Clinical Research Trials and the Treatment of Hypoactive Sexual Desire Disorder

A thesis submitted to the faculty of
San Francisco State University
In partial fulfillment of
The Requirements for
The Degree

AS
36
2017
HMSX
.A48

Masters of Arts
In
Sexuality Studies

By
Rebecca Alvarez
San Francisco, California
May 2017

Copyright by
Rebecca Alvarez
2013, Updated 2017

CERTIFICATION OF APPROVAL

I certify that I have read *Clinical Research Trials and the Treatment of Hypoactive Sexual Desire Disorder* by Rebecca Alvarez, and that in my opinion this work meets the criteria for approving a thesis submitted in partial fulfillment of the requirements for the degree: Master of Arts in Sexuality Studies at San Francisco State University.

Colleen Hoff, Ph.D.
Director of the Center for Research and Education on Gender and Sexuality (CREGS)

Rita Melendez, Ph.D.
Associate Professor of Sexuality Studies

Clinical Research Trials and the Treatment of
Hypoactive Sexual Desire Disorder

Rebecca Alvarez
San Francisco, California
2013, Updated 2017

Abstract: Although the concept of a female sexual dysfunction market has been a popular area of research for the last decade, there is only one drug approved by FDA for the treatment of low desire among women in the United States. Despite advancements in the understanding of psychopharmacology and pathways involved in women's sexual response, pharmaceutical companies continue to face unique challenges when investigating treatments for low desire. The current framework used to define and measure low desire is still under debate and thus makes it challenging to properly measure the efficacy of a proposed drug treatment. This review, along with an analysis of the clinical outcomes of previous drug trials not approved by FDA for the treatment of HSDD, aims to provide comprehensive recommendations for the research and treatment of low desire that could improve future drug trial designs, develop necessary data to support approval of effective treatments and ultimately help the millions of women seeking treatment.

I certify that the Abstract is a correct representation of the content of this thesis.

_____ 5/22/17

Chair, Thesis Committee Date

Table of Contents

Introduction 1
Female Sexual Dysfunction 1
The Drug Approval Process 3
Hypothesis 6
Classification of Low Desire 7
Conflicting Theoretical Frameworks of Low Desire: Medical Vs. Feminist Approach 7
Definitions 9
Etiology 13
Current Treatment of Low Desire 13
US and International Prevalence Rates 14
Female Sexual Response Models 15
Linear Model: 16
Circular Model: 17
Non-Linear Model: 17
Flibanserin and Intrinsa: Previous Clinical Drug Trials in HSDD 18
Methods 20
Analysis 21
Intrinsa 21
Clinical Outcome Data 24
Flibanserin 29
Clinical Outcome Data 33
Others Drug Trials 38
Discussion and Recommendations 39
Clinical Trial Enrollment Must Be Diverse and Represent the Intended Population 41
Additional Research on the Placebo Response 42
Conclusion 44
References 46

Introduction

"There is a medical need for development of drugs with a favorable benefit-risk profile to treat women with sexual dysfunction."
-US Food & Drug Administration Guidance

Female Sexual Dysfunction

Female sexual health, including sexual function and dysfunction, has gained greater recognition by the academia, medical communities, and the pharmaceutical industry within the past two decades. After the US Food and Drug Administration (FDA) approved Pfizer's Viagra for the treatment for male erectile dysfunction (ED) in April of 1998, pharmaceutical companies began turning their attention to concomitant women's sexual health issues and potential pharmacologic treatments that may enhance sexual function in women. Despite the heightened interest in the field of female sexuality and motivation to find potential pharmaceutical interventions, optimal treatment for low desire remains ambiguous with few evidence-based treatments available (Matheiu & Milne, 2008) and only one FDA approved pharmacological treatment in the United States.

Female Sexual Dysfunctions (FSDs) are classified by the Psychiatric community in the Diagnostic Statistical Manual of Mental Disorders (DSM). The DSM-IV classified low desire as Hypoactive Sexual Desire Disorder (HSDD) in 2000. In an attempt to correct, expand and clarify the different sexual dysfunction diagnoses and their respective criteria, low desire became classified as Female Sexual Interest/Arousal Disorder (FSIAD) per the latest version in the DSM-V[1] as of 2013. Despite this evolution of terminology and criteria developed for diagnosis in the DSM, all New Drug Application submitted for low desire to date have been under the HSDD classification. To account for the changing classifications, many researchers and agencies chose to use terms that more simply identify low desire, low arousal or low sexual interest, separately; a general concept of low sexual desire is thus still recognized.

---

[1] The DSM-V was released in May 2013 and classifications of FSD were revised. FSDs are not classified as Female Sexual Interest/Arousal Disorder and Genito-Pelvic Pain/Penetration Disorder.

In recent decades, women have begun a movement to prioritize their sexual health and take notice of their sexual desire levels (Person, 1999). Ever since the 1960's when the development of birth control allowed women to enjoy sex for pleasure, they began to discover and voice a heightened importance of pleasure in sexual relationships. Today, both pleasure and sex have become much more important factors in women's self-assessment of personal happiness and the idea of "good sex" has become one of the adult women's expectations in life (Schwartz & Young, 2009). However, recent studies show that low desire has continued to be the most common sexual complaint among women both in the United States and internationally (Healthy Women, 2009). In the US, the rate of diagnosable HSDD or FSIAD is reported anywhere from 2.3% - 12.5% among women and general low desire rates are even higher between 26.7% to 52.4% (West, 2008) depending on the age, menopausal state and diagnostic criteria used. The majority of women who report low desire also report wanting a treatment solution to increase their sex drive (Healthy Women, 2009).

Based on this information, pharmaceutical companies have a clear incentive to increase Research and Development (R&D) efforts and spark pharmacological advances in the female dysfunction space. Drug companies are also the primary influencers in what is called "the medicalization of sexuality", which represents an intellectual trend whereby medicine, with its distinctive ways of thinking (i.e. models and values) comes to exercise practical and theoretical authority over particular health sectors (Tiefer, 1996). With greater advances in biological research in sexual function stems the classification of new illnesses or dysfunctions, which in turn, allows sponsors to develop, test and ultimately submit New Drug Application for FDA's review. This biomedical conceptualization of sexual dysfunction, however, has also created disagreement among sexuality researchers who claim the pharmaceutical industry is "over-medicalizing" sexuality, especially for women.

The feminist approach in sexuality argues that there is an inherent problem in trying to over-simplify diverse areas of human behavior within a traditional medical paradigm. The idea is

that the medicalization of female sexuality ignores the complex social aspects that influence a woman's sexual desire, interest or arousal. The idea of "normal" desire can thus be misleading to women because it pathologizes sexuality that does not fit the medical definition of normal and ignores the natural variability among women. For example, a medical model of sex fails to address reasons why women may not want to have sex that will unlikely improve with medication (e.g. fatigue, problems with a sexual partner, low self esteem or discontent with their body).

The Drug Approval Process

The drug development and approval process can be viewed as the intersection of science, medicine, politics and business. A sponsor company will work closely with physicians and members of the medical community to conduct various phases of clinical testing of a new drug. Sponsors must collaborate with FDA through a series of phases in order to test a drug treatment, and ultimately have it approved in the United States. The goal of clinical drug trials is to predict the likely risk-benefit outcomes when the drug enters the general population for clinical use (Goldstein, Meston, Davis & Traish, 2006) and obtain approval by FDA for it's commercial sale.

Traditionally, FDA has three major roles in the clinical testing of a drug. The agency enforces a set of guidelines and regulations called Good Clinical Practices (GCP) to define the responsibilities of the key figures involved in the trial. Secondly, FDA protect the rights and safety of subjects participating in the trials by 1) ensuring subjects are not exposed to unnecessary risks 2) ensuring that subjects are exposed to the least possible risk given the benefit anticipated from the experimental therapy and 3) ensuring all subjects are provided with a proper informed consent before entering a trial. Lastly, FDA works with sponsor companies to help decide the nature and quantity of clinical data necessary to establish a drug's safety and effectiveness. Usually a sponsor will indicate the process by providing FDA with its optimal and comprehensive global development plan for a new drug (100). At each subsequent meeting, this plan is reviewed

and updated to refine the sponsor's recommended plan of study for the initial phases of clinical trial testing.

To ensure drug sponsors design clinical trials and are streamlined with current thinking in the specific therapeutic area, FDA has developed and published dozens of general clinical trial guidances as well as therapeutic area-specific clinical guidelines. These documents are updated periodically; in HSDD there have been two therapeutic-specific guidances: *Female Sexual Dysfunction: Clinical Development of Drug Products for* Treatment in 2000 which was later updated in 2016 as Low *Sexual Interest, Desire, and/or Arousal in Women: Developing Drugs from Treatment.*

Although the design of a clinical trial will differ significantly from one drug and disease state to another, sponsors must undergo similar phases of clinical investigation. There are four phases in clinical drug trials, three of which must be completed before a sponsor can apply for approval. Phase I represents the first exposure in humans of a novel agent or device and is typically conducted in healthy individuals. The tolerability of the drug is assessed at various doses and placebo groups are also involved to ensure there is superiority in the drug group. Phase II focuses on the efficacy assessment of the drug and aims to identify an effective dose range to be evaluated in phase III. Phase III tests the drug on a larger scale, usually tested in multi-center, randomized, prospective studies with two or more dose levels of the study drug and a double-blind placebo control condition; the primary objective in this phase is to demonstrate therapeutic benefit. Once this phase is completed, a drug company files a New Drug Application (NDA) where all clinical data are presented to FDA to review. FDA then reviews all data to determine whether results are clinically significant and show that the benefits outweigh the risks in the intended treatment population. A formal review meeting with the Sponsor and FDA Advisory Committee is held to review the clinical data and address any areas of concern.

Phase IV involves final studies either during the approval process or subsequent to approval including post-marketing surveillance studies which are designed to expand the safety

database through long-term tracking of patients after the drug has been approved (Mathieu, 2008). Phase IV studies are designed to increase the understanding of the overall treatment profile in the target population (Goldstein et al., 2006).

