Discrepancies and Talking Points re Woloshin et al.

There is evidence of personal bias and agendas throughout the editorial by Woloshin et al., distorting the science for their own purpose, which is promoting their company concerned with "disease mongering." These strategies are purposefully deceptive and lack scientific integrity in an effort to support their own anti-medication bias. Funding for this company appears to be payment by credit card by the consumer for the authors' opinion on specific medications. Their current website displays flibanserin as the example and includes numerous inaccuracies. This appears to be a clear conflict of interest that is not mitigated by disclosure, bringing to question the editorial oversight of JAMA.

Inaccuracies are reported as fact throughout the editorial, beginning with the first paragraph. The authors seem to implicitly trust the judgment of the FDA with regard to evaluating flibanserin's NDA, but are then quick to implicate that the same FDA crumbled under a bit of patient advocacy and political pressure. The facts are as follows:

- HSDD and treatment with flibanserin are not related to arousal.
- **50% of women taking flibanserin had a meaningful (to them) clinical response**; therefore, 50% would be expected not to respond (not 90%). This 90% number is completely contrived.
- The warning against co-administration with alcohol is **not a "black box" warning.** It is a boxed warning.
- Discontinuation rates due to adverse events were 6% for placebo and 12.8% for flibanserin, in line with other CNS drug rates.
- The original denial of approval by the FDA was because the drug-placebo differences in the daily eDiary endpoint were not statistically different at study endpoint. The **FDA insisted on a daily measure of desire**, which, if you have no sexual desire, is at least annoying and more likely disturbing/distressing. The FDA also insisted on SSEs. Neither measure has been demonstrated to be a valid measure of HSDD. If a prespecified primary endpoint is not met, it is accepted practice that the trial be considered negative and would not provide support for approval. Subsequently, the FDA allowed a validated measure of desire, the FSFI desire score, to be used as an endpoint. The FSFI desire subscale was positive in the original two trials, as were the other measures (FSDS, a measure of sexually related distress, and SSEs**). In all 3 pivotal trials, on all 3 primary and secondary endpoints, flibanserin was superior to placebo**, a feat not achieved with other CNS drugs (probably ever).
- Relationship problems, medical/psychiatric conditions associated with low sexual desire (e.g., depression, endocrine disorders, neurological illnesses, etc.), and medications/substances that contribute to low sexual desire (e.g., many antidepressants, opioids, cannabis, etc.) must be excluded in order to make the diagnosis of HSDD. However, Boehringer-Ingelheim (not Sprout) performed a 3rd efficacy study with less restrictive criteria acceptable to the FDA that had even better efficacy and safety results.
- The authors are mistaken with regard to specific dates and associated facts. After Sprout acquired flibanserin, they resubmitted to the FDA for approval. While an Advisory Committee was not necessary, the FDA rejected the submission demanding additional studies. This decision was appealed (a rare event among larger pharmaceutical companies, fearful of retaliation by the FDA through another drug). While Sprout did not technically "win" the appeal, it should be emphasized that most appeals are denied as a matter of course by the FDA and that the underlying benefit of an appeal is a more clearly defined pathway toward approval, as delineated by the FDA. This was the case with Sprout's appeal and the sponsor performed the additional studies that were requested. This new data was submitted and reviewed by the second FDA Advisory Committee in June 2015 which included the FDA's Division of Drug Safety and Risk Management that stated that the study population was in fact quite similar to the general population of intended users. The result was an 18 to 6 approval vote.
- **The portrayal of the development and regulatory history is intentionally and inaccurately characterized as "failure."** As noted above, the regulatory history is mischaracterized and is devoid of context. The FDA had an extremely large database and an unusually large number of patients enrolled in phase 1, 2 and 3 studies. There is absolutely no basis to conclude that the science was weak.
- **What changed?** In January 2014, **10 women's advocacy group leaders** met with Janet Woodcock (Director of the Center for Drug Evaluation and Research – CDER), the DBRUP division members, and several other FDA employees to discuss the issue of inequality in medications available for the treatment of sexual dysfunction in men vs. women, and the actions of the division in moving the goal posts in the approval process. In that meeting, **the FDA did acknowledge "an unconscious gender bias" which appeared to be impacting the review process of the first drug for HSDD/FSD**. "Even the Score" did not yet exist. The FDA clinical reviewers were part of that paternalism and conservatism. The result of that meeting was that the Public Forum on HSDD/FSD was moved up by 2 years,

