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Is Flibanserin a Safe and Effective Treatment to Increase Sexual Desire in Premenopausal Women with Hypoactive Sexual Desire Disorder?

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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 Flibanserin is a safe and effective treatment to increase sexual desire in premenopausal women with Hypoactive Sexual Desire Disorder.

STUDY DESIGN: Review of three randomized controlled trials published in 2013, 2012, and 2012; selection was based on their relevance to the clinical question and if they contained patient oriented outcomes.

DATA SOURCES: Three peer-reviewed randomized controlled trials comparing the use of Flibanserin to placebo in the treatment of Hypoactive Sexual Desire Disorder were found on PubMed.

OUTCOME(S) MEASURED: For each trial patients were divided into two groups and assigned to either Flibanserin treatment or placebo treatment. Each trial assessed number of satisfying sexual events (SSE), Patient Global Impression of Improvement (PGI-I), and Adverse Events (AEs), events leading to the discontinuation of the trial.

RESULTS: All three trials showed a statistically significant ($p<.05$) increase in mean change from baseline for number of satisfying sexual events when compared to the mean change from baseline of the placebo group. Thorp et al. and DeRogatis et al. both had PGI-I data that expressed the NNT of 6, while Katz et al. showed a NNT of 8. Thorp et al. reported adverse events that showed a NNH of 31, DeRogatis et al. reported adverse events that showed NNH of 12, and Katz et al. reported adverse events that showed NNH of 16.

CONCLUSIONS: Based on all three trials, there is a statistically significant increase in sexual desire with the use of Flibanserin compared to the use of placebo in premenopausal women with HSDD. The analysis of PGI-I showed a moderately low NNT indicating that the drug, Flibanserin, was effective in improving the women’s condition. The analysis of AEs showed a moderate numbers needed to harm indicating that there are risks to taking Flibanserin. All serious safety concerns were investigated and deemed not related to the use of Flibanserin. Flibanserin is a relatively safe drug, and is an effective treatment of HSDD symptoms in premenopausal women.

KEY WORDS: Flibanserin

Introduction:

Hypoactive Sexual Desire Disorder is a sexual disorder characterized by low sexual desire that causes marked distress or interpersonal difficulty.[1] Sexual dysfunction is a very common problem for both men and women, but treatment options for women are disproportionately fewer than they are for men. Historically female sexual dysfunction has been believed to be heavily psychopathologic, while male sexual dysfunction has been viewed as more physiologic. In addition, the topic of sex is culturally taboo to discuss; especially for women in America. Each of these factors may contribute to the disproportion of treatment options for women with sexual dysfunction. This paper assess three double-blind, randomized, controlled trials testing the efficacy and safety of the use of Flibanserin to increase sexual desire in premenopausal women with Hypoactive Sexual Desire Disorder. Throughout the process of the analysis of these randomized control trials, Flibanserin has moved on from trial phase and is now available to the public. Flibanserin is the first and only pharmacotherapy option being offered for the treatment of HSDD.

HSDD effects up to 14% of premenopausal women, and is the most commonly reported type of sexual dysfunction.[2] The total impact that HSDD has on healthcare cost is unknown, but women with a diagnosis of HSDD have a total annual healthcare expenditure that is 16.8% higher than women without HSDD.[3] This

is due to the fact that women with HSDD tend to have on average two more medical office visits per year than women without HSDD.[3]

The exact etiology of HSDD is unknown, but it is thought to be multifactorial. Possible contributing factors include, decreased testosterone or estrogen levels, psychological factors, and sociological factors such as relationship conflict.[4]

Prior to Flibanserin there were no pharmacotheraputics for the treatment of HSDD. Often patients with HSDD see a counselor or a sex therapist to help with psychological factors contributing to the disease. Other treatments consist of herbal remedies. The top herbal remedies are Provestra, Femestril, and Vigorelle.[4] Even though there are multiple options available for the treatment of HSDD, there is no current treatment that is effective in all patients. For this reason there is a need for more treatment options of HSDD. Therefore, determining the safety and efficacy of Flibanserin is important.