To date, there have been three NDAs submitted to FDA for approval of HSDD drug treatments, two of which have been unsuccessful. Both drug companies used the recommendations outlined by FDA's 2000 Draft Guidance for Industry when developing the clinical trial. In 2004, Procter and Gamble was the first drug company to submit an NDA for approval. The company tested a new testosterone patch (NDA 21-769, 2004) treatment for post-menopausal women with HSDD. The results of this study were found to be statistically significant, but the drug was ultimately not approved by FDA because the agency was not convinced the benefits of the drug outweighed the risks for the intended population. Boehringer Ingelheim was the second company to submit an NDA for the treatment of HSDD in 2010 when it proposed a new oral drug tablet (NDA 22-526, 2010) for pre-menopausal women with this condition. The results of this drug were mixed (statistically significant for one of two co-primary endpoints), but the high placebo effect led FDA to vote against approving the drug. A closer look at the study design provided later in this paper will identify the specific concerns FDA had with each drug.

In 2015, Sprout Pharmaceuticals submitted data for a new trial conducted with the previous formulation of Flibanserin, now called Addyi. The company was able to show statistical and clinical significance and also addressed FDA's previous concerns with the placebo group. Addyi was awarded approval on August 18th, 2015 and is currently the only approved drug on the US market that improves low desire.

Hypothesis

A disproportionate number of drugs are approved for men's sexual dysfunction compared to women, 26 to 1, suggesting why major improvements need to be made in how low desire is defined, researched and treated among women. I examine current frameworks for the classification of low desire along with the current sexual response models used in various fields to address this condition. Additionally, I provide a case analysis of the study design, methods and safety results of the two pharmaceutical drug trials rejected by FDA. By examining the shortcomings of previous drug trials and discussing critiques, this paper provides a summary of new and comprehensive recommendations for the treatment of low desire that could improve future drug trial design, develop necessary data to support approval and ultimately continue to help the millions of women who continue to seek effective treatments for low desire.

Classification of Low Desire

Research and theory in the field of female sexual dysfunction are evolving rapidly. In recent decades, there have been major advancements in the biologic factors of female sexual dysfunction and our understanding of how psychophysiological and pharmacology affect sexuality (Goldstein et al., 2006). Some of the leading experts in female sexuality research agree that pharmacological approaches to sexuality within the last decade, along with the "medicalization" of sexuality by those who take issue with the emphasis on pharmaceutical or medical solutions to sexual problems, are controversial and complex.

Conflicting Theoretical Frameworks of Low Desire: Medical Vs. Feminist Approach

Medicalization is a social process through which a human experience or condition is culturally defined as pathological and treatable as a medical condition. Examples of medicalization can be seen in all facets of our current healthcare system: obesity, alcoholism, childhood hyperactivity, etc. (Tiefer, 1996). In the realm of sexual dysfunction, medicalization was first seen in male indications. In the 1980's and 1990's a new classification of sexual dysfunction was emerging as a subspecialty in the field of urology. When Viagra was approved in 1998, the media took on a fascination with medical language and new technologies in erectile function and dysfunction. Today, there are twenty-four drugs that have been approved by FDA for male sexual dysfunction, with erectile dysfunction being the most common indication.

It was not long before attention turned to a similar medicalization of female sexual dysfunction. Experts in both Urology and Obstetrics/Gynecology have classified various FSDs for women: low desire, low arousal, orgasm dysfunction and pelvic pain disorder. Most physicians who specialize in sexual medicine pride themselves on state-of-the-art, evidenced-based, clinical management for sexual health concerns. However, due to the intricacy of the female sexual response, which will be discussed in the next sections, treating sexual dysfunctions

in women is more difficult than it is for men, leaving women frustrated with the trial-and-error approach to their care.

The primary opposing framework to the medical model is the feminist approach, which aims to deconstruct FSD. Leonore Teifer is one of the leading scholars in female sexuality whose aim is to critique the medical model of female sexual dysfunction, including HSDD, FSIAD and other constructed definitions of low desire. In 1999, she, along with a team of women's sexuality researchers, developed an activist campaign, *The New View Campaign* to explain how and why constructs of sexual dysfunction nomenclature could be problematic and an inaccurate representation of the complex issues women face in sexuality throughout their life cycle.

The arguments proposed by Leonore Tiefer and similar researchers highlight why female sexuality is complex and why no single sexual function model would ever fit the entire female population. In her book, *A New View of Women's Sexual Problems*, Tiefer brings up several issues that speak to the complexities of female sexuality[2] and the potential reasons why medical practitioners have not questioned the legitimacy of the DSM diagnostic categories on sexuality. For example, much of the medical model of sexuality constitutes a "successful sexual event" by the presence of orgasm. She challenges the orgasmocentric construction of sexual satisfaction, which is valid and supported by the scientific literature that shows up to 80 percent of women do not orgasm during sex with penetration alone and up to one in three women have trouble reaching orgasm at all (Tiefer, 1996). Despite this information, the FDA, in an attempt to provide guidelines, advised sponsors to design clinical trials with a count for sexual events that are rated as "successful" when orgasm is present. Although physicians, like feminists, have been aware of the controversies surrounding the DSM categorization schema for mental health for almost twenty years, research shows that physicians do not adequately address their patients' sexual

[2] She discusses several concerns with the American Psychiatric Association's nomenclature for women's sexual problems, including: the false equivalency between men and women, the lack of acknowledgement of relational aspects of women's sexuality (e.g. desires for intimacy, wishes to please a partner, or in some cases, wishes to avoid offending, losing or angering a partner), and ignoring differences among women.

complaints. Health care providers don't broach sexuality issues because they lack the training and skills to deal with these concerns, are uncomfortable with the subject, fear offending the patient, have no treatments to offer or feel constrained by time (Berman, Berman, Felder, Pollets, Chhabra, et al., 2003). Additionally, Tiefer explains that physicians rarely need to use the DSM diagnostic code, as it is not required for billing purposes, and therefore "blandly accept the DSMs categorization of sexual dysfunctions", although they make little use of it. (Tiefer, 1996)

The concerns brought forth by women activists and sex researchers, are valid and should be discussed by all those involved in the classification, research and treatment of female sexual problems, including low desire. My position supports the idea that increased collaboration between feminist researchers and the medical community (including the American Psychological Association, which is responsible for the DSM's definition and classification of female sexual dysfunctions) could help create a more comprehensive approach to treatment of low desire among women. Dr. Gina Ogden, a feminist scholar, comments on the New View campaign, "I do want to register one reservation about the perspective of the New View. I cannot help feeling there must be a way to reframe the national understanding of women's sexuality other than by recategorizing women's sexual problems". I agree with Dr. Ogden in that activists of women's sexuality research and the drug industry should work together to reframe the understanding of female sexual complaints, including low desire. By examining the current thinking on FSD and HSDD (i.e. etiology, definitions, sexual response models) along with weaknesses of previous drug trials, I hope to bridge the large gap between medical classification and feminist perspectives on the treatment of low desire among women.

Definitions

When the medical and psychological communities classify low desire as a 'female sexual dysfunction' the most common definition used is from the American Psychiatric Association's Diagnostic for Mental Disorders under the classification of *Hypoactive Sexual Desire Disorder*

(DSM-IV-TR, 2011), or most recently Female Sexual Interest/Arousal Disorder (DSM-V, 2013). The definition of HSDD is defined as "persistent or recurrent deficiency or absence of sexual desire or sexual fantasies", the disturbance must cause "marked distress or interpersonal difficulty". The DSM-IV-TR instructs the clinician to determine if the lack of sexual fantasies or desire for sexual activity are clinically significant. If determined so, the diagnosis of HSDD may be provided, given that the lack of sexual desire is not better accounted for by another medical condition or medication (DSM-IV-TR, 2011). In the DSM-V, FSIAD is defined as "lack of, or significantly reduced, sexual interest/arousal" manifested by at least three qualifying criteria for at least six months and occurring in 75% - 100% of sexual encounters (DSM-V, 2013). The diagnosis from version IV-TR to V (Table 1) was improved by updating the criteria to be more precise and provide a time frame and frequency required to be classified as a dysfunction.

Table 1: Sexual dysfunctions in DSM-IV-TR compared to DSM-V

Female Dysfunctions Classifications	
DSM-IV-Diagnoses	**Changes in DSM-V**
Female hypoactive desire disorder	Female sexual interest/arousal disorder
Female arousal disorder	
Female orgasmic disorder	Unchanged
Dyspareunia	Genito-pelvic pain/penetration disorder
Vaginismus	

The evolving nature of classifications and definitions shows progress in the field, but can make conducting research on low desire difficult because it requires the use of different clinical methodologies and assessment tools[3] (Brotto, 2009). For pharmaceutical companies developing and testing new drugs, the changing definitions are problematic because they leave room for varied medical interpretations at the time of review for approval by FDA.

[3] Epidemiological studies assess the prevalence of low desire in women differently. Populations vary in age (including menopausal state), relationship status (including variance in sexual relationships status –some studies did not require women to be sexually active while others required female participants to be in a heterosexual, committed and sexual relationships for at least three months), method of assessment (in person interviews, computer assisted telephone interviews, questionnaires,) distress measures (some studies did not measure distress levels that would help indicate whether the female participants exhibited symptoms of HSDD).

Another complexity of having evolving classifications is the overlap among diagnostic categories of low desire. The individual disorders in FSD (female sexual interest/arousal disorders, orgasm disorders and vagina pain disorders) correspond to problems in different phases of sexual function. However, problems affecting one phase often interact with other phases in a complex fashion (Laumann, Paik & Rosen 2011). Difficulties in the characterization of the disorder have hampered the development of a diagnostic framework of female sexual dysfunction, and have created problems in the delineation of clear endpoints and outcomes in clinical research.

Critics of the DSM's definition of HSDD point out several flaws. The suggestion that "lack of fantasies" in Criterion A for HSDD was problematic for overpathologizing women (Brotto, 2009). Additionally, the findings on the link between fantasies and sexual desire were few and mixed (Meana, 2010). The DSM-IV-TR and DSM-V also failed to distinguish the difference between desire and arousal[4] as well as the differences between spontaneous and responsive desire, information researchers have found in psychophysiological studies.

Another critique of HSDD is the ability of the clinician to define whether the lack of sexual fantasies and desire for sexual activity are clinically significant. Studies have shown that sexual trainings in medical school and residency programs vary greatly (Byers, 2011). In a study that looked at medical students' confidence with handling sexual concerns from their patients, Miller & Byers (2008) found that graduate students in clinical programs identified "lack of preparation to assess and treat sexual issues" as a serious lack in their clinical training that negatively affected their confidence in treating sexual issues.

