Chapter

Modeling Female Sexual Desire: An Overview and Commentary

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Abstract

Hypoactive sexual desire disorder (HSDD) in women is a condition of low sexual desire that develops over time. Sexual desire normally diminishes over long-term relationships, but is also negatively affected by a demanding lifestyle, poor self-esteem and body image, and loss of intimacy in a relationship. HSDD elevates to a disorder when it is a concern for the woman, arising from conflict with a partner who is interested in a greater frequency of sexual interaction. Two drugs have been marketed (Addyi and Vyleesi) to treat HSDD. Neither drug was originally developed for this purpose, nor is either drug particularly effective. The lack of rational development of drugs to treat sexual disorders in women is due to the mistaken belief that components of female sexuality, such as sexual desire, cannot be effectively modeled in animals. To the contrary, sexual interest, desire, arousal, and reward are measurable aspects of sexual behavior in female rodents. Going forward, basic research using these pre-clinical models should be the starting point for drug development. At the same time, it is not clear that drug development represents the primary therapeutic approach to the problem, with behavioral therapies providing good options for first line of treatments for HSDD.

Keywords: sexual arousal, sexual interest, sexual reward, hypoactive sexual desire disorder, Addyi, Vyleesi, animal models, mesolimbic system, nucleus accumbens, dopamine, glutamate, melanocortin receptors

1. Introduction

Sexual intimacy is an important component of ongoing, stable relationships. When one of the partners loses interest in sex or loses the ability to be sexually aroused, the relationship can be strained. A reduction or absence of sexual interest is the most reported sexual dysfunction for cis-gendered heterosexual women [1]. This loss of sexual desire and interest in having sex becomes a source of distress for which women seek treatment [2]. Because a constellation of environmental, contextual, relationship, and stimulus conditions impact sexual desire, interest and arousal in women, there is no clear cut therapeutic approach, limiting the development of medical interventions for treating women who raise concerns about their low levels of sexual desire and interest.

2. Models of sexual responses in women

Masters and Johnson [3] developed the first model of human sexual responses which were applied to both men and women. For Masters and Johnson there was a linear progression from excitement to plateau, which was followed by orgasm, and ultimately resolution (the refractory period until the re-initiation of sexual activity). In their model sexual desire initiates excitement (or pleasure) which leads to