Objective:

The objective of this selective EBM review is to determine whether or not Flibanserin is a safe and effective treatment to increase sexual desire in premenopausal women with Hypoactive Sexual Desire Disorder.

Methods:

Three double blind, randomized controlled trials, were included in this systematic review. Studies were selected based

on various criteria including populations studied, interventions used, comparisons made, and outcomes measured. In all three studies, the populations being measured consisted of healthy premenopausal women greater than or equal to the age of 18 with a diagnosis of HSDD. The women in the study also had to be in a stable, communicative, monogamous, heterosexual relationship of > 1 year's duration and had to have a sexually functional partner. Each article measured the effects of 100mg of Flibanserin taken orally once daily before bedtime and compared it to the effects of taking a visually equivalent placebo pill at bedtime. Each of the articles also measured desire and improvement in libido by recording the following: number of satisfying sexual events (SSE) and Patient's Global Impression of Improvement (PGI-I). Each article measured safety by recording the number of Adverse Events (AE).

All three articles were researched via the PubMed database and were selected based on relevance to the clinical question. Each article was also selected on the basis that their measured outcomes were patient oriented evidence that matters (POEMS). The Key word entered in the PubMed search was "Flibanserin". All three of the selected studies were peer reviewed journal articles written in the English language published between 2012 and 2013.

The studies included in this systematic review were selected based on the following inclusion criteria: all were primary research studies (randomized controlled trials, cohort studies, crossover studies, etc.), all were published after 1998, all included relevant POEMs, and all evaluated the safety and efficacy of Flibanserin on Hypoactive Sexual Desire Disorder as one of the measured outcomes. Exclusion criteria included women under 18 years of age, women with sexual dysfunctions other than HSDD; any other psychiatric disorder that could impact sexual function; MDD within the previous 6 months; a score of 14 on the Beck Depression Inventory-II; any ongoing serious clinical disorder; or substance abuse in the past year. Statistics reported included standard deviations, p-values, and mean change from baseline. Table 1 below shows the demographics and characteristics of the included studies.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# of Pts	Age	Inclusion	Exclusion	W/D	Intervention
Begonia (2013)	RDBPC	1090	36.5 +/-8	Premenopausal women >18 years old, with diagnosis of HSDD. A Female Sexual Distress ScaleRevised (FSDS-R) score of at least 15, indicating sexual distress, and a Sexual Interest and Desire Inventory-Female receptivity item rating of 0 or 1, indicating little or no receptivity to partner's sexual approach. Women had to be in a stable, communicative, monogamous, heterosexual relationship of > 1 year's duration and to have a sexually functional partner.	Sexual dysfunctions other than HSDD, arousal disorder, or orgasm disorder; any other psychiatric disorder that could impact sexual function; MDD within the previous 6 months; a score of 14 on the Beck Depression Inventory-II; any ongoing serious clinical disorder; or substance abuse in the past year.	233	Flibanserin 100mg qhs
Violet (2012)	RDBPC	585	35.5 +/- 7			152	Flibanserin 100mg qhs
Daisy (2012)	RDBPC	794	35.4 +/- 7			255	Flibanserin 100mg qhs

Outcomes Measured:

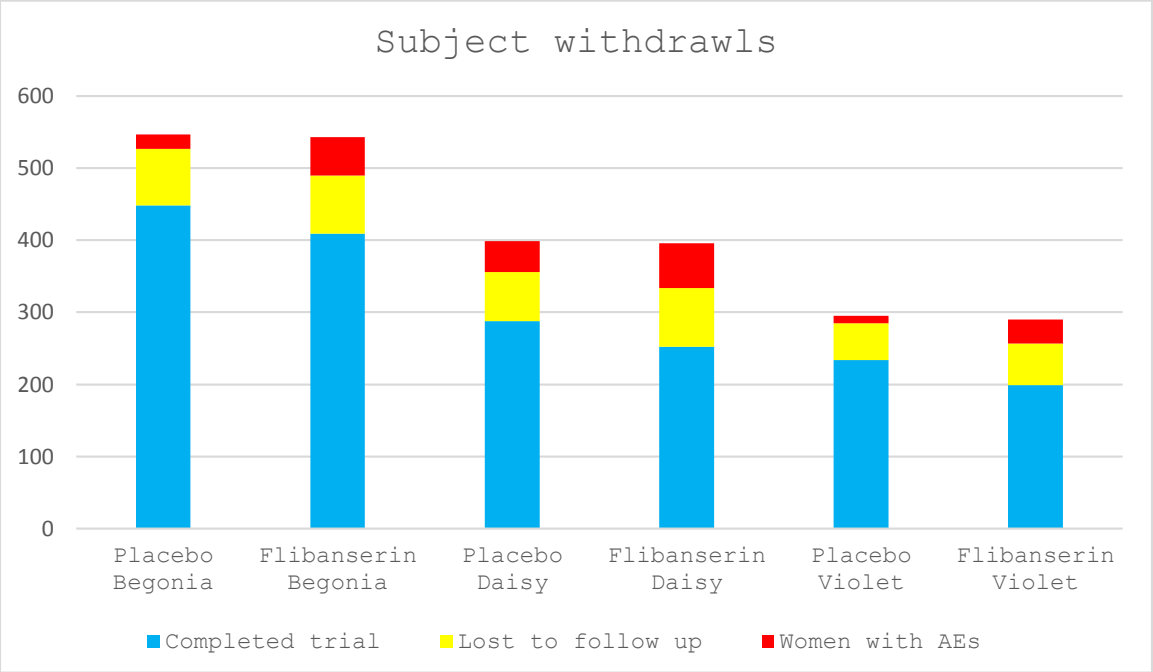
All three articles measured the number of satisfying sexual events (SSE), Patient Global Impression of Improvement (PGI-I), and Adverse Events (AEs). SSE was recorded by the subjects via an eDiary. A sexual event was defined as sexual intercourse, oral sex, masturbation, or genital stimulation by a partner.[1,5,6] In order to measure sexual desire improvement each article used PGI-I. PGI-I consisted of a single question, "How is your condition today compared with when you started the study

medication?" Subjects answered the question on a 1-7 scale 1 (very much improved), 4 (no change), and 7 (very much worse). PGI was measured at weeks 4, 8, 16, and 24.[1,5,6] To determine safety of Flibanserin use, Adverse Events leading to the discontinuation of the trial was measured throughout the duration of the trial.

Results:

Three double-blind randomized controlled trials compared the effects of 100 mg of Flibanserin with a visually equivalent placebo pill on premenopausal women with HSDD. Thorp et al. assigned 399 women to placebo and 396 women to the experimental group. Of the 399 women in the placebo group, 111 discontinued the trial; 43 due to adverse events and 68 due to various reasons such as non-compliance or being lost to follow up. Of the 395 women receiving Flibanserin, 144 discontinued; 62 due to adverse events, and the remaining to other causes.[5] Katz et al. assigned 547 women to the placebo group and 543 women into the Flibanserin group. Of the 547 women in the placebo group, 99 discontinued the trial, 20 due to adverse events and the remainder for various reasons. Of the 543 women in the Flibanserin group, 134 discontinued the trial, 53 due to adverse events.[1] DeRogatis et al. assigned 295 women into the placebo group and 290 into the Flibanserin group. Of the 295 women in the placebo group, 61 discontinued the trial; 10 due to adverse

events. Of the 290 women in the Flibanserin group 91 women discontinued, 33 due to adverse events.[6] Graph 1, seen below, illustrates withdrawal numbers in all three trials.



Graph 1: Subject withdrawals and completions.

All three trials showed a statistically significant ($p<.05$) increase in mean change from baseline for number of satisfying sexual events when compared to the mean change from baseline of the placebo group. These results are illustrated in Table 2 below.

Table 2: Efficacy of Flibanserin in the treatment of Hyposexual Desire Disorder using Satisfying Sexual Events.