Several organizations brought forth proposals to improve current definitions of female sexual disorders, including HSDD, for the DSM-V (Basson, Leiblum, Brotto, Derogatis, Fourcroy et al., 2004). The American Foundation for Urologic Disease (AFUD) proposed to rename the disorder

---

[4] Low desire is characterized as a lack of interest in sex and should be differentiated from sexual arousal, which is the physiological response when in the presence of a sexual stimuli.

as "Women's sexual interest/desire disorder" with the following criteria: "There are absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies and a lack of responsive desire motivations (here defined as reason/incentives) for attempting to have sexual arousal are scarce or absent. The lack of interest is considered to be beyond the normative lessening with the life cycle and relationship duration" (Basson et al., 2004). The American Psychological Association decided to use the proposed naming convention but include additional criteria.

With the updated definition of low desire classified in the DSM-V, attempts to merge sexual disorders of desire and arousal were based on a large body of research that shows a high comorbidity of the two are demonstrated in women and suggests that the separation may have been artificial. However, other experts argue that the new criteria excluded an excessively large number of low desire and arousal patients. The merger of the two disorders is viewed as counterproductive because patients with HSDD often present with incomplete loss of receptivity and are therefore less likely to be included in the new criteria. Moreover, women who would previously meet criteria A for sexual arousal disorder in the DSM-IV version, may not meet the criteria of the merged version in the DSM-V.

Several organizations have provided alternative definitions of low desire. The World Health Organization, (WHO), International Classification of Diseases, (ICD) states "Sexual dysfunction, not caused by organic disorder or disease. Sexual dysfunction covers the various ways in which an individual is unable to participate in a sexual relationship, as he or she would wish. Sexual response is a psychosomatic process and both psychological and somatic processes are usually involved in the causation of sexual dysfunction. Loss of sexual desire is the principal problem and is not secondary to other sexual difficulties, such as erectile failure or dyspareunia." (Emerson, 2010).

Etiology

Desire in women involves interactions between a variety of neurotransmitters, sex hormones and psychosocial factors. Our current understanding of risk factors for low desire is incomplete, and as Clayton (2010) points out, much of the evidence concerning the etiology of low desire comes from epidemiological studies that identify associations with low desire, rather than the cause-and-effect relationships.

Researchers have identified several conditions that may impair the anatomic and physiologic substrates of a woman's sexual response cycle and may be a potential source of dysfunction (Goldstein et al., 2006). Changes in the following systems may negatively impact sexual function in women: endocrine, reproductive, urogenital, vascular, muscular and nervous system. Other factors, such as surgery[5], general health, drugs, lifestyle, communication with a sexual partner or the partner's sexual function may also contribute to low desire in women. Other variables that may affect sexual desire include the aging process, menopause, the presence of co-morbid disease, oral contraceptives and other medications that have been known to lower libido (Clayton, 2010). Thus, low desire can be caused by several factors, and its diagnosis among women is usually multi-faceted.

Current Treatment of Low Desire

Until 2015 when FDA approved the first drug for HSDD, Flibanserin (Addyi) –and so far, the only approved drug in the US —treatment for low desire was, and continues to be, commonly treated by primary care physicians. However, even prior to it's approval, physicians commonly recommend a variety of off-label hormonal therapy (i.e. off-label testosterone injections), sex therapy, cognitive behavior therapy, physical therapy, or other prescription drugs that help with comorbidity of other conditions (i.e. antidepressants, exercise/diet, thyroid

[5] This includes surgical procedures that alter a woman's hormonal levels.

regulation, etc.). Sometimes over the counter (OTC) items such as lubricants or novelty items such as sex toys can be recommended as well.

Studies that have examined women's attitudes and behaviors towards their sexuality including how they deal with sexual health issues have found that few visit their health care provider to discuss the issue. A 2009 study by the Association of Reproductive Health Professionals (Healthy Women, 2009)[6] examined 1,200 women's attitudes and behaviors and found that 39% did not take any steps to "fix" or treat the condition, 38% talked to their partner and only 18% visited their health care provider[7] (Healthy Women, 2009). The juxtaposition of women not discussing sexual concerns regularly with their healthcare provider along with the high prevalence rates reported in the literature suggest that sexual health is often not discussed and thus often left untreated.

US and International Prevalence Rates

There are many confounding factors in assessing prevalence of low desire, HSDD or FSIAD among women due to the variability in assessment tools and methodologies use to determine if a woman meets criteria (Emerson, 2010). The populations assessed also vary by age, menopausal state and relationship status (Brotto, 2009). Some studies look at desire as a general concept among all females, while others simply look at sexually-active post-menopausal women in committed relationships.

In the US, low desire varies from 24-36% and HSDD varies from 8-12% (Brotto, 2009; Clayton, 2010; Emerson, 2010; Mulhall, King, Glina & Hyidsten 2008). Internationally, the Global Study of Sexual Attitudes and Behaviors (GSSAB), an international survey of various aspects of sex and relationships among adults found a prevalence of 26-43% for low desire in their sample of 13,882 women from 29 countries (Meana, 2010). Although this paper examines

---

[6] ARPH partnered with Harris Interactive, a private research group that conducts internet-based market research.

[7] Of the remaining women in this sample, 16% looked for information on the web, 14% "did something else", 13% read books or articles about the condition, 11% talked to family or friends, 6% took over-the-counter supplements, 3% used herbal remedies, 3% took prescription medication, 1% visited a therapist.

the population of woman in the US, the prevalence of low desire is clearly a world-wide sexual health concern among women.

Other studies have also assessed women's attitudes and perceptions of their sexual health to determine the impact low desire has on their overall well-being and quality of life. One recent study found that 4 in 5 women say sex is important to extremely important to their relationship satisfaction, however 30% of women reported they were not satisfied with their sex lives (Healthy Women, 2009). Thirty-six to 45% of women said they had experienced a lack of desire in sexual activity and of these women, two-thirds said it had a negative or very negative impact on their sex lives (Healthy Women, 2009). In general, women with sexual issues reported a negative impact to their health in the form of increased stress and a feeling of being depressed. Some women also reported sleep problems, weight gain/loss, difficulty concentrating and other physical health issues. Low desire can thus have a negative impact on several aspects of female physical and mental well-being and negatively impact her quality of life (Mulhall et al., 2008).

Female Sexual Response Models

The medicalization of sexuality is most commonly associated with the first female sexual response model developed by Masters and Johnson in the 1950's, which aimed to track the physiological process of the sexual response cycle in order to classify and treat deviations from the "normal" sexual response cycle (Clayton, 2010). Since then, several advancements have been made in our understanding of female sexuality, in part by new research on age-related changes, hormones, reproductive events, the impact of relationships as well as the importance of mental well-being and other psychological factors that may play a role in the female sexual response. However, despite some of these substantial improvements in these models over the last 50+ years, female sexual response models tend to be overlooked by FDA and the drug industry when designing and evaluating treatments for low desire. Dr. Raymond Rosen, a leading scholar in sex research and clinical trials, acknowledges that recent advancements in classification of women's

sexual dysfunction have started to take place, but argues "many of the challenges associated with conducting clinical trials for female sexual dysfunction may be attributed to the lack of a clearly defined, empirically supported model of female sexual response and satisfaction".

A closer examination of female sexual response models proposed over time helps identify advancements in the framing of female sexuality and highlight the importance of multiple external factors that can impact a woman's sexual desire.

Linear Model:

Currently, diagnostic categories of women's sexual dysfunction are based on the conceptualization of sexual response depicted by Masters and Johnson in the 1960's (Meana, 2010). Masters and Johnson published two well-known volumes that provided an extensive and detailed portrait of how the human body responds to sexual stimulation, *Human Sexual Response and Human Sexual Inadequacy*, including their well-known four-stage model of the sexual response cycle[8]. Among their most notable findings were the similarities among male and female sexual physiology, the role of vaginal lubrication in female sexual arousal, and the physiology of multiple orgasms (Goldstein et al., 2006). This model is considered pioneering in the field of sexual health as it provided a biologic framework for diagnosing phase-specific diagnoses of various sexual dysfunctions.

However, critiques of this sexual model have voiced concerns, claiming that it is outdated and cannot be generalized to all women. Masters and Johnson's model failed to include a desire phase (West, 2008) and does not take into account non-biologic experiences such as pleasure and satisfaction or place sexuality in context of an intimate relationship. Further, this model erroneously assumes that both men and women follow the same, linear pathway, and thus pathologizes certain behavior among women that might otherwise be considered "normal" with properly designed research studies that account for gender differences. Many women do not

[8] The model includes four phases: excitement, plateau, orgasm and resolution. Each phase is associated with specific genital and extragential changes. These detailed descriptions included changes in blood flow, vaginal lubrication and nipple enlargement (Goldstein et al., 2006).

move progressively and sequentially through the phases, or may not even experience all phases. Additionally, Masters and Johnson viewed orgasm as the goal of sexual activity (Masters & Johnson, 1966). Current research has found that not all women agree with this[9]; although orgasm has several health benefits that foster feelings of connectedness, data show that women are more sexually satisfied by the stimulation and an increase in intimacy, not necessarily the experience of orgasm itself (Meana, 2010).

Circular Model:

Later models developed in the 1980's and 1990's (e.g. Whipple and Brash-McGreer) modified Masters and Johnson's original model to include desire and reflect a circular model (ARHP, 2008). Whipple and Brash-McGreer's model, for example, modified a model proposed by Reed, which comprises four stages: seduction (including desire), sensations (excitement and plateau), surrender (orgasm) and reflection (resolution), to demonstrate that pleasant and satisfying sexual experiences may have a reinforcing effect on women. However, these models are still orgasm-centric and emphasize orgasm as the primary goal.

Non-Linear Model:

Rosemary Basson has proposed one of more recent models of female sexual response. Her model is non-linear and depicts women's sexuality as a highly contextual process that incorporates motivations other than sexual desire; her model includes the importance of emotional intimacy, sexual stimuli and relationship satisfaction (APHP, 2008). She aims to move away from a restrictive view that sexual dysfunctions are solely psychological or biological, but instead recommends factors such as psychosexual development, current context, as well as a

[9] The lack of distinction between male and female differences is problematic because it fails to address aspects of sexual health that are unique to women including hormonal changes with menses and menopause, pregnancy, etc. Also, the feminist prospective of women's sexuality argues that orgasm should not necessarily be viewed as the ultimate goal of sexual activity since there are multiple pleasurable aspects of sex that do not necessarily lead to orgasm.

comprehensive review of medical history to be included in the assessment before diagnosis (Hayes, 2011).