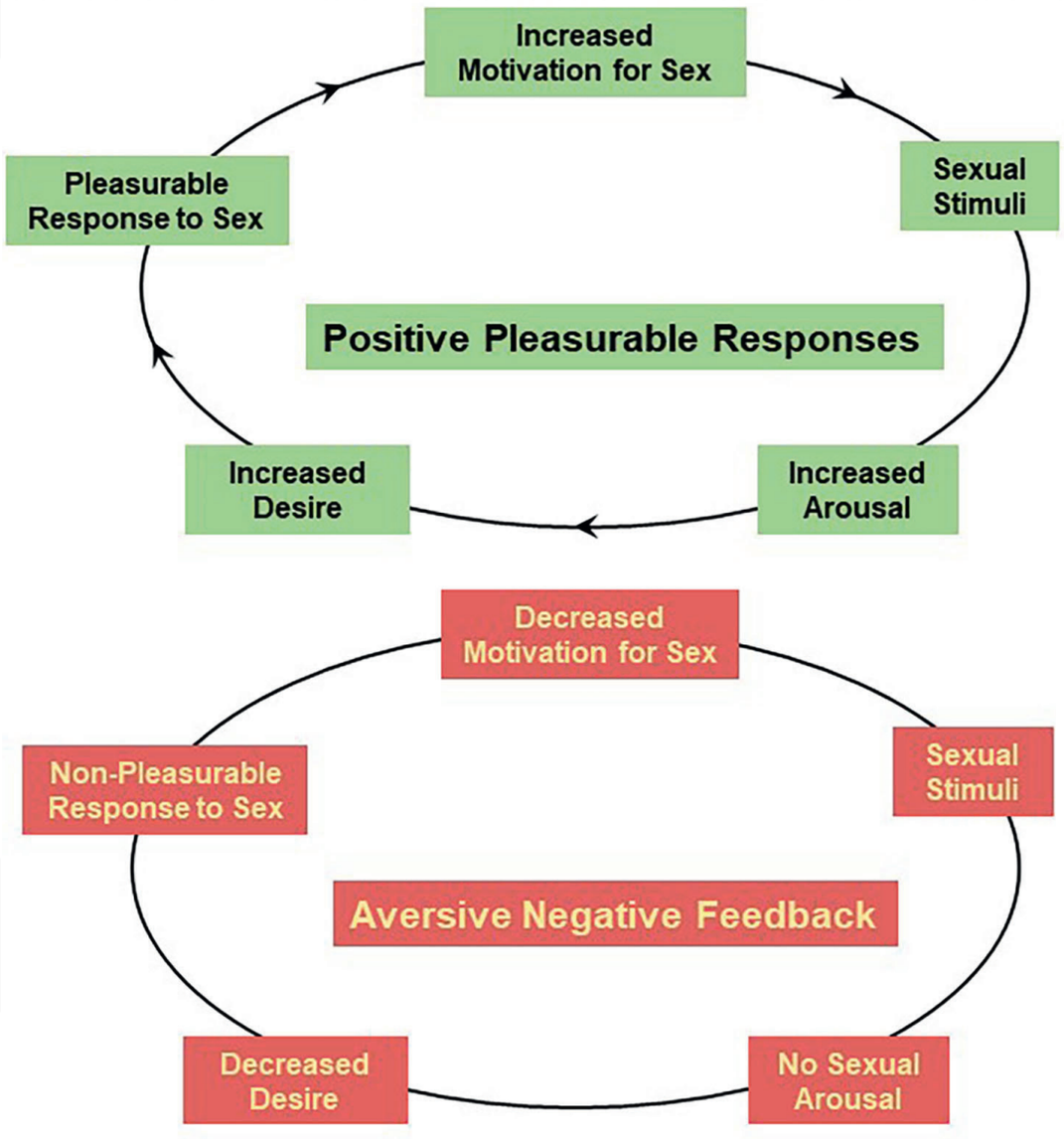

Figure 1.
Sexual Response Cycle in Women. Pictured here is a model of a woman's sexual response cycle based on Basson (2004). When a woman has a positive, pleasurable response to the components of sex, she maintains her interest and desire in sex, as well as her arousal to sexual stimuli. This becomes a positive, feed-forward process that maintains sexual activity in a relationship. The model highlights that there are a number of different components of a woman's sexual response, with all of them interacting. When one of the components is no longer a positive experience and pleasurable, it breaks the cycle, resulting in an negative-feedback reaction that diminishes future sexual activity. Notably, any of the points in the cycle can become dysfunctional, leading to different causes of female sexual dysfunction. When the primary underlying cause is a loss of sexual desire, the condition is termed 'hypoactive sexual desire disorder'.

sexual arousal. Sexual arousal is primarily associated with activation of vaginal autonomic physiological responses. In the intervening years it has become clear that sexual desire and arousal are independent of a woman's psychophysiological responses (e.g., [4–7]. The physiological responses are not coupled to a woman's subjective sexual state [6], and are still activated in response to sexual imagery that women do not find arousing [4].

Early simplified models of sexual responses in women have gradually given way to more intricate models that highlight the complexity of a woman's sexual response [8]. Basson [9, 10] proposed a comprehensive model of sexuality in women that takes into account contextual determinants of sexuality and the role of sexual and nonsexual stimuli in the initiation of sexual desire, interest, and arousal (**Figure 1**). The contextual dependence combined with a number of interacting components gives rise to large variations in the sequences and patterns of the woman's sexual response. What this means is that there are in reality a corresponding variety of potential bases for sexual dysfunctions in women, each depending on its underlying cause.

Embedded in the understanding of the underlying components of the female sexual response is a mechanism through which prior sexual experiences can either promote or interfere with future interest and desire for sex. Both Masters and Johnson's [3] and Basson's [9] models highlight pleasurable responses to sex. These pleasurable experiences become part of a feed-forward process through which desire and interest in sex are maintained (**Figure 1**). In contrast (**Figure 1**), a decrease in pleasure or even aversive responses to sex (e.g., involuntary sex) can feed-back to decrease future sexual interest and desire [1, 11]. As we will discuss, both of these processes can be modeled in animals.

3. Clinical problem

The variety of the components of the female sexual response identify a number of psychological processes that can be disrupted, leading to individual sexual dysfunctions in women (**Figure 1**). With this broad set of definitions for sexual dysfunction, there can also arise different subtypes of these disorders depending on the underlying cause [9]. Classification and diagnostic criteria for hypoactive sexual desire disorder (HSDD) have evolved over the past few decades, with this disorder being the primary target for drug therapies.

3.1 Description and incidence of HSDD

The International Society for the Study of Women's Sexual Health (ISSWSH) has provided guidelines for classifying HSDD in women [2]. Included in the description is the notation that HSDD can be lifelong or acquired. A lifelong lack of sexual desire may be more appropriately thought of being 'asexual', though the ISSWSH view may be beneficial in that it is more broadly encompassing of the range of women who meet the diagnosis of HSDD. In addition, HSDD may be generalized or situational. For the descriptive diagnosis, the criteria for HSDD must have been manifest for at least 6 months. Women classified as having HSSD have some element of low sexual desire, which includes reduced sexual thoughts or fantasies, reduced response to erotic stimuli or sexual stimulation, or a loss of desire to participate in

sexual activity [2]. The diagnosis of HSDD requires that the decreased sexual desire is a source of personal distress.

A limitation in determining the causes of low sexual desire and interest is the degree of inter-individual variability among women. Still, it is striking that studies from across the globe report a rather comparable incidence of low sexual interest and desire. A large scale analysis of data from over 6000 women obtained from Britain's National Survey of Sexual Attitudes and Lifestyles reported that approximately 35% of women had drastically reduced interest in sex for at least a 3 month period in the previous year [1]. This is similar to the frequency among US women of which approximately 30% were dissatisfied with their level of sexual desire [12]. In China about 21% of women have low interest in sex [13], 46% have low interest/desire among Palestinian women [14], approximately 27% of Brazilian women report low sexual desire [15], and 30% of Australian women do so as well [16].

Although viewed as a unified disorder, it is not surprising that there are a number of causes of HSDD [17]. A common complaint among women is that they have very demanding lifestyles with their jobs, family responsibilities, financial issues and general stress [18, 19]. As a result, simple fatigue is a common cause of the loss of sexual desire as the daily demands on a woman increase [18]. Time in a relationship is another key variable, as sexual desire decreases in women the longer they are in a stable relationship [1]. In this context, Basson [9] has noted that assessments of sexual desire should take into account what are normal longitudinal progressions in a woman's sexuality across her life cycle and relationship duration.

Despite the noted variability among women, there are commonly reported underlying causes of low sexual desire and arousal. For example, many women expect intimacy, emotional closeness and their personal self-esteem to emerge from their sexual desires [6]. An exception to this is women with high levels of personal insecurity who do not necessarily seek out sex to achieve emotional closeness [19]. Feelings of intimacy and emotional closeness typically are avoided in women with a negative body image and low self-esteem, leading to decreased levels of sexual desire [12]. Women who feel less connected in their relationship [12] or express low relationship satisfaction [20], may find that their partner disregards their needs in a sexual relationship [21], with the combination of these factors producing low sexual desire.

