# Bremelanotide

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Bremelanotide is a melanocortin receptor agonist which non-selectively activates melanocortin 1 receptor (MC1R), melanocortin 2 receptor (MC2R), melanocortin 3 receptor (MC3R), melanocortin 4 receptor (MC4R), and melanocortin 5 receptor (MC5R) receptors.

Keywords: hypoactive sexual desire disorder ; bremelanotide ; melanocortin receptor agonist

## 1. Introduction

Hypoactive sexual desire disorder (HSDD) is the most prevalent female sexual health disorder [1]. HSDD is defined as persistent deficiency or absence of sexual fantasies and desire, resulting in significant distress or interpersonal difficulty [2]. The criteria based on the Diagnostic and Statistical manual are “persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity: that causes marked distress or interpersonal difficulty” [3]. Women with this disorder may display a lack of motivation for sexual activity, reduced responsiveness to erotic cues, a loss of interest during sexual activity, and avoidance of situations that could lead to sexual activity. Women who suffer from HSDD commonly have reduced self-confidence, self-worth, and impaired body image [2]. Diagnosis of HSDD requires personal distress and a change in sexual desire for a least three months [4][5]. Subtypes of HSDD include those that are due solely to “psychological factors” and “combined factors.” The HSDD can be due to psychological factors, substances, or medical conditions in the combined subtype. The overall prevalence of HSDD ranges from 8–19% [1][6][7][8]. The prevalence of HSDD increases with age and has a higher prevalence in postmenopausal women. The risk is the greatest in younger women in surgical menopause and is associated with a less active sex life and decreased sexual and relationship satisfaction [1]. Women who are premenopausal and experience hypoactive sexual desire have higher levels of distress than postmenopausal women and are more likely to seek help [9]. Women with distressing low sexual desire have a poorer health-related quality of life. Women suffering from this disorder have reported decreased physical functioning, vitality, social functioning, general health, mental health, and a loss of femininity [1][10].

Several factors have been proposed to explain the etiology of low sexual desire and the accompanying distress. These factors include partners and life situation, ethnicity and culture, menopause status, central nervous system activity, and hormonal influences [10]. Married women or women living with a spouse or partner were more likely to have distressing low sexual desire than single women [11]. The PRESIDE study revealed that Caucasian women were more likely than Black women to have low sexual desire [10]. Additionally, brain areas such as the cerebral cortex may play a role in women developing HSDD. When presented with erotic cues, women with HSDD were shown to have weaker cerebral cortex activation in the right hemisphere and less deactivation in the left hemisphere than women who did not have HSDD [12]. Various drugs or conditions that decrease dopamine levels alter brain serotonin at serotonin 2A receptors or increase opioids at mu receptors have also been shown to reduce or inhibit sexual desire [13][14]. Treatment of HSDD includes both psychosocial and biological therapies. Psychosocial therapies include cognitive behavioral therapy, sensate focus therapy, and mindfulness-based cognitive therapy. The current biological therapies for HSDD include flibanserin, testosterone therapy, bupropion (off-label treatment), and buspirone (off-label treatment) [2].

## 2. Hypoactive Sexual Desire

### 2.1. Risk Factors

HSDD often goes underdiagnosed and undertreated due to the private nature of the condition, making it difficult for patients to discuss with physicians. Understanding and identifying risk factors associated with HSDD may help medical providers initiate conversations with patients. Several factors have been associated with a potentially increased risk of HSDD, including biological, psychosocial, and pharmacological influences. Some commonly studied biological risk factors for HSDD include age, hormone level, and other comorbidities [15][16][17]. In a study on sexual distress in US women, Shifren et al. noted that although sexual dysfunction increases with age, actual personal distress about sexual issues

decreases with age. This study reported that sexual distress occurred in 12% of the studied population and was more common in mid-aged (45–64 years) women (14.8%), followed by younger women (10.8%) and older women (8.9%) [8]. Other studies of both US and European women have shown that postmenopausal women and women who have undergone oophorectomy (surgical menopause) have lower sexual desire and a higher risk of developing HSDD than pre-menopausal women with younger surgical postmenopausal women being at greatest risk [18]. This finding suggests that the decrease in estrogen and androgens after either natural or surgical menopause plays a role in losing sexual desire and developing HSDD [17][19]. However, other postmenopausal symptoms, such as vaginal dryness, may also lead to low sexual desire, highlighting the importance of excluding other possible causes when considering the diagnosis of HSDD [20]. Comorbidities that have also been associated with HSDD include chronic medical conditions (diabetes, coronary artery disease, etc.), urinary incontinence, multiple sclerosis, Parkinson's disease, and head injury [17]. Leiblum et al. reported that women with HSDD had significantly more general health issues than women without HSDD [1].