Despite advances in comprehensive female sexual response models, no model of female sexual response is consistently endorsed by all women (Basson, 2000) and critiques of the modern Basson model also exist (ARHP, 2010). For example, researchers have pointed out that desire does not necessarily precede subjective or genital arousal (Tolman, 1999). Furthermore, a study that assessed clinicians' familiarity with female sexual response models (Robinson, Munns, Weber-Main, Lowe & Raymond, 2010) indicated that 30% of health care providers are not familiar with any female sexual response model and less than 25% are familiar with a model other than Masters and Johnson (Robsinson et al., 2010).

The disconnect between clinician knowledge of the complexities of the female sexual response cycles –or even the basic, yet outdated model developed by Masters and Johnson –is problematic and one reason why the prevalence rates of HSDD diagnoses may vary greatly in the United States (Berman et al., 2003).

Flibanserin and Intrinsa: Previous Clinical Drug Trials in HSDD

FDA provides pharmaceutical companies with its recommendations outlined in the 2000 Draft Guidance, *Guidance for Industry Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment,* for developing clinical trials with HSDD indications. The guidance is intended to provide recommendations for sponsor drug companies when designing a trial, selecting the appropriate methodologies and setting appropriate outcome measures (Guidance: FDA, 2000). However, up until 2016 when FDA released an updated version of the Guidance, *Low Sexual Interest, Desire, and/or Arousal in Women: Developing Drugs for* Treatment, Sponsor companies had to work with often unclear or changing definitions and subsequent changes in measures and statistical analyses that assess these conditions.

Between 2000 and 2016, three NDAs were filed for drugs indicated for HSDD: two NDAs for Flibanserin and one for Intrinsa. In 2004, Proctor and Gamble submitted an NDA for a testosterone patch (NDA 21-769, 2004) for treatment of HSDD among surgically menopausal women receiving concomitant estrogen therapy. In 2010, Boehringer Ingelheim submitted an NDA for Flibanserin (Girosa) for the treatment of HSDD among premenopausal women. Neither study was successful in obtaining regulatory approval by FDA. In 2015, Flibanserin (renamed Addyi) submitted new clinical trial data in their NDA and obtained regulatory approval. The two rejected NDAs submitted for the treatment of HSDD will be examined in this paper.

Methods

After providing a critical analysis of the current framework and classification of low desire in the United States, I examined previous drug trials that were submitted to FDA for approval, but not approved. The case analysis was selected as the main method as it allowed me to take a closer look at the study design and outcome data of the two trials. I examined: the study objectives, overall study design, treatment groups, entry criteria and efficacy endpoints. To summarize key components of the trial design and endpoints, I created a protocol synopsis of each study and focused on the Phase III study data, as it reflects the target population and dose proposed for indication.

To enhance the case analysis, this paper combined briefing information during Advisory Committee meetings, Sponsor presentations during Panel, FDA presentations during Panel (including transcripts), questions for the Committee, open public hearing presentations and briefing documents from both the Sponsor and FDA. I discuss the strengths and weaknesses of each drug trial, focusing on FDA's commentary regarding areas thought to be unsubstantiated or lacking. Additionally, I provide recommendations for future drug trials in the sexual dysfunction space based on weaknesses pointed out by FDA, criticisms discussed in the literature review and other key factors in previous clinical trials.

Analysis

Intrinsa

Procter & Gamble Pharmaceuticals, Inc.'s Intrinsa, testosterone transdermal system (TTS) was tested and indicated for the treatment of Hypoactive Sexual Desire Disorder (HSDD) among women who were surgically menopausal and on concomitant oral or transdermal estrogen therapy. The objective of the study was to document the safety profile and efficacy of Intrinsa in producing a clinically meaningful therapeutic response after 6 months of usage. Although most of the FDA Advisory committee agreed that the study results showed clinically significant improvement, in a vote of 14 to 2 (votes for no and yes, respectively) FDA did not approve the patches because it claimed the trial was "inadequate" in assessing the long term safety. Panel members also raised serious concerns about the risks of cardiovascular disease and breast cancer associated with the drug (Moynihan, 2004; FDA Panel minutes, 2004).

Intrinsa is a transdermal testosterone patch delivering a dose of 300Mg per 24 hours that was applied at the abdomen or buttocks and replaced twice a week. Healthy women produce approximately 100 - 400mcg of testosterone per day, with about half of it derived from the ovaries. Testosterone levels begin to naturally decline among women after age 20 (Davison, Bell, Donath, Montalto & Davis, 2005) and have shown to decline as much as 50 per cent[10] after a hysterectomy (Judd & Lucas, 1974). The target population for this study were women who had undergone bilateral salpingo-oophorectomy (removal of the fallopian tubes and ovaries) and hysterectomy at least 6 months prior to screening, and thus most negatively impacted by low levels of testosterone. Decreased levels among women have been shown to have profound negative effects on sexual desire, arousal, orgasm, as well as general energy levels and well being. Increasing these levels via a transdermal patch was thus expected to increase sexual desire.

---

[10] The significant decrease in testosterone levels after a hysterectomy occurs within a few days of surgery. (58)

Data from seven trials (US, Canada, Australia, Europe) were submitted to FDA in 2004 for review. The trials were prospective, randomized, double blind, placebo-controlled multicenter trials. Two trials evaluated multiple dose levels (Study T96006: testosterone 150mcg/day or 300mcg/day; Study 1999068 testosterone 150mcg/day, 300mcg/day or 450mcg/day) and the five others evaluated women at 300mcg/day (Studies 1999092, 200113, 2001134, CMK030993 & Withdrawal study).

A protocol synopsis (Table 2) was created to provide a summary of the key aspects of the trials including protocol design and target population:

Table 2: Intrisa Protocol Synopsis

Sponsor Name	**Procter & Gamble Pharmaceuticals**
Proposed Indication	Intrinsa is indicated for the treatment of hypoactive sexual desire disorder (HSDD) in surgically menopausal women receiving concomitant estrogen therapy.
Investigational Products	Intrinsa (testosterone transdermal system) Transdermal patch. Thin, clear, oval matrix -type transdermal patch consisting of three layers: a translucent backing film, an adhesive matrix drug layer, and a protective release liner that is removed prior to application. Each patch surface is stamped with T001.
Dose	The recommended daily dose of testosterone is 300 micrograms. This is achieved by applying the patch twice weekly on a continuous basis. The patch should be replaced with a fresh patch every 3 to 4 days. Only one patch is to be worn at a time.
Objectives	Assess efficacy and safety of transdermal testosterone in surgically menopausal (SM) women with HSDD Primary endpoint: The primary efficacy endpoint was the change from baseline in the total frequency of satisfying sexual events at 24 weeks (sum of the 4 consecutive weekly frequencies on SAL questions 3 and 6 during Weeks 21-24). Secondary endpoint: Secondary endpoints were the sexual desire domain score of the PFSF and the PDS Score (Distress) at 24 weeks.

Clinical Trials & Design

Phase II and III trials had an 8-week pre-treatment baseline period followed by a 24-week randomized double-blind placebo controlled treatment period. All trials were multi-centered, employed validated instruments (SAL and PFSF) and incorporated an open label safety study after 25 weeks to monitor long term safety.

Phase III

1) 4 Phase III
2) Concurrent multinational trials (US, Canada, and Australia)
   a. 8-week pre-treatment baseline period
   b. 24-week randomized double-blind placebo controlled treatment period
   c. 1:1 treatment group to placebo group
3) Open label safety: weeks 25 → ongoing

Study Phase/ #	**N @ T dose** (mcg/day)	**N @ Placebo dose**	**Estrogen Therapy**	**Comments**
III 2001133	N= 283 @ 300	N= 279	Oral and transdermal	24-week pivotal
III 2001134	N= 266 @ 300	N= 266	Oral and transdermal	24-week pivotal
III: CMK030993 Exit interview study	N= 64 @ 300	N= 68	Oral and transdermal	Meaningful Rx benefit (MICD)*
III: Withdrawal study	N= 102 @ 300	N= 103	Oral and transdermal	Persistence of Rx benefit-withdrawal
Total	N= 715@ 300	N= 716		

Measures

3 Validated Instruments

1) Sexual Activity Log© (SAL©)
   a. 7-day recall weekly diary measuring sexual activity
2) Profile of Female Sexual Function© (PFSF©)
   a. 30-day recall measuring domains of sexual function
3) Personal Distress Scale© (PDS©)
   a. 30-day recall measuring distress related to lack of interest in sex

Eligibility Criteria

Key Inclusion criteria:

- Post-operative onset of low sexual desire with significant distress
- Bilateral oophorectomy and hysterectomy ≥6 months prior to study
- 20-70 years old
- Stable dose of estrogen (oral or TD) for ≥3 months prior to study
- Stable monogamous relationship for ≥1 year with partner present >50% of the time

Key Exclusion criteria:

- Serious medical conditions
- Malignancy
- - History of breast cancer or estrogen-depending neoplasia (prior to study entry)
- - Any other cancer (5 year)
- Depression or other psychiatric conditions
- Androgen or other confounding medications
- Dyspareunia
- Ongoing relationship disturbances

Statistical Analyses

All efficacy analyses are based on the change from baseline in the total sexual activity at Week 24, using the intent-to-treat (ITT) population and last observation carried forward (LOCF) for withdrawn subjects.

Clinical Outcome Data

Phase III trial data reflects the efficacy data in the proposed dosage of intended treatment (also referred to as Pivotal trials) and will thus be the primary focus of the case studies. Since Intrinsa was the first product submitted to the FDA for a proposed treatment in HSDD, the committee especially focused its review on the examination of the enrolled population to see if it accurately reflected the US population. It also closely reviewed outcomes for each endpoint as compared to baseline and all adverse events[11] reported throughout the trial. The efficacy data for Phase III is presented below as shown in the NDA submitted in 2004 to FDA and areas of weakness are highlighted.