A psychological mechanism underlying low sexual desire in women (at least in heterosexual cis-gendered women) may be based on how they view male facial attractiveness and male sexual imagery. Among women not reporting sexual problems, their inherent level of disgust predicted their responses to sexually arousing stimuli [22]. When divided by a median split for disgust as a variable, sexual arousing stimuli increased the report of disgust in women with a high disgust trait. In contrast, women with a low disgust trait reported that sexually arousing stimuli were desirable and further reduced their levels of disgust. General levels of disgust are not different between women with low sexual desire and controls [23]. However, when viewing erotic male imagery the low sexual desire group exhibited more negative facial affect (as measured by facial EMG recordings) and reported increased levels of disgust. Similarly, women classified as having hypoactive sexual desire disorder reported lower ratings of facial attractiveness for male faces than did the control females [24].

3.2 Diagnostic criteria

Hypoactive sexual desire disorder first appeared in the Diagnostic and Statistical Manual of Mental Disorders, DSM-III, and was characterized by reduced or absent

sexual fantasies and/or interest in sexual activity. The diagnostic criteria were expanded on in the DSM-IV. Here, Criterion A included reduced sexual fantasies and desire for sexual activity. Criterion B noted that there had to be personal distress or relationship concerns that resulted from reduced sexual desire. Finally, the reduced sexual desire is not better accounted for by another Axis I disorder, a physiological reaction to medication, or medical condition (Criterion C). Because the frequency of sexual activity may be primarily determined by the demands of a partner, rather than intrinsic levels of sexual desire, the number of sexual encounters was not included as a criterion. Interestingly, distinctions were made as to whether the reduced sexual desire was situational or generalized, as well as whether it was lifelong or acquired. The DSM-5 perhaps took a step back in characterizing sexual disorders (e.g., [25]) by combining previously distinct components of sexuality (e.g., sexual desire and sexual interest) into single categories, thus failing to recognize the complexities of a woman's sexual response. Criteria for duration of reduced sexual desire or interest and the frequency of sexual interactions were added. Those critical of the combination of sexual arousal and interest into a single category in the DSM-5 (e.g., [25]) argued that this would not improve diagnostic accuracy and make it more difficult to diagnose these sexual dysfunctions in women, though an analysis by O'Loughlin et al. [26] did not support this contention. Embedded in these clinical criteria is the interesting notion that there are disconnects between how clinicians or women themselves view sexual desire and the problems associated with sexual desire [27].

4. Current drug therapeutics

Since 2015 there have been two FDA approved drugs for HSDD, Addyi and Vyleesi. These drugs differ in their mechanisms of action on the nervous system, the routes of administration, and the frequency of administration. The drugs share the feature that they are minimally effective, at best, for treating HSDD.

An interesting trait of women who report HSDD is that they are particularly susceptible to the placebo effects of administered drugs [28–31]. A meta-analysis was conducted that reviewed studies of women enrolled in clinical trials for various sexual dysfunctions [31]. The trials included approximately 2000 women receiving various drug treatments. Across these trials, placebo effects accounted for approximately 68% of the treatment effects in the studies. The magnitude of the placebo effect makes it more difficult to detect specific contributions of individual drugs to any clinical benefit and highlights the role of cognitive processes in HSDD.

4.1 Addyi (Flibanserin)

Deeks [32] reviewed the timeline for the development and approval of Addyi for the treatment of HSDD in premenopausal women. Flibanserin was first developed by Boehringer Ingelheim as an antidepressant. Though the drug was abandoned as an antidepressant, there were reports from some of the women in the clinical trials of a libido-boosting effect of the drug. Boehringer Ingelheim sold the rights to flibanserin to Sprout Pharmaceuticals who conducted clinical trials on premenopausal women with HSDD. Based on these trials, Sprout submitted a new drug application to the US FDA for flibanserin in 2013. The drug was not approved and Sprout appealed the decision. A second new drug application was filed in early 2015, and the drug, branded Addyi, was approved (with some restrictions) by the FDA later in 2015.

The FDA restrictions included warnings against using alcohol or cytochrome P450 enzyme inhibitors while taking Addyi, and also provided a warning for women who had impaired liver function.

4.1.1 Mechanism of action (receptor specific)

The mechanism of action of flibanserin has been comprehensively reviewed by Stahl et al. [33]. Flibanserin is primarily an agonist at serotonin $5HT_{1A}$ receptors and an antagonist at $5HT_{2A/2B}$ receptors [34]. In addition, it has mixed actions at dopamine D4 receptors. The idea behind developing a drug that acts at different receptor sites is that it can be clinically effective at lower doses, thus mitigating some of the off target side effects. Besides the specific receptor binding, flibanserin has indirect effects on synaptic communication by increasing release of other neurotransmitters, primarily dopamine and norepinephrine [35]. Because the brain operates through functional circuits, it is not surprising that flibanserin modulates activity at a number of brain regions and local circuitry. Stahl [36] has gone on to hypothesize that the microcircuits modulated by flibanserin underlie its therapeutic effectiveness, though this has not been demonstrated.

4.1.2 Therapeutic effectiveness

Thus far, flibanserin has been clinically tested in premenopausal women in stable cis-gendered heterosexual relationships who reported either generalized or acquired HSDD [37]. In the clinical trials of flibanserin, women self-reported moderate improvements to the baseline assessment of HSDD [38, 39]. One primary outcome measured was the number of "satisfying sexual events" per month. Women taking 50 mg flibanserin reported an average increase of 1.4 sexual events per month, slightly higher than the 0.8 events per month for the placebo group. Women on the higher dose of 100 mg flibanserin reported an increase of 1.6 events. Despite the statistically significant increase in the 100 mg dose compared to controls, calculations of effect size ($d = 0.18$ to 0.22) and odds ratios (1.5 to 1.67) were small, indicating minimal effects on sexually satisfying events [40]. The other primary outcome measure, monthly change in "desire score" on a scale of 0–3, did not reveal significant differences between women taking placebo and those taking flibanserin. These analyses, despite FDA approval, provide little evidence that flibanserin either improves sexual desire or the frequency of sexual interactions for women with HSDD.

