between the Placebo group and the 100mg Flibanserin group was statistically significant with $p < 0.001$ and the results are shown in Table 6. The Flibanserin group showed a mean change in baseline of the number of SSE of 2.5 when compared to the Placebo group of 1.5. Table 7 shows the number of AE in each treatment group and the Placebo group had 50.5% of women reporting an AE and nearly 62.2% of women taking 100mg Flibanserin reporting an AE. Approximately 3.7% of the placebo group discontinued due to an AE while 9.6% of 100mg Flibanserin discontinued the study.

Table 5: Number of SSE in Katz et al Study[2]

| **Type of Study** | **# of SSE over 4 weeks (SD)** |
|---|---|
| 100mg Flibanserin | 2.5(2.5) |
| Placebo | 2.7(2.9) |

Table 6: Mean change from Baseline of SSE[2]

| **Type of Study** | **Mean change from Baseline (Std Deviation)** | **P value** |
|---|---|---|
| 100mg Flibanserin | 2.5(4.6) | P <0.001 |
| Placebo | 1.5(4.5) | P<0.001 |

Table 7: AE Analysis[2]

| **Type of Study** | **% of AE reported** | **Percent who discontinued due to AE** |
|---|---|---|
| 100mg Flibanserin | 62.2% | 9.6% |
| Placebo | 50.5% | 3.7% |

The Simon et al study used postmenopausal women diagnosed with HSDD, unlike the previous two studies which looked at premenopausal women. Women were blindly randomized to two different groups which took either Placebo or 100mg Flibanserin qhs daily for 24 weeks. The inclusion criteria included postmenopausal women with at least one ovary and the other inclusion criteria included in Table 1. Exclusion criteria included similar criteria in both of the

previous studies discussed and is also included in Table 1. The number of SSE between the Placebo group and the 100mg group were similar and are displayed in Table 8. Both the placebo group and the Flibanserin group showed that the number of SSE over a 4-week period was 2.0. The placebo group showed a mean change of SSE from baseline of 0.6 while the Flibanserin group showed a 1.0 mean change with a p-value equal to 0.004, showing statistical significance and this data is included in Table 9. The number of AE, shown in Table 10, reported in the Placebo group was 51.7% with 3.5% of women dropping out compared to the Flibanserin group, which reported 63.4% of AE and 8.1% of women dropping out of the study.

Table 8: Number of SSE in Simon et al Study[5]

| **Type of Study** | **# of SSE over 4 weeks (SD)** |
|---|---|
| 100mg Flibanserin | 2.0 (2.2) |
| Placebo | 2.0 (2.4) |

Table 9: Mean change from Baseline of SSE[5]

| **Type of Study** | **Mean change from Baseline (Std Deviation)** | **P value** |
|---|---|---|
| 100mg Flibanserin | 1.0 (0.1) | P =0.004 |
| Placebo | 0.6 (0.1) | P=0.004 |

Table 10: AE Analysis[5]

| **Type of Study** | **% of AE reported** | **Percent who discontinued due to AE** |
|---|---|---|
| 100mg Flibanserin | 63.4% | 8.1% |
| Placebo | 51.7% | 3.5% |

DISCUSSION:

Flibanserin, or its trademark name Addyi, is a serotonin 1A receptor agonist and a serotonin 2A receptor antagonist that is the only FDA approved drug to treat premenopausal women diagnosed with HSDD.[6] Though the drug is said to improve sexually satisfying events and improve sexual desire, it is still widely unknown the mechanism the drug takes to improve

symptoms.[6] Flibanserin is contraindicated in those with liver impairment, those who drink alcohol and those taking moderate to severe CYP3A4 inhibitor medications due to drug interactions.[7] This drug does contain a Boxed Warning that highlights the risk of both hypotension and syncope especially in those consuming alcohol while using the medication.[7] The FDA approved Flibanserin with a risk evaluation and mitigation strategy (REMS), which requires both physicians and pharmacists that would prescribe this medication to undergo training to ensure adequate patient counseling on the risk of using alcohol.[7] Flibanserin was previously used in depression studies and failed to show efficacy but subjects reported having a decreased sexual dysfunction, which led to studies looking at the use of this drug and HSDD.[6]

