FACT SHEET 7: HISTORY OF FSD DRUGS[i]
The Hype, The Problems, & The Current Status

Only 2 drugs for FSD have reached the FDA advisory committee level and both were rejected for reasons of safety and efficacy. But many companies have tried - and many continue to try - to cash in on the "Hunt for the Pink Viagra." Read this summary, and then consider whether all this effort makes any sense.

1) Alista (alprostadil) by Vivus

- **The Hype:** Vivus went to great lengths to massage clinical trial endpoints.[ii]
- **Problem:** No meaningful benefit beyond the placebo.
- **Current Status:** Alista did not make it to the FDA approval stage.

2) Botox (Botulinum Toxin) by Allergan, Inc.

- **The Hype:** In 2011, the FDA approved clinical trials to test Botox to treat vaginismus in the US. Though not FDA approved, Dr. Pacik promotes Botox in a book titled *When Sex Seems Impossible*, and in a You Tube video, he exhorts women who have tried the procedure off-label to share their success stories online.[iii]
- **Problem**: Pacik's Phase I trials involved injecting 150 units of Botox intravaginally in 30 patients. Then, while still under local anesthetic, a "penis sized" dilator is inserted. The patient is encouraged to move the dilator in and out several times over the next hour. After discharge from the surgical centre, they are to keep a 'size 4 out of 6' dilator in their vagina for 24 hours and then return for 1-2 days of assisted dilation. It then takes months of self-administered dilation to achieve pain free sexual intercourse. No independent data.[iv]
- **Current Status:** Phase I clinical trials completed.

3) Bremelanotide (peptide hormone Melanotan) by Palatin Technologies (co-sponsor *Even the Score* campaign)

- **The Hype:** Sheryl Kingsberg, PhD, claims that bremelanotide "demonstrated robust efficacy across multiple measurements of female sexual dysfunction" in clinical trials. She says these results "speak to its great potential as a treatment option for the many women with FSD."[v]
- **Problem**: In Phase 2B trials, bremelanotide showed an increase in the number of Sexually Satisfying Events (SSEs) of 0.8 (2.9) with 1.75 mg and 0.7 (2.4) for 1.25 mg versus the placebo (2.3), a measure determined subjectively by each participant. These results are minimal but the placebo effect is impressive. Side effects in this case included mild to moderate facial flushing, nausea, emesis, and increased blood pressure.
- **Current Status:** Phase 2B Clinical Trials completed. Plans for phase 3 clinical studies have been delayed by FDA as a result of concerns over risk to the benefit ratio.

4) Femprox (alprostadil) by Apricus Biosciences

- **The Hype:** Apricusbio "corporate strategy" documents brag that "*high value assets such as Femprox for female sexual arousal disorder ('FSAD)*" show *great potential for shareholder value.*[vi]
- **Problem:** Femprox is the same drug as Alista but compounded with a new vasodilation delivery.
- **Current Status:** Phase II clinical trials have been completed but Phase III has not been approved.

5) Flibanserin (serotonergic/adrenergic) first by Boehringer Ingelheim (BI), now by Sprout (founder of the *Even the Score* campaign)

- **The Hype:** During clinical trials for Flibanserin, women's desire problems were framed by BI PR as brain-based in a 'Sex, Brain, Body Campaign' featuring celebrity endorsement by former model and soap star Lisa Rinna. BI also funded a Discovery Health Channel documentary about HSDD.[vii]
- **Problem:** This pill was tested in Phase III trials on 5,000 pre-menopausal women in heterosexual, monogamous relationships of one year or longer diagnosed with HSDD in North America and Europe. In public statements, BI focused only on the North American data, of only 1,300 women. Clinical trial participants were asked to evaluate their sexual desire and activities, recording SSEs. Compared to placebo, women taking Flibanserin had only an extra 0.7 SSEs per month. This benefit did not represent a sufficient margin to outweigh the potential risks associated with taking a daily antidepressant without knowing its long-term effects. During trials, 14% of study participants taking Flibanserin withdrew due to side effects such as "dizziness, nausea, fatigue, somnolence and insomnia."[viii]
- **Current Status:** Flibanserin was denied FDA approval on June 18th, 2010. However, Krychman and Kingsberg in the *Formulary Journal,* a 'drug management journal for managed care and hospital decision makers,' discussed Flibanserin as an investigational treatment in Phase III of research with no mention that it was denied FDA approval and no disclosures to BI.[ix] In 2011, Flibanserin was purchased from BI by Sprout Pharmaceuticals[x]. The chief operating officer at Sprout has stated, "with this study and other information included in our resubmission, Sprout claims that it has addressed the concerns raised by the FDA during its previous review." Their first resubmission was rejected in 2013. However, they plan to re-submit.