4.1.3 Clinical considerations and adverse effects

Flibanserin is typically prescribed as a daily oral dose taken in the evening [41]. As typical of serotonergic drug treatments, it takes a period of weeks for the positive effects of the drug, though the side effects can occur earlier. The differential between the onset of the drug's effectiveness and the side effects causes about 12% of the women to discontinue use of the drug. The recommendation is that women continue a daily course of treatment for 8 weeks before discontinuing the medication [41]. Because of potentially harmful drug interactions, women are advised to avoid consumption of alcohol or several other prescription medications, and women who are breastfeeding or have liver complications are advised not to take flibanserin [42, 43]. Sleepiness and sedation are possible side effects of the drug. As we noted, flibanserin

was rejected twice by the FDA prior to its eventual approval in 2015, due to the FDA's own assessment of the clinical effectiveness versus safety of the drug.

4.1.4 Incongruence of mechanism with a benefit for low sexual desire

As noted, the primary actions of flibanserin are as an agonist at $5HT_{1A}$ receptors and an antagonist at $5HT_{2A/2B}$ receptors. Pre-clinical studies in rodents consistently demonstrate that $5HT_{1A}$ agonists *inhibit* different components of female sexual behavior [44]. Thus, developing a drug that acts as a $5HT_{1A}$ receptor agonist to treat low sexual desire in women makes little sense neurobiologically. Further, serotonergic systems in women are also associated with inhibition of sexual interest and arousal, as low libido is a common complaint of women taking SSRIs for depression and is a basis for discontinuing use of the antidepressant medication [45]. Besides its primary actions on serotonin receptors, flibanserin has secondary effects on a number of transmitter systems [35]. Further, as flibanserin needs to be taken daily for weeks prior to seeing any benefit for HSDD, it may be that synaptic compensations, and not the initial actions of the drug on neurotransmission underlie potential therapeutic benefits for HSDD. Regardless, these are after-the-fact arguments that disregard a rational development of a drug to treat HSDD would not include $5HT_{1A}$ receptor agonism as part of its pharmacological profile.

4.2 Vyleesi (Bremelanotide)

Vyleesi is the first and only FDA-approved as-needed treatment for premenopausal women with acquired, generalized hypoactive sexual desire disorder [46]. "Acquired" means that the woman was happy with her level of sexual desire in the past, but it has over the years declined to a point of concern. "Generalized" means that the woman's level of sexual desire remains the same, no matter the sexual activity, situation, or sexual partner.

4.2.1 Mechanism of action

Bremelanotide (earlier known as PT-141), is a synthetic variant of α-MSH which was developed as a proerectile drug [47]. As a peptide, the thought was that the drug would be broken down and rendered inactive in the digestive tract. As such the drug was formulated to be given either intranasally or by self-injection. Levels of the drug peak after about 30 min when administered intranasally. The half-life of bremelanotide following injection is about 3 hours [48]. There are 5 subtypes of the melanocortin receptor, and bremelanotide has high affinities at the MC1, MC3 and MC4 receptors. The MC1 receptor is primarily in the periphery and is related to skin pigmentation. Consequently, hyperpigmentation is a side effect of bremelanotide administration [48]. The MC3 and MC4 receptors reside primarily in the central nervous system and are thought to mediate the effects of bremelanotide on sexual desire, with MC4 receptors receiving the greatest attention.

4.2.2 Therapeutic effectiveness

Phase III clinical trials were conducted on premenopausal women with generalized or acquired HSDD to test the effectiveness of bremelanotide to improve low sexual desire. In these trials women self-reported that bremelanotide increased sexual desire

and reduced distress significantly more than placebo [46]. Notably, the desire score, rated on a 6-point scale, improved by either 0.5 or 0.6 points (in each respective trial) in the bremelanotide groups, while the sexual desire score improved by 0.2 points in the placebo group in each trial. Similarly, the sexual distress score, rated on a 4-point scale, was reduced by 0.7 in the bremelanotide groups and 0.4 in the placebo groups in each trial [46]. Though statistically significant, it has been questioned whether differences of 0.4 points in desire and 0.3 points in distress between the placebo and drug treatments are clinically meaningful. One limitation in assessing the true therapeutic effectiveness of the drug was that 8 of 11 efficacy outcomes that the authors of the study planned to investigate were never discussed, while several others were reported that were not planned prior to the study [49]. These changes in the planned outcome reporting between the a priori and post-hoc outcomes raise concerns regarding the objective evaluation of the drug's efficacy.

4.2.3 Clinical considerations and adverse effects

The data on side effects of repeated administration of bremelanotide come from two clinical trials. One consideration is that the drug needs to be injected subcutaneously about 45 minutes prior to engaging in sexual activity [46]. Further, the side effect profile of the drug is notable, with 40% of women experiencing nausea. Other side effects reported are flushing, injection-site reactions, changes in skin pigmentation (based on the affinity for peripheral MC1 receptors), headaches, and even vomiting.

4.2.4 Incongruence of mechanism with a benefit for low sexual desire

Bremelanotide was originally developed as a permanent skin tanning agent. One of the developers of the drug injected himself to see if it would work. He was surprised to discover that the injection produced a long-lasting erection [50]. As a consequence, the drug received further interest as an adjunct to treat male erectile dysfunction [51]. Bremelanotide works by imitating the effects of α-MSH on melanocortin receptors in the central and peripheral nervous system resulting in increased blood flow, which causes an erection. The (misguided) thought was that bremelanotide would become the female "Viagra", despite clear evidence that HSDD does not arise in women from impaired genital physiological arousal [52]. Instead of being a physiological issue, HSDD has at its roots complex psychological issues. Unsurprisingly, independent analyses of the few clinical trials which investigated the effects of bremelanotide for women with HSDD conclude that the drug is at best minimally effective [53].