Adverse Events were reported in all three studies but a minimal amount of subjects opted out of the study due to the AE as seen in Table 4, 7 and 10. Most AEs were mild to moderate with no severe AEs due to taking 100mg Flibanserin or the Placebo. The most common side effects included dizziness, somnolence and nausea.[1,2,3]

All three studies analyzed showed an increase in the number of SSE in pre- and postmenopausal women with HSDD with the use of 100mg Flibanserin versus Placebo. In the Katz et al study, though 100mg Flibanserin was shown to increase the number of SSE, the magnitude of improvement was found to be less than the DeRogatis et al study or the Katz et al study. Postmenopausal women generally have a higher risk of dyspareunia and sexual arousal disorders which could have led to a lesser improvement of SSE in postmenopausal women.

This review supports the use of 100mg Flibanserin in the treatment of HSDD but there a considerable amount of limitations to all three studies. In both DeRogatis et al and Katz et al extensive exclusion criteria were used such as women in unstable relationships, those diagnosed with depression, those with a partner suffering from sexual dysfunction and a long list of

contraindicated medications. In Katz et al, nearly 1/3 of all patients screened were ineligible due to exclusion criteria.[2] In Simon et al, subjects were excluded with similar criteria except the list of contraindicated medications was greatly reduced. Though exclusion criteria was used to rule out other causes of decreased libido, it's possible that many women can suffer from HSDD in other settings and that these studies were not fully representative of all women.

CONCLUSION:

Based on this systematic review and chosen studies, 100mg Flibanserin is an effective treatment for premenopausal and postmenopausal women diagnosed with HSDD. The data found in these three studies are consistent with the beneficial effects of Flibanersin as well as its overall safety. No serious AEs were judged by researchers to be related to study medications; therefore, it should be a consideration when looking to treat patients for HSDD. Though, no serious AEs were found, there are some limitations to be considered when prescribing this medication such as the use of alcohol and Flibanserin, use of CYP3A4 drugs or liver dysfunction. Physicians should be well informed of the contraindications as well as the drug interactions of Flibanserin before prescribing it.

REFERENCES:


1. Derogatis LR, Komer L, Katz M, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: Efficacy of flibanserin in the VIOLET study. *J Sex Med*. 2012;9(4):1074-1085. doi: 10.1111/j.1743-6109.2011.02626.x [doi].

2. Katz M, DeRogatis LR, Ackerman R, et al. Efficacy of flibanserin in women with hypoactive sexual desire disorder: Results from the BEGONIA trial. *J Sex Med*. 2013;10(7):1807-1815. doi: 10.1111/jsm.12189 [doi].

3. Foley K, Foley D, Johnson B. Healthcare resource utilization and expenditures of women diagnosed with hypoactive sexual desire disorder. *J Med Econ*. 2010;13(4):583-590.

4. International Society for Sexual Medicine. How is HSDD Treated? http://www.issm.info/sexual-health-qa/how-is-hsdd-treated/. Accessed October 9, 2016.

5. Simon JA, Kingsberg SA, Shumel B, Hanes V, Garcia M,Jr, Sand M. Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: Results of the SNOWDROP trial. *Menopause*. 2014;21(6):633-640. doi: 10.1097/GME.0000000000000134 [doi].

6. Federal Drug Administration. Flibanserin. Advisory Committee Web site. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM449088.pdf. Updated 2015. Accessed December 10, 2016.

7. Fischer A. FDA approves first treatment for sexual desire disorder. U.S Food and Drug Administration Web site. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm458734.htm. Published August 2015. Updated 2015. Accessed December 10, 2016.