6) Intrinsa (testosterone patch) by Proctor & Gamble:

- **The Hype:** With Intrinsa in the pipeline, numerous P&G funded medical conferences were organized in the early 2000s, focused on women's low desire as caused by low testosterone.[xi]
- **Problem:** A high placebo effect was reported using "Sexually Satisfying Events" (SSEs) as an endpoint. Drug benefit went from three to four SSEs per month. There were also safety issues. According to the FDA, there was insufficient information about the long-term dangers of estrogen and P&G did not have an adequate post-approval surveillance plan. Combined estrogen and testosterone therapy remains controversial as little research has been done on long-term effects on women, especially if they start taking it in their twenties and thirties.[xii]

- **Current Status:** Intrinsa was denied FDA approval in 2004. It was approved in 2006 in the EU for pre-menopausal women who had undergone hysterectomies, but its makers withdrew it in 2012, for marketing reasons.[xiii]

7) Libigel (testosterone gel) by BioSante

- **The Hype:** Its makers claim it is a "revolutionary step forward in improving women's female sexual health." It was an early (<2005) testosterone product, but never had great data.[xiv]
- **Problem:** Disappointing results from Phase III trials in 2011 due to large placebo response.
- **Current Status:** BioSantePharma's website is gone as of 2014 after merger with Ani Pharma.

8) Lorexys (buproprion and trazadone) by S1 Biopharma

- **The Hype:** According to its makers, "Lorexys targets hypo-active sexual desire disorder, the most common type of female sexual dysfunction."
- **Problem:** Hypo-active sexual desire disorder is no longer in the DSM5. Both components, used as antidepressant and antianxiety medications, have severe side effects in some patients.
- **Current Status:** Currently in Phase 2a clinical trials. The FDA has granted Lorexys 505(b)(2) status because its components already have safety records.

9) Lybrido (testosterone + sildenafil)/ Lybridos (testosterone + buspirone) by Emotional Brain

- **The Hype:** The announcement of phase III clinical trials of both drugs caused Dr. Irwin Goldstein to declare, "2013 is the year of the woman."[xv] In a New York Times interview, the creators of Lybrido are concerned about it being too effective, potentially spurring bouts of "female excess" and "crazed binges of infidelity."[xvi] Dr Andrew Goldstein bragged, "You want the effects to be good but not too good."
- **Problem:** Studies so far do not support a clinically meaningful benefit as compared to placebo, and recent publications in J. Sex Med have been criticized as being based on flawed methodology and failures to declare conflicts of interest.[xvii]
- **Current Status:** In March, 2013 an application for further testing for Lybrido and Lybridos was made by its makers, Emotional Brain, a company based in the US and the Netherlands.

10) Osphena (selective estrogen-receptor modulator) by Shionogi and QuatRx

- **The Hype:** Osphena mimics estrogen to treat symptoms of 'vulvo-vaginal atrophy,' the thinning of vaginal tissue caused by a reduction in estrogen levels.[xviii] It is no surprise that with the approval of Osphena, terminology for 'vulvo-vaginal atrophy,' a contested diagnosis to begin with, has been broadened under the label 'genito-urinary syndrome of menopause.' While Osphena is entirely different from Viagra, there were numerous headlines like: "Pharma's race for a 'pink Viagra' finally has a winner, and the promises for it are grand."[xix]

- **Problem:** The 'vulvo-vaginal atrophy' diagnosis is controversial as many menopausal women experience it as a 'normal' part of aging. The 'significant improvement' with Osphena is based on two studies funded by manufacturer including women who self-reported their "most bothersome symptom" (MBI) as "vulvovaginal dryness." Over 12 weeks, 806 and then 605 women experienced improvement of less than half a percent in 'MBI' compared to women taking the placebo. Side-effects and risks included blood clots, urinary tract infections, cancer, stroke, increased instances of hot flashes, and yeast infections. Due to Osphena's similarity to estrogen, critics have also expressed concern over potential off-label use as menopausal HRT.
- **Current Status:** FDA approved for the treatment of menopausal vulvo-vaginal atrophy as of March, 2013.