5. Preclinical models of female sexual desire

Colloquially the belief is that animals have sex for the purpose of reproduction, whereas people primarily have sex for the pleasure they receive. This dichotomous view has been rejected both from neurobiological [54] and anthropological [55] perspectives. Instead, the parsimonious view is that (at least) all mammals engage in sex for the pleasurable/rewarding consequences. Neurobiologically, this view focuses on the mesolimbic system as the hub integrating external stimuli and experiences into subjective reward and pleasure [33]. Others have effectively reviewed the underlying neurobiology of female sexual behavior in rodents. In this section we will focus on

how rodents have been effectively utilized to model components of female sexuality and how these models can be used to develop a rational translational strategy for developing therapeutics for women with sexual dysfunctions.

5.1 Rodent models

Female rats and hamsters have been the primary rodent models for dissecting components of the female sexual response, with each species providing a somewhat different insight. For both rats and hamsters, males approach the female from the rear and initiate a mounting attempt. This mount triggers the female's sexual posture, lordosis, which makes her vagina accessible for penile insertion (**Figure 2**). This mount only lasts up to a few seconds and may end with penile insertion (termed mount with intromission, or just intromission), or not (mount without intromission, or just mount). The intromissions are key and after a number of mounts with intromission, the male will intromit and ejaculate. The female's behavior while the male is approaching and mounting differs greatly between rats and hamsters. Female rats, after a male mounts escape the male and will actively run around with the male in pursuit. The female then stops, permitting the male to catch her and mount with or without intromission. If the male mounted without intromission the female will let the male catch up to her more quickly than if the male intromitted. This frequency of intromissions and their temporal patterning is important reproductively as there

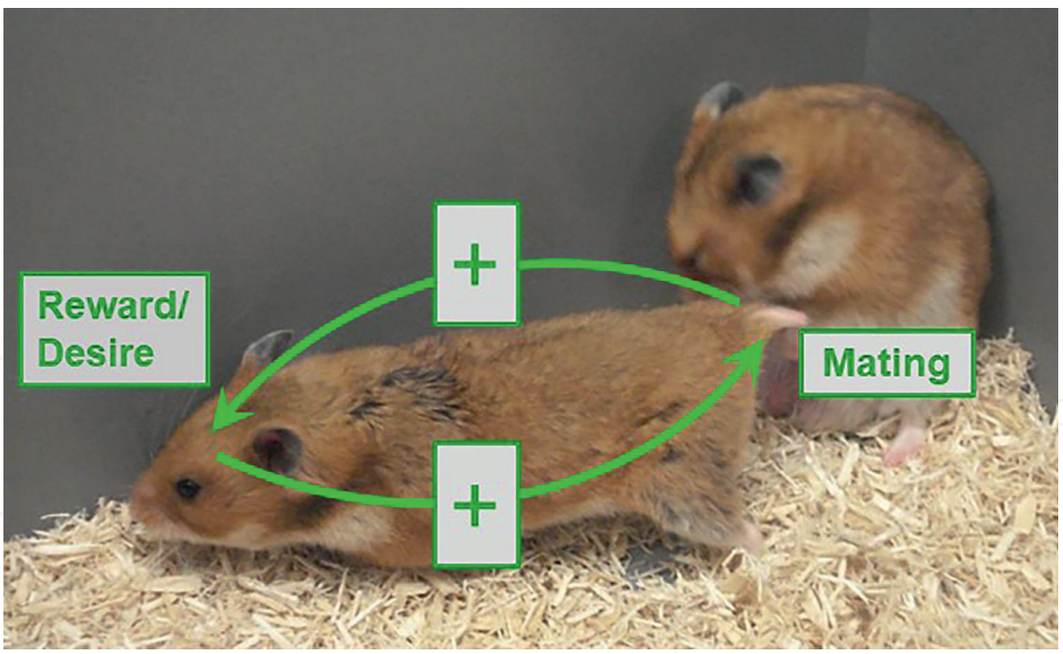

Figure 2.
Rodent Sexual Response Cycle. Sexual behavior in the female hamster involves a relatively immobile posture (termed 'lordosis') in which the female arches her back, making her vagina accessible to the mounting male. Vaginal intromission by the male is a sexually-rewarding stimulus for the female. Sexual experience produces a positive feed-forward process increasing the female's interest in and desire for sex in future encounters with males. With multiple sexual interactions with male hamsters, the female develops increased sexual interest and motivation for sex, as measured in a conditioned place preference paradigm. During sex with the male the female makes subtle perineal movements (a measure of sexual desire) that align her vagina with the point of contact of the male's penile thrusts. These movements become more efficient with repeated experience, increasing the male's ability to achieve insertion. In female hamsters, the combination of the rewarding/motivating consequences of sex (sexual interest) and the ability to regulate the likelihood of the male gaining vaginal intromission (sexual desire) are both dependent on mesolimbic dopamine neurotransmission.

is an optimal pattern that ensures fertilization upon ejaculation. In contrast, female hamsters retain a rather immobile lordosis posture between mounting attempts by the male (**Figure 2**). The male hamster may mount with or without intromission. For female hamsters there is no temporal component to receiving optimal stimulation for fertilization, rather it is the percentage of mounts that include intromission that impacts successful reproduction. As we will see, the female hamster can influence the percentage of intromissions by the male.