Overall, P&G's data shows that all primary and secondary endpoints were statistically significant based on the ANCOVA analysis method (Table 3). Patients receiving the 300 mcg/day testosterone transdermal system experienced an increase in the frequency of total satisfying episodes per 4 weeks that was significantly greater than the increase for patients on placebo. Patients receiving the 300 mcg/day testosterone system also experienced an increase in sexual desire that was significantly greater than the increase observed in placebo patients. Distress associated with low desire was significantly decreased with 300 mcg/day testosterone treatment compared with placebo in both studies (NDA 21-769, 2004).

---

[11] An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. A serious adverse event (SAE) is defined as any untoward medical occurrence that at any does 1) results in death 2) is life-threatening 3) requires inpatient hospitalization or causes prolongation of existing hospitalization 4) results in persistent or significant disability/incapacity 5) is a congenital anomaly/birth defect or 6) requires intervention to prevent permanent impairment or damage.

Table 3: Changes in Total Sexually Satisfying Episodes, Sexual Desire and Personal Distress - Phase III Studies

Endpoint Study Number	Testosterone dose (mcg/day)	n	Baseline Mean[a]	Mean Change from Baseline at Week 24[a,b]	Efficacy Analysis Method	Results p-value[c]
	Frequency of Total SSEs					
	Phase 3 Trials					
2001133	0	273	2.94	0.98	ANCOVA	p=0.0003
	300	276	2.82	**2.13**		
2001134	0	255	3.19	0.73	Wilcoxon Rank Sum[b]	p=0.0010
	300	258	3.04	**1.56**		
	Sexual Desire Score [range 0 to 100]					
2001133	0	269	20.82	6.90	ANCOVA	p=0.0006
	300	269	19.79	**11.85**		
2001134	0	257	23.37	6.21	ANCOVA	p=0.0006
	300	252	21.67	**11.38**		
	Personal Distress Score [range 0 to 100]					
2001133	0	266	62.57	-16.31		
	300	268	64.78	**-23.55**	ANCOVA	p=0.0006
2001134	0	258	66.38	-18.27		
	300	254	66.61	**-24.34**	ANCOVA	p=0.0091

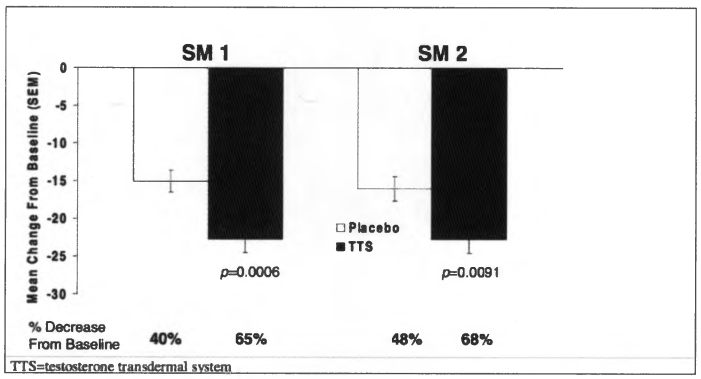
[a] For frequency of total satisfying sexual episodes, baseline mean and mean change from baseline at Week 24 refer to the average 4-week frequency.
[b] Mean change from baseline adjusted for age, estrogen therapy route, pooled centers, and baseline value.
[c] For frequency of total satisfying episodes in Study 2001134, the ANCOVA model assumption of normality was severely violated; therefore, unadjusted mean change from baseline (i.e. no covariate adjustment) is shown and Wilcoxon rank sum analysis was conducted.

Baseline: According to information provided in P&G's NDA, the overall mean scores at baseline in the two phase 3 studies for the SAL 4-week frequency of total satisfying sexual events, PFSF sexual desire, and personal distress were consistent with mean scores from other studies with women who considered themselves to have few satisfying sexual activities, low sexual desire, and were distressed about their lack of sexual desire. Baseline disease severity as judged by the three main endpoints was similar between the active and placebo treatment groups across the four studies (NDA 21-769, 2004) (Table 4).

FDA, however, provided critique of the ethnic and age breakdown of the study population; the committee stated that African American women, especially those between the ages of 40-44, were dramatically underrepresented in the study and not reflective of the US population of women with hysterectomies. In the trials, African American participants accounted

for 6% of the total participants while Caucasian women accounted for 89%. FDA pointed out that the rate of hysterectomies is higher among African American women as compared to Caucasian women (16.9/1000 as compared to 10.8, respectively).

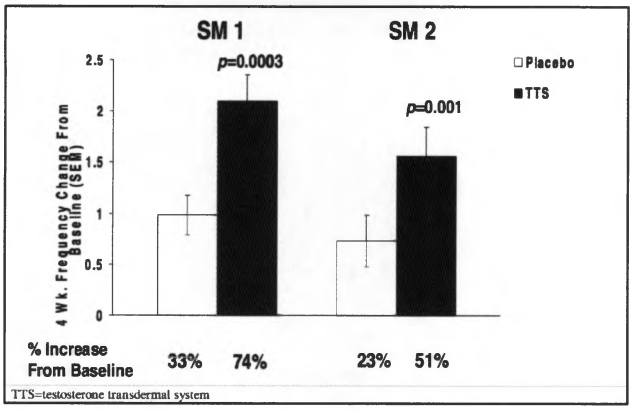
Table 4: Changes from Baseline in Sexual Desire – Phase III



Changes in Sexually Satisfying Events: The mean change from baseline in SSEs for the last recorded 4-week period in Phase 3 studies, as compared to placebo, show subjects treated with 300 mcg/day TTS had an increase in the frequency of total SSEs. Based on the findings, P&G concluded that an increase of 1.1 events per four weeks was the minimally important clinical difference. The results show an average increase of 2.13 and 1.56 events from baseline were seen and therefore the primary endpoints were met.

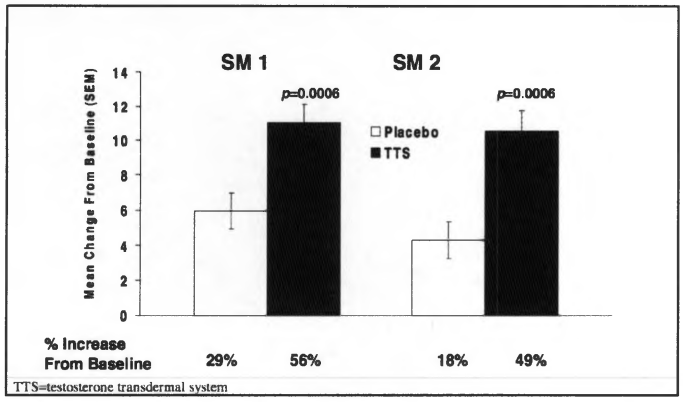
However, the placebo group also showed improvement of the average increase in SSEs as compared to baseline: 0.98 and 0.73 events. FDA agreed that although the TTS group values were statistically significant, the women in both the placebo and TTS groups had an increase of 1 or 2 more SSE events (Table 5). Therefore, although P&G showed statistical significance, both arms exhibited similar improvement and FDA questioned whether the results were clinically significant "The critical question is the clinical significance of the change with active treatment yielding, on average, one more satisfying sexual event per 4 weeks compared to placebo" (FDA Panel minutes, 2004).

Table 5: Change from Baseline in Frequency of Satisfying Sexual Activity - Phase III



Change in Sexual Desire: The mean change from baseline in sexual desire at week 24 in Phase 3 studies, as compared to placebo, shows subjects treated with 300mcg/day TTS had a increase in desire. Based on P&G's assessments, an increase of ≥ 8.9 points on a scale of 1 to 100 on the Desire domain of the PFSF was the minimally important clinical difference. The results show a mean change increase in desire of 11.85 and 11.38 for the treatment groups from baseline as compared to 6.9 and 6.1 for the placebo groups (Table 6). The analysis for these results show statistical significance. Yet, similar to the primary endpoint, FDA expressed concerns on whether the results were clinically significant, "The clinical significance of the increase with active treatment yielding, on average, an increase of 5-6 points more than placebo on a scale of 100 is unknown" (FDA Panel minutes, 2004; NDA 21-769, 2004).

Table 6: Change from Baseline in Sexual Desire - Phase III



Change in Personal Distress: The PDS measures personal distress associated with subjects' low desire for, and lack of interest in, sex. The PDS instrument contains 9 items in a single domain. Subjects filled out the questionnaire based on their experiences and feelings over the preceding 30 days. A decrease in the PDS score indicates a decrease in a patient's distress. Across the two Phase 3 trials, the baseline score for distress ranged from 62.57 to 66.38 for the placebo group and from 64.78 to 66.61 for the TTS group, which corresponds to an average answer of "often" being distressed for the 9 questions. The Least-Squares Means difference between the change in placebo and TTS scores was approximately 7.3. Results were statistically significant.

Update on Intrinsa: In 2006 P&G filed to patent their method for treating menopausal women transdermally with testosterone (Patent US20080015170), however it is still not an FDA approved product. The transdermal testosterone patches are prescribed off-label today for both naturally menopausal women and for women not on concomitant estrogen.

Flibanserin

Boehringer Ingelheim's Flibanserin was tested and indicated for the treatment of Hypoactive Sexual Desire Disorder (HSDD) among premenopausal women. The objective of the study was to document the safety profile and efficacy of Flibanserin in producing a clinically meaningful therapeutic response after 24 weeks of treatment. However, in a vote of 11 to 0 (votes for no and yes, respectively), FDA did not approve the drug because it *"felt that that the efficacy of flibanserin was not sufficiently robust to justify the risks*." (FDA Panel minutes, 2010).

Flibanserin is an orally administered, non-hormonal, small molecule with two main pharamacologic targets in the brain: post-synaptic 5-HT1A receptors (agonoism) and 5-HT2A receptors (antagonism). The drug was first clinically evaluated in depression, but after data from Phase II studies were performed, data suggested that it might increase sexual desire in women. The drug leads to region-specific increases in neurotransmitters dopamine and norepinephrine, and also decreases serotonin.

Data from two primary phase 3 trials (US, Canada) were submitted to FDA in 2010. The trials were prospective, randomized, double-blinded with a placebo arm. The total study duration was 28 weeks and consisted of a four-week baseline period for all HSDD parameters followed by a 24-week of blinded treatment period. Eligible subjects were randomized to the placebo group, or treatment group (Study 511.71: flibanserin 50 mg qhs or 100 mg qhs; Study 511.75: flibanserin 25 mg BID, 50 mg BID or 100 mg qhs).[12]

A protocol synopsis (

[12] An up-titration was used in Study 511.75 for subjects on the two higher doses, whereby they initially received 50 mg qhs for 14 days and then were titrated up to their final doses.