Studies have also reported psychosocial risks related to HSDD, including depression, relationship status, and culture. Depression can both lead to and be a result of HSDD, which is why it is important to determine the onset of depressive symptoms in relation to low sexual desire and personal distress [10]. A study by Whalin-Jacobsen et al. looked at the association of androgen levels and psychosocial factors with HSDD and found that androgen levels were associated with low sexual desire but not with HSDD [21]. However, relationship length and depressive symptoms were positively associated with HSDD, underlining the importance of using a biopsychosocial model to understand and diagnose HSDD [12]. The prevalence of low sexual desire has been reported to be similar among surgically postmenopausal women of European descent; however, HSDD was more prevalent in France (22%) than in Germany (7%), which suggests that culture plays a role in developing HSDD [15].

Finally, it is important to consider pharmacological risks eliciting HSDD symptoms. Selective Serotonin Reuptake Inhibitors (SSRIs) cause an increase in serotonin, which is considered an inhibitory signal of the sexual drive leading to a blunted sexual response and distressing low sexual desire. Opioid consumption can also be a cause of hypoactive sexual desire [22]. Opioids can inhibit ovarian sex hormones and adrenal androgen production, which was found in a study that looked at women who were chronically using sustained-action opioids [22][23]. Opioids exert their effects on adrenal androgen production through their inhibitory effects on the hypothalamo-pituitary-adrenal axis [23]. However, pharmacologically induced HSDD does not fit the *Diagnostic Statistical Manual* IV (DSM-IV) criteria of HSDD.

### 2.2. Pathophysiology

The pathophysiology of HSDD is thought to be centered around inhibitory and excitatory hormones, neurotransmitters, and specific brain anatomy [16][24][25]. Estrogen, testosterone, progesterone, and dopamine positively affect sexual desire, whereas serotonin, opioids, and prolactin negatively affect sexual desire. Studies on rats suggest that estrogen and testosterone exert their excitatory effect on sexual response via increasing dopamine release and synthesis, respectively [26][27]. Conversely, serotonin reduces dopamine's positive effect on sexual response, leading to its inhibitory effect [25].

There is support in animal studies that testosterone also has a role in sexual desire. A study performed by Maseroli et al. looked at non-aromatized androgen dihydrotestoerone (DHT) and sexual behavior in female rats. The rats who were primed with estrogen and received DHT displayed significantly more appetitive behaviors compared to the negative controls [28]. The authors concluded that the administration of DHT enhances sexual behavior. This argues that testosterone does play a role in sexual desire, suggesting that it may also play a role in hypoactive sexual desire.

Neuroimaging studies have shown that HSDD is related to a sexual desire brain network (SDBN) involving different areas of the brain that are either excited or repressed by sexual stimuli. These studies suggest that atrophy of excitatory areas and hyperactivity in inhibitory areas may lead to an increased risk of HSDD [24]. This study also reports that this SDBN upholds the top-down processing model of HSDD, suggesting that women with HSDD focus their attention more on evaluating their response to sexual stimuli rather than on allowing themselves to be stimulated.

## 3. Current Treatment

Since a variety of biological, psychological, and social factors cause HSDD, current treatments follow a biopsychosocial approach when evaluating and treating patients affected by the disorder [17][29][30]. Literature sources agree that there are significant challenges in the treatment of HSDD due to the lack of structured treatment regimens and clear clinical guidelines, so treatments may vary on an individualized basis. Recommended treatments start with office-based counseling before progressing to psychotherapy and/or pharmacotherapy [17]. Prior to discussing the available treatment

options, it is important to note that approved treatments are limited in women with HSDD who are postmenopausal. In this section, the current treatment will be discussed.