5.1.1 Behavioral paradigms for assessing interest

An incentive motivation testing arena consists of a large oval area with two small cages fitted to the outside wall. A wired mesh separates the small cages from the oval arena [56, 57]. The female rat is placed in the oval arena and the opposite-sex rat is placed in one of the two cages. The amount of time the female spends touching and in close-proximity to the cage with the male is used as the assessment of sexual interest [58–60]. A critical component of this test is that no sexual interactions occur, meaning that motivation is tested in the absence of actual copulation.

Similar to the incentive motivation testing arena, the three-compartment test box consists of a large Plexiglas arena divided into three equal sized compartments. The two dividers separating the middle from the outer chambers contain a small opening that allows the female subject to move freely between the three compartments. The stimulus male is confined because of the size of the opening or physically restrained in one of the two outer compartments. The amount of time the female spends in the compartment containing the stimulus male is used as the assessment of sexual motivation. Here too, physical interaction between the male and female is prevented, thus this is a measure of motivation in the absence of sexual behavior.

5.1.2 Behavioral paradigms for assessing arousal

Pacing chambers are arenas that have been optimized in such a manner that it allows the female rat control over the timing of sexual interactions with a male. One example is the bilevel arena, which consists of two elevated platforms that are separated on either side by narrow ramps [61, 62]. The male is placed on the bottom platform and the female is placed on the top platform. Because an adult female rat is smaller than adult male rats, the female can move freely either up or down between the two platforms to approach or escape the male, pacing the interaction. A variation of this testing arena utilizes a two-compartment unilevel pacing chamber [63] that has a small aperture which because of its size is accessible only by the female. Collectively, these pacing chambers result in the female controlling, limiting and terminating the number and amount of sexual interactions by the male [64, 65]. In these set-ups the active behavioral displays by the females are an accurate representation of their internal arousal state.

5.1.3 Behavioral paradigms for assessing sexual desire

Female hamsters assume the lordosis posture in the presence of a male even without physical contact. When an inexperienced male is tested with an inexperienced female, the male achieves intromission approximately 40–50% of the time [66]. The female's immobility gives an observer a misleading impression that the female

is not an active participant in the sexual interaction. If the female's perineum (the area around the vagina) is treated with a topical anesthetic, the male will not achieve intromission [67]. Indeed, the female makes subtle postural movements that align the location of her vagina with the male's point of thrusting.

An interesting element of this copulatory interaction with the male is that the percentage of time the mounting male gains intromission increases up to 80% if the female hamster is given repeated sexual experience. The behavioral goal for the female seemingly is to receive vaginal stimulation from the male. With sexual experience the female learns to better control her perineal movements to maximize the receipt of vaginal stimulation, i.e., experience increases her level of desire in future sexual interactions.

5.1.4 Behavioral paradigms for assessing sexual reward

An interpretation of the sexual desire paradigm for female hamsters is that the females find vaginal stimulation to be rewarding and thus with experience they change their behavior to receive more stimulation from the male's intromissions. In this view, mating for female rodents has rewarding consequences that maintain their interest, desire, and arousal in future encounters with males.

The primary way that sexual reward is measured in female rodents is with a conditioned place preference (CPP) apparatus [68, 69]. The CPP apparatus is often a three-chambered apparatus with two outer chambers that differ in some physical element (e.g., type of bedding on the floor and/or hue of the walls of the chamber), separated by a smaller central chamber. Females are initially placed in a center compartment and then permitted to explore the three chambers freely to determine an initial preference between the two outer chambers. After establishing the initial chamber preference, females are given repeated sexual behavior tests in one of the compartments and are placed alone in the other compartment for the same period of time and testing sessions. This allows for follow-up testing where the female again explores all of the chambers to assess an increase in preference for the chamber paired with sex. This is an example of contextual conditioning in which the sexual experiences result in a drive towards cues previously associated with sex, an endpoint suggesting sexual reward.

Female rats do not develop a CPP if the male rat is allowed to control the pacing of the sexual interaction. Females only display a place preference for sexual intercourse if they are allowed to pace the frequency and duration of sex [63, 70]. This is an adaptable behavior in that the optimal pattern of sexual interactions is both rewarding and maximizes fertility, even if these processes are neurobiologically independent.

5.2 The neurobiology of desire and reward

These behavioral tasks can be used to identify mechanisms underlying sexual interest, motivation, desire, arousal and reward. The literature to date is too vast to summarize here, so we provide a brief overview and highlight a few examples.

5.2.1 The reward circuit

The canonical reward pathway [71] in mammals (including people) has at its heart dopaminergic neurons arising in the ventral tegmental area (VTA), and projecting to

the medial prefrontal cortex (PFC) and nucleus accumbens (NAc). In turn, the PFC modulates activity in the NAc. It is theorized that dopamine release in the nucleus accumbens underlies reward processing [72–74].

If this pathway underlies sexual desire and reward, for example, manipulating it should affect the behavioral paradigms we just discussed. A dramatic finding comes from studies in which the region including the NAc was damaged in female rats [75, 76]. The females were given hormones to make them sexually responsive. When placed with males, the females fought off the male's mounting attempts rather vigorously. If the male was able to mount, the female showed a normal lordosis response. These lesions seemingly eliminated sexual desire and arousal, though sparing circuits mediating the expression of the sexual response itself.

Chemically damaging the dopamine terminals in the NAc originating from the VTA, eliminated the effects of sexual experience on sexual desire in the hamster model [66]. Despite the females' repeated sexual experience, the percentage of mounts with intromission by the males was the same as in sexually inexperienced female hamsters. Again, the females showed normal levels of lordosis, but had a decreased desire for mating with the male.

As a last example, dopamine receptor antagonists were given to female hamsters prior to each of the sex conditioning tests in the CPP paradigm [68]. When given the post-test to explore the apparatus after conditioning, the females did not spend any more time in the sex behavior chamber, indicating that the dopamine receptor blocker prevented the rewarding consequences of sex.