Table 7) was created to provide a summary of the key aspects of the trials including protocol design and target population.

Table 7: Intrisa Protocol Synopsis

Sponsor Name	**Boehringer Ingelheim**
Proposed Indication	Flibanserin is indicated for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in premenopausal women.
Investigational Products	Oral tablet. Flibanserin is an orally administered, non-hormonal small molecule. It has two main pharmacological targets in the brain: post-synaptic 5-HT1A receptors (agonism) and 5-HT2A receptors (antagonism) that lead to region-specific increases in the neurotransmitters dopamine and norephinephrine and decreases in serotonin.
Dose	100 mg PO once daily at bedtime
Objectives	To document the safety profile and efficacy of flibanserin in producing a clinically meaningful therapeutic response after 24 weeks of treatment in premenopausal women with HSDD Co-Primary endpoints: • Change in the number of satisfactory sexual events (SSEs) from the four-week baseline to the 28 days prior to the final clinic visit (without spanning into the previous clinic visit) • Change in the eDiary sexual desire score from the four-week baseline sum to the 28 days prior to the final clinic visit (without spanning into the previous clinic visit). Secondary endpoints: • Change in Distress from baseline to endpoint as assessed by the total score for the FSDS-R. • FSFI domain for sexual desire.

Clinical Trials & Design

The two pivotal trials were prospective, randomized, double-blind, North American (US and Canada) studies in premenopausal women with general acquired HSDD. The total study duration was 28 weeks and consisted of a four week baseline period followed by 24 weeks of blinded treatment. Following screening and consent, eligible subjects entered the trial and began treatment.

Phase III

4) 7 Phase III studies. Studies 511.71 and 511.75 were the Pivotal trials.

In Study 511.71, eligible subjects were randomized to one of three treatment groups:

a. placebo
b. flibanserin 50 mg qhs
c. flibanserin 100 mg qhs

In Study 511.75, subjects were randomized into one of four treatment groups:

d. placebo
e. flibanserin 25 mg BID
f. flibanserin 50 mg BID or
g. flibanserin 100 mg qhs

Study Phase III	**Objective**	**Design**	**Flibanserin Doses** (mg)	**# Subjects**	**Duration (wks)**
511.70 **US**	Efficacy/Safety	R, DB, PC	25 BID 50 qhs 50 BID	Flibanserin - 1,042 - 350 @ 25 BID - 340 @ 50 qhs - 365 @ 50 BID Placebo - 350	24
511.71 **US/Can**	Pivotal Efficacy/Safety	R, DB, PC	50 qhs 100 qhs	Flibanserin - 585 - 295 @ 50 qhs - 290 @ 100 qhs Placebo - 295	24
511.74 **US/Can**	Long-term safety	Open-label (24+ wk)	flexible regimen: 50 qhs 50 BID 100 qhs	Open-label Flibanserin -912 Placebo – 170	24
511.77 **EU**	Efficacy/Safety	R, DB, PC	50 qhs 100 qhs **titrated**	Flibanserin - 631 - 314 @ 50 qhs - 317 @ 100 qhs Placebo - 318	24
511.75 **US/Can**	Pivotal Efficacy/Safety	R, DB, PC	25 BID 50 BID 100 qhs **titrated**	Flibanserin – 1,185 - 396 @ 25 BID - 393 @ 50 qhs - 396 @ 100 qhs Placebo - 399	24
511.84 **US**	Long-term safety and efficacy; Flexible-done	Open-label, uncontrolled	Flexible regimen: 50 or 100 qhs 25 or 50 BID	Flibanserin – 1,725 from Studies 511.70, 511.71 & 511.75	52 (Ongoing)
511.118 **EU**	Long-term safety and efficacy	Open-label, uncontrolled	Flexible regimen: 50 or 100 qhs 25 or 50 BID	Flibanserin – 470 from Study 511.77	28 (Ongoing)

Measures

4 Validated Instruments

1) Sexually Satisfying Events
2) eDiary Sexual Desire Score
3) 13-item Female Sexual Distress Scale – Revised (FSDS-R)
4) Female Sexual Function Index (FSFI)

Eligibility Criteria	Key Inclusion criteria: • Women aged ≥18 years with primary diagnosis of generalized acquired HSDD (DSM-IV-TR) of ≥24 weeks duration assessed by trained, expert clinician using standardized, structured interview • Premenopausal according to the STRAW criteria • FSDS-R (distress) score of ≥15 • In a stable, communicative, monogamous, heterosexual relationship for ≥1 year • Sexually functional partner Key Exclusion criteria: • Sexual pain disorders, sexual aversion disorders • Psychiatric disorders likely to affect sexual functioning including Major Depressive Disorder • History of any serious ongoing clinical disorder • Use of medication that, in the investigator's opinion, may enhance or diminish the patient's sexual function within 4 weeks prior to entering the study • Medications known to impact sexual desire (i.e. opioids, SSRIs)
Statistical Analyses	The primary efficacy analysis was based on the full analysis set (FAS). The FAS consists of women who were randomized to a treatment group, received at least one dose of study medication, and had at least one on-treatment efficacy assessment.

Clinical Outcome Data

Subject Enrollment and Disposition: Phase III trial data reflects the efficacy data in the proposed dosage of the ITT population. A total of 2,462 premenopausal women were randomized to placebo or treatment with Flibanserin at different doses over the two primary phase 3 trials. As expected in any trial, there are discontinuation rates, however FDA highlighted the difference in completion rates between both arms. "It is noteworthy that more placebo subjects (~75%) completed the two 6-month trials than did the Flibanserin 100 mg qhs-treated subjects (~64-69%)" (FDA Panel minutes, 2010; NDA 22-526, 2010). The reasons for discontinuation included: adverse events, consent withdrawn, lost to follow-up, non-compliance with the protocol, lack of efficacy and other. FDA's comments imply the higher discontinuation rates in the treatment arms may suggest concerns with efficacy and tolerability of the drug.

Other areas of concern by FDA included the demographic make up: approximately 86% of women enrolled were white non-Hispanics and 89% had a high level of education (partial college, college graduate or post graduate). There was also an extensive list of medications that were exclusionary of participation in the trials: a detailed list of over 250 medications were listed as in the exclusion criteria that needed to be reviewed with each participant prior to enrolling in

the study. Similar to the comments made by FDA for the Intrinsa application, the efficacy trials lacked a diverse population and limited the generalizability of the trial results, particularly the safety findings.

Change in Sexually Satisfying Events: Flibanersin 100 mg qhs led to a statistically significant increase from baseline as compared to the placebo group. The mean change from baseline in SSEs in the treatment group was 3.8 and 5.3 events. However, similar to the Intrinsa trial results, the placebo group also showed similar improvement on the average increase in SSEs as compared to baseline: 3.4 in both primary phase 3 studies (

Table 8).

Changes in Sexual Desire: The mean change from baseline in sexual desire at week 28 in the phase 3 studies, as compared to placebo, shows subjects treatment with 100 mg qhs had an increase in desire, but did not demonstrate statistically significant improvement as compared to placebo. As assessed by the eDiary scores, the change from baseline for the treatment groups was 1.0 and 0.8 whereas the placebo group was almost identical at 0.9 and 0.8 (

Table 8). An agreement made by BI and FDA on the protocol design and statistical analysis plan stated that if one primary endpoint was not met, secondary endpoints would not be analyzed. Although results of those secondary endpoints were statistically significant and presented to FDA, they were not considered in the application.

Challenges with the new technology of eDiary also posed challenges throughout the trial. Originally, BI allowed women a 72-hour window to enter data on SSEs and desire with the rationale that women would be likely to remember accurately such events for up to three days. However, the company decided to shorten the recall period to a 24-hour window of data entry in an effort to improve the women's recall accuracy. As a result of the shorter window, compliance was lower than anticipated since participants who would forget to enter their data every night. FDA was unconvinced that eDiaries and a shorter recall were the best method to capture desire data. They did not think it was appropriate to alter the pre-specified method of assessing sexual desire. Those who voted against the drug's approval also felt that changing the method should have been addressed earlier than the Phase 3 trial. (FDA Panel minutes, 2010; NDA 22-526, 2010). The two members that voted yes noted that FSFI (Female Sexual Function Index) was a standardized tool and although imperfect, was well-known and published in literature. The eDiary, however was not a verified tool and it's use as the appropriate methodology was discussed repeatedly (FDA Panel minutes, 2010).

Table 8 Primary and Most Important Secondary Endpoints – Studies 511.71 and 511.75 (FAS-LOCF)

Treatment Arm	N	Baseline (4 weeks)	N	End of Treatment (approximately Weeks 21-24)	Change from baseline (over 4 weeks)*	Placebo-Subtracted Change	p-value**
SSEs							
Study 511.71							
Flibanserin 100 mg qhs	280	3.0 (2.8)	275	4.6 (4.2)	1.6 (3.8)	0.8	**0.005**
Placebo	288	2.7 (2.8)	286	3.5 (3.6)	0.8 (3.4)		
Study 511.75							
Flibanserin 100 mg qhs	377	2.6 (2.9)	373	4.4 (5.3)	1.9 (5.3)	0.8	**0.024**
Placebo	388	2.7 (2.8)	382	3.7 (3.8)	1.1 (3.4)		
eDiary Desire							
Study 511.71							
Flibanserin 100 mg qhs	280	12.9 (10.5)	275	21.2 (17.1)	9.1 (1.0)	2.2	0.132
Placebo	288	11.8 (9.6)	286	18.1 (16.2)	6.9 (0.9)		
Study 511.75							
Flibanserin 100 mg qhs	377	12.0 (9.8)	373	20.1 (17.9)	8.5 (0.8)	1.7	0.346
Placebo	388	10.2 (8.8)	382	16.9 (16.9)	6.8 (0.8)		
Distress – FSDS-R Item 13							
Study 511.71							
Flibanserin 100 mg qhs	280	3.2 (0.9)	280	2.4 (1.2)	-0.8 (0.1)	-0.4	**0.0001**
Placebo	290	3.2 (0.8)	289	2.7 (1.1)	-0.5 (0.1)		
Study 511.75							
Flibanserin 100 mg qhs	380	3.3 (0.7)	380	2.5 (1.2)	-0.7 (0.1)	-0.3	**0.0006**
Placebo	389	3.2 (0.8)	389	2.7 (1.1)	-0.5 (0.1)		
Distress – FSDS-R Total							
Study 511.71							
Flibanserin 100 mg qhs	280	30.7 (10.0)	280	21.6 (12.3)	-8.9 (0.7)	-3.9	**<0.0001**
Placebo	290	30.1 (9.9)	289	25.2 (11.4)	-4.9 (0.7)		
Study 511.75							
Flibanserin 100 mg qhs	380	30.6 (9.3)	380	22.9 (12.5)	-7.8 (0.5)	-2.5	**0.0004**
Placebo	389	30.2 (9.9)	389	25.3 (11.9)	-5.2 (0.5)		

Others Drug Trials

A variety of drugs, hormonal agents, and topical transdermal formulations for female sexual dysfunction are currently under development (Goldstein et al., 2006; 77, clinicaltrials.gov), however most Sponsor companies do not end up submitting an NDAs to FDA due to poor outcome data. Previous drug trials conducted for HSDD indications include Lybridos (oral tablet), Lorexys (oral tablet) and Bremelanotide (hormone injections). Clinical trials with a variety of testosterone treatments have also been completed: Testosterone Transdermal System (testosterone patches), BP101 (testosterone nasal spray) and Libigel (testosterone gel).