occurring in October 2014. Women with HSDD spoke eloquently at that meeting, describing their personal struggles, the impact of HSDD on themselves, their relationships, and every aspect of their lives, and asking for gender equality in available choices for treatment. **The stories of those women, speaking publicly about such a private pain, impacted the FDA by increasing understanding and awareness, rather than by applying any kind of "pressure".**

- The **alcohol study** was an excessive, far from real life, contrived study. Requiring consumption of the alcohol equivalent of ½ to 1 full bottle of wine in 10 minutes at 9 a.m. on a light breakfast after a 10 hour fast, and then taking a drug meant to be dosed at bedtime (when you would normally lie down to sleep), and monitoring dizziness and fainting seems designed purposely to cause problems. The authors' suggestion that dangerous adverse events occurred with flibanserin when taken with "2 alcoholic drinks" inaccurately portrays the severity of the alcohol challenge study. The majority of people studied were men because women could not tolerate the amount of alcohol on an almost empty stomach. The real alcohol information lies within the Phase 3 trials: 39% of the premenopausal women reported at study entry that they were social or moderate drinkers. During the 6 months of each study, a total of 0.3% of women receiving placebo reported some kind of adverse event related to hypotension or syncope (i.e., syncope, vasovagal syncope, postural dizziness, loss of consciousness, decreased BP, hypotension, circulatory collapse) while a total of 0.5% of women receiving flibanserin reported any of the same set of adverse events. In addition, further examination of the safety data indicates that there was no difference between self-reported alcohol users and non-users for the same set of related adverse events. Hypotension and syncope are reported to have an annual incidence of 6% in the general population, and accounts for 3% of ER visits and 1-6% of hospitalizations. Thus, the women in the flibanserin trials appear to be much healthier in this regard than the general population.
- **In phase 3 trials in premenopausal women, there were 3 cases of hypotension in the flibanserin 100 mg qhs treatment group** (N=1,543) and zero cases in the placebo group, yielding a placebo-corrected rate of 0.2% overall. In comparison, the product insert of an already approved and widely prescribed antidepressant Wellbutrin states that the incidence of hypotension was 2.5% in the Wellbutrin group versus 2.2% in the placebo group, yielding a placebo-corrected rate difference of 0.3%. For all doses of flibanserin in phase 3 trials, there were 4 cases of hypotension out of a total of almost 4,000 patients (3,973 to be precise). Even taking into account the extreme case of syncope, the rate was 0.1% in the placebo group, 0.3% in the flibanserin 100 mg qhs group and 0.2% for all flibanserin doses combined. The rate of syncope with Wellbutrin was 1.2% versus 0.5% for placebo. That's a differential of 0.7% with Wellbutrin compared to 0.2% for flibanserin 100 mg – 3.5 times higher for Wellbutrin. As already mentioned above, even when related AE terms (i.e., syncope, vasovagal syncope, postural dizziness, loss of consciousness, decreased BP, hypotension, circulatory collapse) were added together for flibanserin, the rate was 0.3% in the placebo group, 0.5% in the flibanserin 100 mg qhs group, and 0.4% for all flibanserin doses combined. That analysis for Wellbutrin is not readily available, but even so, all of these related AE terms give a grand total differential of 0.2% for flibanserin 100 mg.
- **Flibanserin is NOT a failed anti-depressant**. In early clinical trials treating patients with major depressive disorder, flibanserin had similar efficacy to paroxetine in reducing depression assessed by the Hamilton Rating Scale for Depression. Pharmaceutical companies consider many different factors in revising or terminating drug development programs.
- **FDA briefing document website**: http://www.fda.gov/downloads/AdvisoryCommitteesmeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM449088.pdf