These studies support the idea that the mesolimbic system underlies the feedforward effects of the pleasurable responses to sex in females. With decreased activity in this pathway, females become indifferent to the positive components of sexual interactions. In extreme cases, a loss of mesolimbic system input can make sex aversive and underlie the elimination of sexual desire.

5.3 Application of preclinical models to the development of therapeutics

Prior rodent studies with bremelanotide suggested that the drug enhanced sexual arousal in female rats during sexual interactions with males. In this section we review the results of those studies along with our own unpublished data on bremelanotide effects on sexual reward in female hamsters.

5.3.1 Bremelanotide increases sexual arousal

Previous behavioral studies in bilevel arena pacing chambers demonstrated that peripheral administration of bremelanotide (50, 100 or 200 μg/kg) increased proceptive behaviors indicative of sexual arousal in female rats [77, 78]. Similar effects in female rat sexual arousal were reported following systemic treatment of melanotan II, a bremelanotide analogue [79]. Injection of bremelanotide directly into the brain of female rats also increased sexual arousal and this effect was blocked with a melanocortin receptor antagonist [77].

5.3.2 Bremelanotide does not enhance sexual reward

The questionable efficacy of the FDA-approved drug Vyleesi prompted us to return to preclinical foundations to examine its effects in our female Syrian hamster model of sex reward. We aimed to determine whether sex alone or with

bremelanotide would increase behavioral responding indicative of reward in the CPP apparatus.

From our prior studies we knew that 5 CPP conditioning sessions produced full sexual reward, whereas 2 sessions was minimally effective [80]. Further, by activating intracellular signaling in the NAc we could enhance the rewarding effects of 2 weeks of CPP conditioning such that the levels of conditioned reward were equivalent to that of females receiving 5 weeks of CPP [80]. Based on this positive outcome, we reasoned that bremelanotide given prior to each of 2 CPP sessions should increase sexual reward. To model the administration of bremelanotide for sexual desire in women we injected it systemically prior to the sexual conditioning session (Borland, unpublished results).

Consistent with our prior studies, the 5 CPP sessions produced maximal levels of sexual reward, with the 2 CPP sessions significantly less effective. We should note that in this study the shorter (2-week) period also increased reward. Females that had 2 CPP sessions paired with bremelanotide (regardless of dose) did not display an increase in preference for the sexually conditioned chamber (i.e., no evidence of sexual reward). To the contrary, bremelanotide actually decreased levels of sexual reward in conjunction with 2 CPP sessions. The lack of effect of bremelanotide on CPP in our hamsters is consistent with a similar absence of action on sexual reward in female rats [77].

5.3.3 Bremelanotide does not Increase MC3R or MC4R expression

To better understand the neurobiology underlying this inhibitory effect of bremelanotide, we then assessed mRNA expression of MC4R in the mesolimbic system from the hamsters in the CPP study. Interestingly, sexual experience resulted in an increase in MC4R expression in the nucleus accumbens, but not the dorsal striatum (a negative anatomical control region). Consistent with the CPP results, there was a decrease in the expression of MC4R in the nucleus accumbens for females that received bremelanotide prior to the 2 CPP sessions compared to control females.

Both MC3R and MC4R are expressed in the VTA. Neither sex nor bremelanotide treatment affected MC4R mRNA expression in the VTA. However, bremelanotide resulted in a decrease in MC3R expression in the lateral region of the VTA compared to controls. Taken together, our findings provide no evidence to support the use of bremelanotide for increasing reward derived from female sexual experiences and in fact provide evidence to support a negative effect in the reward/motivation circuit.

5.3.4 Synthesis

From the combination of studies investigating bremelanotide effects on arousal and sexual reward in female rodents, we can conclude the following: 1) In female rats bremelanotide treatment increases arousal during copulation in female rats. 2) In female rats and hamsters bremelanotide failed to increase sexual reward in CPP tests. 3) In fact, in female Syrian hamsters bremelanotide treatment not only fails to enhance sexual reward, but actually decreases sexual reward in CPP tests. 4) Finally, bremelanotide decreased MC4R expression in the nucleus accumbens and MC3R expression in the VTA.

Collectively, although bremelanotide may enhance sexual arousal in female rodents, it fails to enhance sexual reward and inhibits melanocortin neurotransmission in

the reward circuit. This pattern of preclinical findings would not have supported the development of bremelanotide as a drug to promote sexual desire in women.

6. Commentary

Nappi [7] presented an expert opinion on the relative lack of drugs to treat female sexual dysfunction. She highlighted the wide range of causes for sexual dysfunction in women, as opposed to simply erectile dysfunction in men. She noted that we still have an incomplete understanding of a woman's sexuality, which is a prerequisite to developing treatments. She also pointed out that female sexual dysfunction is not a life-threatening clinical problem, so that it is important to balance the clinical effectiveness of drugs with the drug's safety for the women taking them. Finally, Nappi [7] was concerned with drugs that needed to be taken chronically (e.g., Addyi), and hoped that on-demand medications (e.g., Vyleesi) could be developed. Nappi's commentary is still very current and meaningful, and rational drug development (in her view) will only be achieved through the cooperative partnership of sexual experts, pharmaceutical companies and medical agencies [7].

6.1 A rational approach to drug development

In Section 4 we described how Addyi and Vyleesi went to clinical trials with remarkably little preclinical data supporting their effects on sexual behavior in animal models. If developing drugs to treat sexual dysfunction in women is an important endeavor, the starting point has to be investment in basic research in both the public and pharmaceutical sectors. This research should be designed to take advantage of current animal models (and develop new animal models [81]) to identify potential molecular targets for therapeutics. This is how drug development begins for essentially all diseases and is only emphasized here because this message clearly was lost in the development and marketing of drugs for HSDD in women.