Of these treatment options, Libigel by BioSante in 2011 was referenced as one of the "most promising" treatment options with a simple-to-use absorbent testosterone gel. The study was a randomized, double-blind, placebo-controlled, multi-center cardiovascular events-driven, adaptive design comparison of daily LibiGel testosterone gel verses identical placebo gel. There were 3,656 (their protocol called for up to 4,000) patients randomized. Although results appeared promising, the BioSante printed a press release in December of 2011 sharing that Phase III results indicated that the treatment group did not appear to be statistically significant when compared to the placebo group. Other weaknesses of this trial included an ungeneralizable sample: predominately Caucasian women with specific conditions: hypertension and dyslipidemia who were not taking estrogen and were naturally menopausal. Despite this and due to the high prevalence of off-label testosterone prescriptions written for women in the US with low desire, some pharmaceutical experts have speculated that the drug may be re-tested and submitted to FDA for approval in the future.

As of May 2017, there are two open studies actively recruiting participants for HSDD: Addyi phase four studies and BP101, a phase one study. Ivix is evaluating BP101's frequency, seriousness, and severity of adverse events, including events of dose-limiting toxicity in healthy volunteers receiving different doses of the nasal spray as compared to placebo after multiple administrations.

Discussion and Recommendations

A case analysis of Intrinsa's and Flibanserin's NDAs highlight the complexities involved in clinical trial design and the intense scrutiny in which FDA evaluates the therapeutic benefit observed in phase three data. Intrinsa presented data from 1,431 participants who were enrolled in phase three studies: 715 were randomized to treatment with TTS at 300mcg and 716 were randomized to a placebo patch. The primary efficacy endpoint of change from baseline in the total number of SSEs was met with an average increase of 2.13 and 1.56 events from baseline in treatment groups. The secondary endpoint of change from baseline in total sexual desire was also met with an average increase in desire of 11.85 and 11.38 in treatment groups. These changes were statistically significant, although FDA deemed them as not clinically significant due to a variety of reasons.

Flibanserin presented data from a total of 2,462 women randomized to various treatment groups at various doses or placebo. The co-primary endpoint of change from baseline in SSEs was met with an average increase of 3.8 and 5.3 in treatment groups. The co-primary endpoint of change from baseline in total sexual desire was not met due a minimal change of 1.0 and 0.8 in the treatment groups. Not showing statistical significance of the co-primary endpoint was the main reason the drug was not approved. However, similar to the feedback provided on the Intrinsa trial, FDA has several critiques of the Flibanserin study design and clinical outcomes between the treatment and placebo groups.

Multidisciplinary Collaboration to Develop Proper Methodologies for Low Desire

The validated instruments by which low desire (and HSDD) is measured need to be streamlined across sponsors, sexuality researchers and FDA. In the Flibanserin trials, the co-primary endpoint data of sexual desire was captured via a daily eDiary entry and analyzed in four-week intervals. The eDiary daily sexual desire question was a standard question asked in FSD studies: "Indicate your most intense level of sexual desire" with possible responses of 0 (no

desire), 1 (low desire), 2 (moderate desire) or 3 (strong desire). However, FDA critiqued the implementation of the eDiary methods because it was not captured in the same manner as the FSDS-R, which measured distress levels. B&I used the FSDS-R 13-item questionnaire to measure distress levels but modified the use of seven-day recall, rather than the four-week recall used in the original development of the instrument. The company believed the shorter recall window was important to accurately capture distress levels throughout the month. The effect of the modification concluded that the instrument, with the seven-day recall, had good discriminant validity, high test-retest reliability and a high degree of internal consistency. However, FDA expressed concern with the modification of the instrument and attributed the lack of synchrony between the measures of distress and the co-primary efficacy endpoint of desire to a potential reason why desire the desire endpoint was not shown as statistically significant. If sponsor companies had a greater variety of validated measures for sexual desire and distress combined, available at various recall periods, it would eliminate the need for modification of measures and disagreement about their effectiveness.

In addition to the lack of validated measures for sexual desire in the space, FDA officials are apprehensive about incorporating new technologies into trial design (100). Officials have noted that innovative trial methods present challenges as they may have "enhanced risk" by presenting unknown practices. This was alluded to several times in the Agency's comments in Flibanserin's NDA. The new eDiary method for capturing retrospective information meant that women only had a 24-hour window for data entry, which created concerns with analyzing study endpoints with large amounts of missing data. An expert consensus on best practices of eDiaries or similar technologies should be held in order to develop evidence-based practices of mobile technologies in clinical trials, and specifically discuss the implications of sexual health trials.

A precursor to developing the most accurate measures for sexual desire is agreeing on its definition, inclusion criteria and etiology. As discussed, there is a lack of common pathophysiologic model or clear-cut consensus regarding the diagnostic classification of female

sexual dysfunction. The disconnect between the medical community and female sexuality researchers will continue to present challenges in developing consistent standards of measurement (Goldstein et al., 2006).

Female sexual response models, especially current models such as the one proposed by Basson, can help re-define low desire and better target women who could benefit from treatment. Her model highlights factors in the sexual response cycle such as psychosexual development, current context, as well as a comprehensive review of medical history to be included in the assessment before diagnosis rather than minimizing the condition to simply psychological or biological. FDA has also acknowledged that the classification of HSDD is under-development and Sponsor companies often overlook the sexual response models tied to these definitions. Further, clinicians themselves are rarely familiarized with female sexual response models beyond the basic one developed in the 1950's by Master's and Johnson (Goldstein et al., 2006). A closer look at the progress of these models over time helps explain women's sexual arousal and highlights the importance of emotional and interpersonal factors that are critical components of women's sexuality. Having a clear framework to discuss and diagnose low desire is necessary to develop the appropriate methodologies needed to evaluate common endpoints in clinical trials including sexually satisfying events, sexual desire and sexual distress. Validated measures that capture a comprehensive and clear diagnosis with the ability to rule out other relationship or biological factors (proposed by Basson) and used validated eDiary technologies will streamline the way trial data are used and analyzed.

Clinical Trial Enrollment Must Be Diverse and Represent the Intended Population

FDA expects that clinical trials will accurately reflect the intended population of the drug. However, FDA critiqued enrollment populations in both Intrisa and Flibanserin trials. With Intrisa, the indicated population consisted of women who were surgically sterile. Based on this medical condition, P&G should have aimed to enroll subjects in a manner such that it represented

the US population of women with hysterectomies. African American women have higher rates of hysterectomies than white women, therefore they were underrepresented in the clinical trial.

Flibanserin also lacked demographic diversity of its enrolled participants, but more notably, they excluded a significant number of women with an extensive list of over 250 exclusionary medications. FDA pointed out that the women enrolled in the pivotal efficacy studies were generally healthy, without any significant medical conditions or concomitant medications. Since the clinical trial had strict guidelines about who could participate, the results of that population may not apply to the general population; the extensive list of medications may have limited the generalizability of the trial results. Furthermore, FDA reviewed all adverse events carefully and determined that women who did take certain concomitant medications had higher rates of adverse events. For example, women receiving Flibanserin and using hormonal contraceptives tended to have slightly higher overall rates of AEs compared to those taking placebo with a hormonal contraceptive. If the intended use of the drug is to include women on concomitant medications, the trials must be designed in a way to include these women. The solution to testing the correct population is not simple, but having the variety of validated measures as suggested earlier, would help address some of these population concerns.

Additional Research on the Placebo Response

The placebo response is a complex phenomenon that represents cognitive, behavioral motivational, and possibly relational mediating factors. Large placebo effects (30-70% response rates) are commonly observed in clinical trials of female sexual dysfunction (Goldstein et al., 2006). Procedural factors that may increase a placebo response include: instructions given to trial participants, behavioral changes required to participate in a trial, changes in partner behavior, and interactions with study staff (Brandford, 2013). In Female Sexual Dysfunction trials, this is especially true since an expectation of increased desire, for example, may lead women to additional changes in sexual behavior in their relationship. Studies also show that increased

sexual communication may increase the frequency of sex. For example, one study found that positive relational disclosures after sexual activity were related to increased trust, relationship satisfaction, closeness with one's partner and more frequent SSEs (Denes, 2012). The Flibanserin study required women to record daily information on their eDiary. Factors such as increased communication with a partner due to participation in a new sexual health study or when recording daily eDiary information at night were not accounted for in the study design. This kind of information needs to be considered methodically in sexuality trials with women and controlled for in outcome analyses.

In researching the literature for suggestions on how to improve placebo effects with FSD trials, very few publications were found. One suggestion to improve the placebo effect is to use single-blinded, lead-in procedures with exclusion of identified placebo responders (Goldstein et al., 2016), although the article that offered this suggestion stated that the approach has not been widely employed in FSD trials to date and thus it is unknown how placebo values would be affected.