11) Tefina (testosterone) by Trimel Pharmaceuticals

- **The Hype:** In May, 2012, Trimel announced a Phase II study of 240 U.S. patients, with sites in Canada and Australia to follow. The success of Tefina, an intra-nasal, gel testosterone, will be measured by "the increase in the occurrence of orgasm compared against baseline levels."[xx] During a CBC radio interview, when the Australian lead investigator Dr. Susan Davis was asked about testosterone safety issues raised in the Intrinsa trial, she claimed there were "no androgen side effects" associated with Tefina, even though clinical trials were hardly underway. Of critics and skeptics she stated, "It is a sexist and inappropriate concept to say it's not an appropriate drug for women […] maybe they (the critics) have a problem. Maybe they're frigid."[xxi]
- **Problem:** Barbara Mintzes, an independent drug reviewer also interviewed by the CBC, pointed out that androgen drugs are always treated as 'category X drugs' for pregnancy and will therefore always be considered to have risks.
- **Current Status:** Clinical trials have been approved by regulators in Canada and Australia. Phase II is now underway.

12) Viagra (sildenafil citrate) by Pfizer

- **The Hype:** Early discussions of FSD, using language such as "vaginal engorgement insufficiency" and "clitoral erectile insufficiency, explained women's sexual problems as vascular issues best treated by a vascular, Viagra-like drug."[xxii]
- **Problem:** Pfizer could not prove any meaningful benefit to women's sexual arousal. Trials by independent researchers showed benefits to women with spinal-cord problems, but Pfizer didn't choose to pursue the small market.[xxiii]
- **Current Status:** Not approved for FSD but still used for this purpose off-label (see below).

13) Drugs Not Approved for FSD But Prescribed Off Label:

- **The Hype:** Physicians frequently prescribe to women Viagra, Levitra, Cialis, and testosterone replacements such as AndroGel and Testim approved for use in men. A definitive medical textbook on FSD edited by I. Goldstein et al. recommends off-label drugs, prescribing testosterone for "low libido," estrogen for "diminished arousal," and "systemic agents that are dopamine agonists, such as buproprion" for "low libido, orgasmic function, and sexual function."[xxiv] Drs. Jennifer and Laura Berman directly encourage women to take Viagra off-label in their best-selling books, stating in one book, "a vasodilator like Viagra or one of the other drugs like it (Cialis or Levitra) should be considered if you have low arousal, especially if your doctor thinks the problem may be caused by nerve damage, aging, lack of use, or hormonal deficiencies."[xxv]
- **The Problem and the Current Status:** These drugs have not been approved for FSD. Efficacy and safety has not been established.

14) Miscellaneous Compounds In Development:

- Prasterone
- TGWOO-AA
- TBS-2
- PL-6983
- S1-307
- S1B-3006

Conclusion:

A pharma-funded campaign is currently urging the FDA to 'Even the Score' by approving FSD drugs for women. However, sexism at the FDA is not the reason that FSD drugs have failed so far. Poor efficacy, a strong placebo effect, and valid safety concerns have plagued all the FSD drugs developed thus far. There are many reasons that these drugs may have not been effective in increasing women's sexual enjoyment, chief among them the heterogeneity of female sexuality and, of course, research demonstrating that sexual problems are mostly shaped by interpersonal, psychological, and social factors. Nevertheless, industry-sponsored physicians and popular media continue to drum up great hype over the possibility of a 'pink Viagra.'

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[i] Of course this is incomplete. The public does not know the half of what's been going on!

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[xiii] http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2012/06/WC500128837.pdf

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