Bremelanotide for Hypoactive Sexual Desire Disorder

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The medicalization of decreased sexual interest is a controversial subject; nevertheless, two medical treatments have been approved for hypoactive sexual desire disorder (HSDD) in women. These are flibanserin (Addyi) and bremelanotide (Vyleesi).¹,²

Bremelanotide

Bremelanotide received marketing approval from the US FDA on June 21, 2019. It was approved for use in premenopausal women diagnosed with acquired, generalized HSDD.² The drug is a nonselective agonist at melanocortin (MC) receptors 1-5, and its action on MC4 and downstream targets in the central nervous system may explain its benefits in HSDD.³

Bremelanotide is an analogue of the naturally occurring peptide alpha-melanocyte-stimulating hormone.⁴ Being a peptide, bremelanotide has poor oral bioavailability and needs to be self-administered by the parenteral route, using an auto-injector, at least 45 min before its effect is desired. Injection is by the subcutaneous (sc) route, into the abdomen or thigh; this has 100% bioavailability, in contrast with the previous intranasal formulation under development that was associated with inconsistent bioavailability.²,³ Bremelanotide is associated with few to no drug–drug interactions and, unlike flibanserin, does not adversely interact with alcohol.³

Bremelanotide: Efficacy and Adverse Effects

The efficacy of bremelanotide (1.75 mg sc) for HSDD in women was studied in 2 24-week, Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trials⁵; these were the “RECONNECT” studies. The pooled sample included 1267 women. The mean age of the sample was 39 years. The sample was 86% white.

The Female Sexual Function Index (FSFI) desire domain score at baseline was approximately 2.0; both groups improved across time, and at endpoint, bremelanotide was (significantly) superior to placebo by 0.3 points in a pooled analysis; the effect size was 0.39.

The distress item score on the Female Sexual Distress Scale was approximately 2.9 at baseline; again, both groups improved across 24 weeks, and at endpoint, bremelanotide was (significantly) superior to placebo by 0.33 points in a pooled analysis; the effect size was 0.27.

For both desire and distress analyses, the benefits were apparent at 4 weeks, which was the first post-treatment assessment point, and the benefits were sustained to the 24-week endpoint assessment. The response rate was 58% vs 35% for drug vs placebo. Improvement in the number of satisfying sexual events, however, did not differ significantly between drug and placebo.

Adverse events more common with bremelanotide vs placebo included nausea (40% vs 1%), flushing (20% vs 0%), headache (11% vs 2%), and vomiting (5% vs 0%). Nausea occurred with a median onset of 30 min after injection. The median duration of nausea was 2.4 h. The nausea mostly resolved spontaneously; few women required to take an antiemetic.

Systolic and diastolic blood pressure increased by about 3 mm Hg and 2 mm Hg, respectively. These changes developed within 2 h of injection and lasted for less than 8 to 10 h. Pulse rate, however, showed a small decrease.

Of 856 women who completed the study, 70% of bremelanotide and 87% of placebo patients were willing to continue into a 52-week open-label extension phase treatment with active drug.

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Bremelanotide: Long-Term Safety and Efficacy

There were 684 women in the extension phase; about 21% of these women dropped out due to adverse events (most of these were placebo-treated women who were started on bremelanotide during the extension phase), and only 272 patients completed the 52-week study. The adverse effect rate was almost exactly the same as in the double-blind studies: nausea in 40%, flushing in 21%, and headache in 12% of women. FSFI desire scores further improved by 1.25 to 1.30 points in women who had received drug during the double-blind phase, and by 0.70 to 0.77 in those who had received placebo. Distress scores further improved by 1.4 to 1.7 in those who had received drug and by 0.9 in those who had received placebo.6

Bremelanotide: Special Considerations

Bremelanotide doses should be separated by at least a day to avoid increases in blood pressure; and dosing should not exceed 8 occasions a month, to reduce the 1% risk of potentially permanent hyperpigmentation. The drug should be avoided in women with uncontrolled hypertension or other cardiovascular disease. It should be used with caution in patients with severe renal or hepatic disease. There are no data on safety during pregnancy and lactation.3

HSDD: How Large Is the Treatment Effect?

Pyke and Clayton7 examined the effect size (ES; Cohen’s d) of treatments for HSDD with specific reference to testosterone, flibanserin, and bremelanotide vs placebo controls as compared with psychotherapy vs wait-list controls. They found that the mean ES was 1.0 for pharmacological interventions vs 0.55 for drug placebo; and the mean ES was 1.0 for psychotherapies vs 0.05 for wait-list controls.

These findings imply that the smaller contrast between drug and placebo controls and the larger contrast between psychotherapies and wait-list controls are not because of greater efficacy of psychotherapies; it is because of the lesser efficacy of the psychotherapy control condition. This implies that criticisms of the apparently smaller (relative) benefits with HSDD drug interventions are unjustified.

HSDD: How Large Is the Placebo Effect?

Weinberger et al8 examined the placebo effect size in RCTs conducted in women with sexual dysfunction including but not limited to HSDD. These authors searched electronic databases and other sources and identified 8 RCTs that had a placebo arm and that examined outcomes using the FSFI. There were 2236 women in the treatment arms and 1723 women in the placebo arms in these RCTs. The treatments included flibanserin, bupropion, onabotulinum toxin A, intravaginal prasterone, intranasal oxytocin, ospemifene, and bremelanotide. The authors found that, with treatment, mean FSFI scores improved by 5.35 points; with placebo, the mean improvement was 3.62 points. The authors suggested that placebo accounts for two-thirds of the treatment effect and that, therefore, more efficacious interventions are required for female sexual dysfunction.

References

1. Sathyanarayana Rao TS, Andrade C. Flibanserin: approval of a controversial drug for a controversial disorder. Indian J Psychiatry. 2015;57:221-223.
2. Dhillon S, Keam SJ. Bremelanotide: first approval. Drugs. 2019;79:1599-1606.
3. Mayer D, Lynch SE. Bremelanotide: new drug approved for treating hypoactive sexual desire disorder. Ann Pharmacother. 2020 [Epub ahead of print].
4. Pfaus J, Giuliani F, Gelez H. Bremelanotide: an overview of preclinical CNS effects on female sexual function. J Sex Med. 2007;4(suppl 4):269-279.
5. Kingsberg SA, Clayton AH, Portman D, et al. Bremelanotide for the treatment of hypoactive sexual desire disorder: two randomized phase 3 trials. Obstet Gynecol. 2019;134:899-908.

6. Simon JA, Kingsberg SA, Portman D, et al. Long-term safety and efficacy of bremelanotide for hypoactive sexual desire disorder. Obstet Gynecol. 2019;134:909-917.

7. Pyke RE, Clayton AH. Effect size in efficacy trials of women with decreased sexual desire. Sex Med Rev. 2018;6:358-366.

8. Weinberger JM, Houman J, Caron AT, et al. Female sexual dysfunction and the placebo effect: a meta-analysis. Obstet Gynecol. 2018;132:453-458.