### 3.1. Office-Based Counseling

Initially, office-based counseling may help treat HSDD with basic education and recommended lifestyle changes to improve sexual desire [31]. Clinician reluctance to discuss sexual health is a significant barrier for treating patients with HSDD. As a result, clinicians must be proactive in identifying sexual concerns and determining the best available treatment options. One popular approach for office-based counseling is the PLISSIT model, an approach used for the treatment of sexual disorders. The model incorporates permission to discuss problems and emotions, limited information on basic sexual function education and resources, specific suggestions to address problems with directives, and the need for more intensive treatment [32].

### 3.2. Psychological

Subsequently, psychological intervention has been recommended as a next treatment modality if office-based counseling is ineffective or severe psychiatric issues, such as trauma or abuse, are revealed for individual cases. Studies have suggested a collection of separate interventions for female sexual dysfunction include cognitive-behavioral therapy (CBT), mindfulness meditation therapy (MMT), and exercises for couples. However, although controlled trials support the use of CBT and MMT for the treatment of HSDD, the efficacy of these interventions has not been supported by scientific and regulatory standards for drug treatment trials. Specifically, trials testing the efficacy of psychological treatments lack the scientific and regulatory standards necessary for significant results. Standards include reproducibility of intervention, randomizations, adequate control, and/or outcomes of clinical relevance [33]

### 3.3. Pharmacological

A variety of pharmacological treatments have been tested for HSDD through randomized controlled clinical trials. However, current treatment options approved by the FDA are still limited for women with the disorder. Treatment options focus on the inhibitory and excitatory pathways linked to the regulation of responses for sexual cues. There are ongoing investigations for novel treatments against HSDD cover hormone therapies and centrally acting drugs intended to regulate these neural pathways [31]. Studies have measured efficacy using patient-reported outcomes of sexual desire [34][35].

### 3.4. Off-Label Treatments

Alternative pharmacological approaches have been studied using off-label medications. One of the most common treatments tested for HSDD has been testosterone. Testosterone is the primary sex hormone associated with the regulation of sexual desire, and low levels in postmenopausal women are associated with loss of libido and decreased sexual activity [17]. HSDD has been hypothesized to occur due to low circulating androgen levels arising from either post-menopause or surgical removal of the ovaries [36][37]. Currently, data support that testosterone treatment shows efficacy in women with low levels and a decrease in sexual desire [38][39][40][41][42][43]. Likewise, combination therapy of estrogen and methyltestosterone has been shown to be a viable treatment for HSDD. However, studies evaluating testosterone treatment for HSDD have not evaluated long-term treatments nor have they established detailed results on safety and tolerability [44]. Currently, treatments incorporating testosterone with other medications such as sildenafil are being evaluated for improved sexual functioning [45].

Another off-label treatment being tested for HSDD is bupropion. Bupropion, a dopamine and serotonin reuptake inhibitor, shows a lower incidence of sexual dysfunction in patients with major depressive disorder [46][47][48][49][50]. In studies evaluating women with HSDD, bupropion had a significantly increased rate of release compared to placebo [51][52]. It is thought that the increased availability of dopamine is what helps to decrease the risk of sexual dysfunction and could be the reason it may be helpful in treating HSDD.

### 3.5. Approved Agents

Flibanserin (postsynaptic 5-hydroxytryptamine 1A agonist and 2A antagonist) was the first agent approved by the FDA for the treatment of HSDD [53]. Flibanserin functions by decreasing serotonin levels and increasing both dopamine and norepinephrine levels [13][54]. Flibanserin has a high affinity for 5-$HT_{1A}$ receptors in the hippocampus and the prefrontal cortex [55]. It also has agonist activity at the 5-$HT_{1A}$ postsynaptic receptors, which has some downstream effects in altering the levels of other monoamines, including dopamine [55]. Flibanserin also causes a net increase in norepinephrine concentrations in the prefrontal cortex through the disinhibition of the locus coeruleus noradrenergic neurons [55]. These neurotransmitters have been associated with excitatory and inhibitory responses to sexual cues implicated in HSDD [13].

Clinical trials have demonstrated that subjects experienced improved satisfying sexual events after taking flibanserin compared to that of the control group [56][57][58][59][60][61][62][63][64]. Flibanserin was initially rejected for approval by the FDA in 2010 due to concerns over efficacy and safety data [53][65]. The most common adverse events included somnolence and dizziness, which researchers have explored with alcohol use [54][62]. Finally, Bremelanotide, which is the main focus of this paper, is a melanocortin receptor agonist and has been recently approved by the FDA for the treatment of HSDD [10][66].