Study	Flibanserin 100 mg. Mean change from baseline (SD)	Placebo Mean change from baseline (SD)	P value
Thorp et al.	1.9 (.3)	1.1(.2)	<.01
DeRogatis et al.	1.6 (.23)	.8 (.2)	<.01
Katz et al.	2.5 (4.6)	1.5 (4.5)	<.001

All three randomized control trials reported PGI-I scores after the 24 weeks of the trial was over. Data from these trials were reported as continuous data that was later converted into dichotomous format to evaluate efficacy of treatment. Thorp et al. reported PGI-Is that showed 47% of women who were taking Flibanserin felt an improvement in their condition while 30.3% of women taking placebo felt that their condition had improved; that results in a NNT of 6.[5] DeRogatis et al. reported PGI-Is that showed 50% of women who were taking Flibanserin felt an improvement in their condition while 30.3% of women taking placebo felt that their condition had improved; that results in a NNT of 6.[6] A NNT of 6 means that if 6 people were treated with Flibanserin, one person would benefit more than that of people taking placebo. Katz et al. reported PGI-Is that showed 51.8% of women who were taking Flibanserin felt an improvement in their condition while 37.7% of women taking placebo felt that their condition had improved; that results in a NNT of 8.[1] The results for PGI-I are illustrated in Table 3 seen below.

Table 3: Efficacy of Flibanserin in the treatment of Hyposexual Desire Disorder using PGI-I.

Study	CER	EER	RBI	ABI	NNT
Thorp et al.	.303	.500	.650	.197	6
DeRogatis et al.	.303	.470	.55	.168	6
Katz et al.	.377	.518	.374	.141	8

Adverse events data from all three trials was reported as continuous data and was later converted into dichotomous format to evaluate safety of treatment. Thorp et al. reported adverse events in 13.4% of those taking Flibanserin and 10.1% of those taking placebo, resulting in a NNH of 31.[5] A NNH of 31 means that it takes 31 people to be treated with Flibanserin before 1 adverse event happens that wouldn't have otherwise happened using the placebo. DeRogatis et al. reported adverse events in 11.4% of those taking Flibanserin and 3.4% of those taking placebo, resulting in a NNH of 12.[6] Katz et al. reported adverse events in 9.6% of those taking Flibanserin and 3.7 % of those taking placebo, resulting in a NNH of 16.[1] The results of adverse events are illustrated in Table 4 seen below. The most common adverse effects reported in all three trials were somnolence, dizziness, nausea, and fatigue.[1,5,6] In all three cases, the serious adverse events were deemed not related to the drug by the investigator.

Table 4: Safety of Flibanserin in the treatment of Hyposexual Desire Disorder using.

Study	CER	EER	RRI	ARI	NNH
Thorp et al.	.034	.114	2.35	.08	12.5→12
DeRogatis et al.	.101	.134	.327	.033	30.3→30
Katz et al.	.037	.096	1.59	.059	16.96 →16

Discussion:

Using three double-blind RCT's, this meta-analysis reviewed the safety and efficacy of Flibanserin in improving the sexual desire in premenopausal women ≥18 years old with HSDD. All three trials showed that in premenopausal women with HSDD taking 100mg of Flibanserin before bed was associated with a statistically significant increase in sexual desire expressed by SSE. The analysis of PGI-I showed a moderately low NNT indicating that the drug, Flibanserin, was effective in improving the women's condition. The analysis of AEs showed a moderate numbers needed to harm indicating that there are risks to taking Flibanserin. All serious safety concerns were investigated and deemed not related to the use of Flibanserin.

Conclusion:

Based on the three studies above, it can be concluded that Flibanserin is effective at improving the condition and increasing sexual desire in women in premenopausal women with HSDD, but the risks and benefits must be weighed on an individual basis. No serious or life threatening risks have been identified as a result of the use of Flibanserin. Flibanserin is a relatively safe drug and is an effective treatment of HSDD symptoms in premenopausal women.

Reference

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