6.2 Pathologizing the normal

Basson et al. [9] developed a comprehensive model of female sexuality that emphasized the complexity of a woman's sexual response. At the same time that this model is a valuable contribution to understanding female sexuality, it also highlights the individual variability in sexual responses among women, making it difficult to define what a normal response pattern is. If we cannot define a normal sexual response, then how do we define sexual dysfunction in women [82–84]. Basson et al. [82] disagree with DSM criteria that quantify numbers of sexual fantasies or whether a woman initiates sexual activity as determinants of sexual dysfunction. They assert that few or no sexual fantasies are not a pathology, nor is it pathological if a woman does not initiate sexual activity.

Based on earlier arguments, Meixel et al. [84] lay out a historical account of the many examples of the drug industry's marketing strategy of "condition branding". With condition branding, the drug company creates a medical condition to support the development of a drug. In the example of Addyi, HSDD was elevated in significance as a treatable source of distress as part of the rebranding of the drug to address the disparity in the treatment of sexual dysfunction in men and women. It is disturbing that drug-company supported continuing medical education (CME)

modules were developed to "educate" clinicians about this disorder. Meixel et al. [84] note (p. 860):

"Specific marketing messages that we identified within the CME modules included the following:

1. Hypoactive sexual desire disorder is very common and underdiagnosed.

2. Hypoactive sexual desire disorder can have a profound effect on quality of life.

3. Women may not be aware that they are sick or distressed.

4. Hypoactive sexual desire disorder and distress can have other names.

5. Clinicians should initiate conversation with their patients about their sexual health.

6. Clinicians find it difficult to discuss their patients' sexual concerns and lack training and confidence in the diagnosis of sexual problems.

7. Clinicians need tools and resources to help them diagnose hypoactive sexual desire disorder.

8. Simple tools, including the decreased sexual desire screener (DSDS) and Female Sexual Function Index (FSFI) can assist clinicians in diagnosing hypoactive sexual desire disorder.

9. A major barrier to clinicians talking about hypoactive sexual desire disorder/female sexual dysfunction is the lack of medications.

10. It is problematic that there are medicines available to treat sexual problems for men but not women."

Key elements in the continuing education modules to be noted here are that the lack (at the time) of medications for HSDD was an impediment for physicians to have discussions about sexual desire with their patients and that women may have HSDD even if they are unaware of it.

6.3 Therapeutic approaches

A starting point for therapy may lie in reassuring women that their sexual feelings are not abnormal and are shared by many other women [82]. This does not alleviate tensions and conflict in a relationship, but can more effectively set the stage for other therapeutic approaches. For example, changing a women's view of herself can aid in communication with her partner about her sexuality to alleviate interpersonal conflicts [82]. Knowing that her feelings are normal and shared will boost self-esteem and relieve personal insecurities, both of which are barriers to promoting relationship satisfaction and feeling sexually desirable. This is clearly a simplistic approach that in isolation will not be sufficient for most women [85]. Still, this is an important component of any therapeutic plan.

Given that fatigue is a key factor underlying low sexual desire in women, approaches to reduce lifestyle stress and fatigue may be helpful. Mindfulness strategies can be helpful in this regard [86–89] and have the advantage of being easy to apply and are inexpensive. Presumably other lifestyle approaches may also be beneficial when HSDD results from these types of life events.

Cognitive processes impact HSDD when women view their own behavior, rather than relationship issues, as central to their levels of sexual desire. A rather thorough review [90] supports a role of cognitive behavioral therapies in treating women with HSDD. The goals of these approaches are straightforward, aiming to increasing the rewarding experiences for women and improve relationships through cognitive restructuring and communication. As with mindfulness strategies, cognitive behavioral therapy can be conducted through online training as well as in person.

Drugs should be a last line of treatment [2, 91], and used perhaps in conjunction with behavioral therapies. The worry with drug therapies is that they necessarily carry side effects that vary in severity. This is unavoidable with any compound that affects neurotransmission, as there will be direct and indirect effects on chemical transmission that are spread throughout the central nervous system, beyond the specific circuits targeting the behaviors in question [36].

7. Conclusions

It is abundantly clear that low levels of sexual desire reduce the likelihood that women will initiate or engage in sexual activity with a partner. Even if the reduction in desire is a natural product of the amount of time in a relationship, this can still strain relationships and be a personal source of distress for women. As sexual desire has underlying psychological bases, it seems on the surface that different types of counseling and behavioral therapies would be the best approach to treatment for women for which this is a problem. Perhaps guided by the absence of approved treatments for sexual dysfunction in women, the FDA approved two drugs (Addyi and Vyleesi) to treat HSDD, despite questionable effectiveness in clinical trials. The intent to develop drugs to treat HSDD is laudable, though only if effective on their own or in conjunction with other therapies. The mistake made for current drugs is that they were not developed to treat HSDD, but rather were recast from their original developmental purpose (an antidepressant medication for Addyi and a permanent skin tanning agent for Vyleesi). If drug development for treating HSDD is to be effective in the future, it must start with a rational approach based on animal models of female sexuality. Following the basic research, a cooperative interdisciplinary effort that includes basic research on human sexuality, sex therapies, and of course pharmaceutical control will meet the challenge of drug development for HSDD and other sexual disorders in women.

We finish this chapter with a caveat. The research on models of female sexuality and the research cited in this chapter are focused on cis-gendered heterosexual women. We spoke of the individual variation in responses among these women and it should be clear that variation is dramatically amplified when we consider individuals across the range of personal sexual identities. A clear goal of future studies should be to broaden the scope of this research to address the need for gender identity-based approaches to basic research and the development of appropriate therapeutics.

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Conflict of interest

The authors report no conflicts of interest, financial or otherwise, with the content of this chapter. In addition, the opinions and conclusions expressed in this chapter are those of the authors alone, and do not necessarily reflect the views of the National Institutes of Health.

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