## 4. Bremelanotide

Bremelanotide is a melanocortin receptor agonist which non-selectively activates melanocortin 1 receptor (MC1R), melanocortin 2 receptor (MC2R), melanocortin 3 receptor (MC3R), melanocortin 4 receptor (MC4R), and melanocortin 5 receptor (MC5R) receptors. Activation of MC4R receptors modifies brain pathways involved in sexual responses [67]. Stimulation of MC4R receptors can also cause a transient increase in blood pressure and a decrease in heart rate [68]. Bremelanotide is contraindicated in individuals with uncontrolled hypertension or cardiovascular disease [69]. Activation of MC1R receptors may contribute to the adverse effect of hyperpigmentation [67]. Bremelanotide is able to be administered intranasally or as a subcutaneous injection. The subcutaneous route has 100% bioavailability and is associated with fewer side effects [68]. The recommended dosage of bremelanotide is 1.75 mg injected subcutaneously in the abdomen or thigh at least 45 min prior to sexual activity. Individuals should take only one dose every 24 h. Individuals should refrain from taking more than eight doses of bremelanotide per month.

### 4.1. Mechanism of Action

The mechanism of action of bremelanotide is better understood for treating male sexual dysfunction compared to female sexual dysfunction. In males, bremelanotide primarily acts on MC3R and MC4R to help treat erectile dysfunction. The stimulation of the melanocortin receptors, in general, causes a local increase of nitric oxide in the penis leading to vasodilation and penile erection [70][71]. In females who suffer from HSDD, abnormal sexual responses are due to an imbalance of various neurotransmitters. Amongst these neurotransmitters, dopamine, and melanocortin stimulate attention and desire while norepinephrine and oxytocin stimulate sexual arousal [72]. In females, administration of bremelanotide acts primarily on the presynaptic MC4R and stimulates the release of dopamine to portions of the nucleus accumbens, medial preoptic area, verbal tegmental area, arcuate nucleus, and the medial and basolateral amygdala [66]. These brain areas are involved in regulating the motivational, arousal, and appetitive aspects of sexual behavior [73].

### 4.2. Pharmacodynamics of Bremelanotide

Bremelanotide is a non-selective agonist of the melanocortin receptors but is thought to mainly act as an MC3R and MC4R receptor agonist. It is important to note that agonism of the melanocortin receptors may lead to increased melanin expression, which can lead to hyperpigmentation [74]. The main adverse effects of bremelanotide include transient increases in systolic and diastolic blood pressure, nausea, headache, and hyperpigmentation [75]. In a study addressing the pharmacodynamics of bremelanotide, researchers monitored ambulatory blood pressures of premenopausal women who received the drug daily for eight days. They found a mean increase of 1.9 mmHg (daily SBP) and 1.7 mmHg (daily DBP). Elevated SBP and DBP measurements peaked at 2.8 mmHg 4–8 h after receiving a dose of bremelanotide and at 2.7 mmHg 0–4 h after receiving a dose, respectively.

### 4.3. Pharmacokinetics of Bremelanotide

After subcutaneous administration of bremelanotide, its mean maximum plasma concentration reaches 72.8 ng/mL, and AUC is 276 hr*ng/mL. Bremelanotide's Cmax level reaches its plateau after a 7.5 mg dose administration. It takes about 1 h for Bremelanotide to reach its maximum plasma concentration and does have 100% bioavailability with a subcutaneous injection. It is noted to be 21% protein-bound in the serum [74]. After a subcutaneous dose of bremelanotide, its half-life is 2.5 h and has a mean clearance of 6.5 +/− 1.0 L/h. Bremelanotide is a 7 amino acid chain and its metabolism consists of multiple hydrolysis reactions [74]. It is renally excreted (64.8%), with some fecal excretion (22.8%). Renal and hepatic impairment causes an increase in bremelanotide's AUC. Bremelanotide decreases gastric emptying and has been shown to decrease the rate and extent of absorption of other orally administered drugs, particularly indomethacin and naltrexone. If patients are taking these drugs, they should avoid taking bremelanotide [75].

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