



Discrepancies and Talking Points re Jaspers et al.

There is evidence of personal bias and agendas throughout the paper by Jaspers et al., distorting the science. These strategies are purposefully deceptive and lack scientific integrity:

- The authors claim to have done the first systematic review and meta-analysis on the effect of flibanserin in women with HSDD. **The first systematic meta-analysis of flibanserin is by Gao Z, Yang D, Yu L, and Cui Y.** The efficacy and safety of flibanserin in women with hypoactive sexual desire disorder: A systematic review and meta-analysis. *The Journal of Sexual Medicine* 2015;12:2095–2104.
- **The abstract contains only the biased conclusions** (see below).
- In the current paper, **the authors included the following inappropriate studies** in which:
 - Doses and dosing regimens found to be ineffective (too low) or intolerable (dosed in the morning) were used in order to either increase numbers of side effects or to suggest the drug doesn't work
 - A study that was terminated early because the original developer ended the flibanserin program and not because the subjects chose to discontinue. Nevertheless, these numbers were incorrectly included such that the overall efficacy was diminished.
- The authors indicate that more subjects taking flibanserin dropped out than those receiving placebo. This is not unique to the flibanserin program. **In any drug trial, more people drop out on active drug than placebo. Dropout rates are consistent with other central nervous system (CNS) active drugs**, especially given the 6-month duration of the trials (most CNS studies are 4-8 weeks). With regard to drug approval, more people should benefit from drug than placebo. This was certainly the case with flibanserin, as demonstrated by the responder rates in the three pivotal Phase 3 trials. Using the Patient Global Impression of Improvement that was agreed upon by the FDA, responder rate for sexual desire was 43–51% in women treated with the 100 mg bedtime dose of flibanserin versus 31-39% for placebo treatment. In addition, the responder rate for decreased distress related to change in sexual desire was 50–60% in women treated with the 100 mg bedtime dose of flibanserin versus 40-48% for placebo treatment. **All of these differences were highly statistically significant** and the placebo response rate was not unusual for CNS-active drugs or sexual medicine drugs.
- **Authors' interpretation of bias in the available data is itself biased. No studies would meet the criteria that they used (see below):**
 - Their interpretation of risk of bias (they claim that “*high quality*” efficacy and safety data from randomized, double-blind, placebo-controlled trials results in “*very low quality*” evidence) **demonstrating their anti-medication bias.**
 - They suggest that *being overweight* represents higher functioning (which the authors feel distorts the data) which is the opposite in the US (authors are European) where **obesity is associated with lower socioeconomic status.** Further, there is no supporting evidence from the Phase 3 data to suggest that body mass index was significantly associated with change in efficacy.
 - Their interpretation that only *5 of 8 studies have been published in peer-reviewed journals suggests a serious limitation to the quality of their evidence.* This is clearly a weak argument. **The non-publication of studies in a drug development program does not necessarily reflect on their quality. Further, all data is accessible publicly on clinicaltrials.gov** (where all studies are listed, and available data and analysis published), and in the FDA/company briefing document.
 - The authors claim “women with a wide range of diseases and medication uses were excluded from study participation”. **It should be noted that exclusion of relationship problems, medical conditions and medications that may cause low desire is required for the diagnosis of HSDD.** Only **6% of women** who were screened for study inclusion were excluded due to medical conditions and medications. **In general, women with HSDD are typically a healthy population.**
 - Authors expressed concern about failure of an initial primary endpoint (daily eDiary to assess sexual desire) which was required by FDA when no clear pathway for appropriate endpoints had been established. This endpoint was found to be a poor measure of women's sexual desire. **Endpoint measures of importance are sexual desire and distress about level of sexual desire.**