Conclusion

Recent efforts to treat Female Sexual Dysfunction, in particular the most common sexual complaint reported by women, low desire, have led to increased research and clinical trials. As the medical community continues to identify the problems women face with low desire and define them in a way that addresses symptoms, pharmaceutical companies are simultaneously trying to develop and test new drugs in clinical trials. There are tensions in this field; the medical and pharmaceutical communities seeking treatments and feminist researchers who argue that pharmaceutical companies are driving the medical community to "overmedicalize" female sexuality. These researchers prefer to view treatments as more comprehensive rather than focus on one-model that includes a "normal" versus "abnormal" approach. Despite these opposing frameworks, both perspectives add value to the female sexuality field and lead to biological and pharmacological advancements for women who struggle with low desire difficulties.

After a case analysis of the two NDAs rejected by FDA for HSDD drugs, it is clear that more research is needed to develop the proper measures for evaluating SSEs, changes in desire and changes in distress levels. To conduct a multi-million dollar drug trial over several years and not have a clear consensus by the medical community and FDA on the questionnaires and recall methods used for the study endpoints is illogical and unheard of in other therapeutic areas. Combining questionnaires, such as sexual desire and distress would also be beneficial. Lastly, as technology continues to advance, it is critical to establish best practices for mobile technologies in collection of clinical trial data.

Drug treatments for low desire must be generalizable. Low sexual desire trials are often designed to treat women in one specific menopausal state (i.e. Intrinsa for surgically menopausal women and Flibanserin for premenopausal women) to account for hormonal differences that may impact patient safety or the effectiveness of the drug. With this consideration, however, drug companies must ensure that their enrolled subjects represent the larger intended treatment group.

Intrinsa failed to enroll a higher proportion of surgically sterile African American population, as is seen in the US population of women with hysterectomies.

Study designs must better account for the placebo response. Drug companies are not considering factors such as increased sexual communication and disclosure with a sexual partner once a woman is enrolled in a study. By working closely with sexual communication experts and female sexuality researchers, the medical community could improve methodological considerations and better control these factors in outcome analyses.

There are several factors discussed that highlight the unique problems in the conceptualization, assessment and treatment of low desire in women. A multidisciplinary examination of low desire is needed to clarify how to best frame the condition prior to developing clinical trials. Agreed upon frameworks and methodologies need to then be consistently implemented in female sexual dysfunction trials in order to standardize expectations for endpoint thresholds and advance outcomes of trials designed for new pharmacological treatments.

References

Advisory Committee for Reproductive Health Drugs [FDA Meeting Minutes, November 3, 2004].

Advisory Committee for Reproductive Health Drugs [FDA Meeting Minutes, June 17, 2010].

Basson, R. (2005). Women's sexual dysfunction: revised and expanded definitions. *Canadian Medical Association Journal, 172*(10), 1327-1333. doi:10.1503/cmaj.1020174

Basson, R. (2000). The Female Sexual Response: A Different Model. *Journal of Sex & Marital Therapy, 26*(1), 51-65. doi:10.1080/009262300278641

Basson, R., Leiblum, S., Brotto, L., Derogatis, L., Fourcroy, J., Fugl-Meyer, K., Schultz, W. W. (2004). Revised Definitions of Women's Sexual Dysfunction. *The Journal of Sexual Medicine, 1*(1), 40-48. doi:10.1111/j.1743-6109.2004.10107.x

Berman, L., Berman, J., Felder, S., Pollets, D., Chhabra, S., Miles, M., & Powell, J. A. (2003). Seeking help for sexual function complaints: what gynecologists need to know about the female patient's experience. *Fertility and Sterility, 79*(3), 572-576. doi:10.1016/s0015-0282(02)04695-2

Bradford, A. (2013). Listening to Placebo in Clinical Trials for Female Sexual Dysfunction. The Journal of Sexual Medicine, 10(2), 451-459. doi:10.1111/j.1743-6109.2012.02941.x

Brotto, L. A. (2009). The DSM Diagnostic Criteria for Hypoactive Sexual Desire Disorder in Women. *Archives of Sexual Behavior, 39*(2), 221-239. doi:10.1007/s10508-009-9543-1

Byers, E. S. (2011). Beyond the birds and the bees and was it good for you?: Thirty years of research on sexual communication. *Canadian Psychology/Psychologie canadienne, 52*(1), 20-28. doi:10.1037/a0022048

Clayton, A. H. (2010). The pathophysiology of hypoactive sexual desire disorder in women. *International Journal of Gynecology & Obstetrics, 110*(1), 7-11. doi:10.1016/j.ijgo.2010.02.014

Davison, S. L., Bell, R., Donath, S., Montalto, J. G., & Davis, S. R. (2005). Androgen Levels in Adult Females: Changes with Age, Menopause, and Oophorectomy. The Journal of Clinical Endocrinology & Metabolism, 90(7), 3847-3853. doi:10.1210/jc.2005-0212

Denes, A. (2012). Pillow Talk: Exploring Disclosures After Sexual Activity. *Western Journal of Communication, 76*(2), 91-108. doi:10.1080/10570314.2011.651253

Diagnostic and statistical manual of mental disorders: DSM-IV-TR. (2011). Washington, DC: American Psychiatric Association.

Diagnostic and Statistical Manual of Mental Disorders: DSM-5. (2013). Arlington, VA: American Psychiatric Association.

Emerson, C. R. (2010). Review of low libido in women. *International Journal of STD & AIDS, 21*(5), 312-316. doi:10.1258/ijsa.2010.009461

Flibanserin (Girosa) [Review of NDA 22-526 Division of Reproductive and Urologic Drug Products]. (2010, May 20).

Goldstein, I., Meston C., Davis S. & Traish, A. (2006). *Women's sexual function: study, diagnosis and treatment*. London: Taylor & Francis.

Hayes, R. D. (2011). Circular and Linear Modeling of Female Sexual Desire and Arousal. *Journal of Sex Research, 48*(2-3), 130-141. doi:10.1080/00224499.2010.548611

Holmberg, D., & Blair, K. L. (2009). Sexual Desire, Communication, Satisfaction, and Preferences of Men and Women in Same-Sex Versus Mixed-Sex Relationships. *Journal of Sex Research, 46*(1), 57-66. doi:10.1080/00224490802645294

Intrinsa (Testosterone Transdermal System) [Review of NDA 21-769 *Division of Reproductive and Urologic Drug Products*]. (2004, November 3).

Kaschak, E., & Tiefer, L. (2002). *A new view of women's sexual problems*. New York: Harrington Park.

Judd, H. L., Lucas, W. E., & Yen, S. S. (1974). Effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer. American

Journal of Obstetrics and Gynecology, 118(6), 793-798. doi:10.1016/0002-9378(74)90490-6

Laumann, E, Paik, A., Rosen, R. (2011). Sexual dysfunction in the united states: Prevalence and predictors. *Journal American Medical Association, 281*(6), 537-546.

Masters, W. H., & Johnson, V. E. (1966). *Human sexual response*. Boston: Little, Brown and Company.

Mathieu, M. P., & Milne, C. (2008). *New drug development: a regulatory overview*. Waltham, MA: Parexel International.

Meana, M. (2010). Elucidating Women's (hetero)Sexual Desire: Definitional Challenges and Content Expansion. *Journal of Sex Research, 47*(2-3), 104-122. doi:10.1080/00224490903402546

Miller, S. A., & Byers, E. S. (2008). An exploratory examination of the sexual intervention self-efficacy of clinical psychologygraduate students. Training and Education in Professional Psychology, 2(3), 137-144. doi:10.1037/1931-3918.2.3.137

Moynihan, R. (2004). FDA panel rejects testosterone patch for women on safety grounds. *Bmj, 329*(7479), 1363-1363. doi:10.1136/bmj.329.7479.1363

Mulhall, J., King, R., Glina, S., & Hvidsten, K. (2008). Importance of and Satisfaction with Sex Among Men and Women Worldwide: Results of the Global Better Sex Survey. *The Journal of Sexual Medicine, 5*(4), 788-795. doi:10.1111/j.1743-6109.2007.00765.x

Person, E. S. (1999). *Sexual Century*. Yale University Press.

Robinson, B., Munns, R. A., Weber-Main, A. M., Lowe, M. A., & Raymond, N. C. (2010). Application of the Sexual Health Model in the Long-Term Treatment of Hypoactive Sexual Desire and Female Orgasmic Disorder. *Archives of Sexual Behavior, 40*(2), 469-478. doi:10.1007/s10508-010-9673-5

Search for Studies. Retrieved March 22, 2017, from https://clinicaltrials.gov/

Sexual Health Fundamentals: The Top 10 Things You Need to Know About Female Sexuality.

Association of Reproductive Health Professionals (n.d.). Retrieved March, 2010, from http://www.arhp.org/uploadDocs/SHF_Top10.pdf

Schwartz, P., & Young, L. (2009). Sexual satisfaction in committed relationships. Sexuality Research and Social Policy, 6(1), 1-17. doi:10.1525/srsp.2009.6.1.1

Tiefer, L. (1996). The Medicalization of Sexuality: Conceptual, Normative, and Professional Issues. *Annual Review of Sex Research, 7*, 252-283.

Tolman, D. L., & Szalacha, L. A. (1999). Dimensions of Desire. *Psychology of Women Quarterly, 23*(1), 7-39. doi:10.1111/j.1471-6402.1999.tb00338.x

West, S. L. (2008). Prevalence of Low Sexual Desire and Hypoactive Sexual Desire Disorder in a Nationally Representative Sample of US Women. *Archives of Internal Medicine, 168*(13), 1441. doi:10.1001/archinte.168.13.1441

What You Need to Know: Female Sexual Response. *Association of Reproductive Health Professionals* (n.d.). Retrieved March, 2008, from http://www.arhp.org/uploadDocs/FSRfactsheet.pdf

Women's Sexual Health Survey [HealthyWomen]. (2009, June 5).

Women's Sexual Health Survey: Provider Survey [HealthyWomen]. (2009, October 26).

Štulhofer, A. (2015). Medicalization of sexuality. *The International Encyclopedia of Human Sexuality,* 721-817. doi:10.1002/9781118896877.wbiehs297

U.S. Food and Drug Administration/Center for Drug Evaluation and Research. (2016). Low sexual interest, desire, and/or arousal in women: Developing drugs for treatment.

U.S. Food and Drug Administration/Center for Drug Evaluation and Research. (2000). Female sexual dysfunction: Clinical Development of Drug Products for Treatment.