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- **Satisfying sexual events (SSEs) don't matter to women, but the authors have focused on this because the absolute numbers are small.** SSEs were just a way for the FDA to count something rather than relying on women's report of their experience of desire and distress on validated scales. Much has been made of the fact that study subjects reported SSEs even though they were diagnosed with HSDD. The women *on average* were participating in sex 5 times a month when they entered the trial, but feeling satisfied with only about half the time (i.e., 2.5 SSEs per month). It should be emphasized that about half the women reported less than 2 SSEs per month at study entry and about 1 in 5 women reported zero SSEs per month. In addition, the meaning of "satisfying" was intentionally left to the patient to define and women commonly provide numerous and varying definitions of satisfying. As has been reported previously in the media, using absolute numbers, the mean improvement in the completed trials that used 100 mg at bedtime of flibanserin was 1 additional satisfying sexual event per month over placebo, but **the relative mean increase was a doubling or 100% increase in SSEs with 100 mg flibanserin at bedtime.**
- The authors feel the studies are "light on details" even though the data are exhaustive.
- The authors claim the data lack "blinding ascertainment" despite the fact that these are double-blind studies and that "effect and precision estimate" of every outcome is also lacking. These statistical concerns were not brought up by the FDA. Thus, the authors seem to be employing a standard that remains undefined, as if to say "we can raise the bar higher than you can jump".
- **The Forest plot favors flibanserin efficacy results in all studies** except for SSEs in the inadequately dosed study (no 100 mg dose tested) and the prematurely terminated study.
- The authors themselves state that **"Adverse effects were mild or moderate in intensity, and serious AEs were equally low in flibanserin and placebo users."** Earlier in their article, they state that **"The absolute number of serious AEs"** (e.g. death, life-threatening, hospitalization, etc.) **"was small, and the risk ratio did not differ between flibanserin and placebo users."**

With specific regard to this article being a meta-analysis of HSDD the following are the facts:

- The inclusion of many different kinds of studies, including studies that were closed out early is not appropriate in the efficacy analysis. Yet, despite this, the combined overall efficacy, as determined by Jaspers et al., was statistically significant in favor of flibanserin, including desire assessed by daily electronic diary.
- **Leaving out distress in this analysis**, especially for their "risk-benefit" analysis, **indicates a fundamental misunderstanding of the condition of the HSDD.**
- **The women recruited into the study were representative of the target population and reflective of epidemiological data.** The FDA did not impose such requirements of studies in surgically menopausal women or women with comorbidities. It is not unusual for cohorts of patients with different characteristics to be studied in the post-marketing period, but these do not alter the efficacy and safety findings of a drug in the indicated population. The approved indication was in premenopausal women who tend to be relatively healthy and do not take many concomitant medications. The most prevalent concomitant medications were over the counter analgesics, seasonal allergy treatments, and hormonal contraceptives. None of these were assessed to have significant impact on the overall safety of flibanserin.
- **Safety data must be understood in context:** Safety profiles are strictly for exploratory purposes and usually simply tabulated with little or no inferential statistical analyses. It has been proposed by some to use Chi-Square or Fisher's Exact Test to obtain p-values, but there is little research and no widespread agreement. Further, an adverse event is defined as "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product." It is not clear what the authors mean when they state that "Investigator-defined drug-related AEs and severe AEs were underreported (2 studies each)." All AEs were reported in all trials whether it was considered treatment-related or not. Further, adverse events are reported at the discretion of the investigator and translated into standardized terms under a system called MedDRA. Yet, there is little uniformity on how an event is defined or reported. Thus, **adverse events are spontaneous and non-adjudicated reports.** For flibanserin, any given AE was episodic, most often lasting several minutes. The great majority of these AEs were experienced within the first 2 – 4 weeks.



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- **While one can calculate p-values for AE rates between two different treatment groups (as Jaspers et al. have done), it is problematic due to several reasons:**
 - For any given adverse event, the small numbers of events results in extremely imprecise estimates.
 - There are usually many different adverse events that are reported and this brings in the issue of multiplicity of comparisons. For example, it is not unusual to have up to 500 separate terms describing AEs in a typical clinical trial. If a p-value were calculated for each pairwise comparison, one would expect by chance alone that 5% of the AEs will have a $p < 0.05$.
 - Evaluation of safety includes an extremely large number of evaluations, and a very high number of permutations and combinations, inadequate statistical power, no meaningful control of type I and II error, and the p-value is difficult to interpret.
 - In contrast, efficacy evaluations are limited in number and prespecified by the statistical protocol, have adequate statistical power and rigorous control of type I and II error, and the interpretation of p-values are well-established.