Treatment of HSDD: Daily vs PRN

SUE GOLDSMITH, CSE, CCRC, IF
SAN DIEGO SEXUAL MEDICINE
Disclosures

Research: AMAG Pharmaceuticals, BTL, Endoceutics, Ipsen, Strategic Science & Technologies

Consultant/Advisory Board: AMAG Pharmaceuticals, Duchesnay, Ipsen, Sprout, Strategic Science & Technologies

Speaker: AMAG Pharmaceuticals, Ipsen
Hypoactive Sexual Desire Disorder

HSDD manifests as any of the following for a minimum of 6 months:

- Lack of motivation for sexual activity as manifested by:
  - Decreased or absent spontaneous desire (sexual thoughts or fantasies); or
  - Decreased or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity;
- Loss of desire to initiate or participate in sexual activity, including behavioral responses such as avoidance of situations that could lead to sexual activity, that is not secondary to sexual pain disorders;
- And is combined with clinically significant personal distress that includes frustration, grief, guilt, incompetence, loss, sadness, sorrow, or worry.

Psychosocial-Neurobiology of Sexual Response

- High Inhibition
- Low Inhibition
- High Excitation
- Low Excitation

- HSDD
- Sexual Arousal Disorder
- Anorgasmia/Delayed Orgasm
- Sexual Pain Disorder
- Persistent Genital Arousal Disorder
- Premature Ejaculation
- Without Sexual Dysfunction
- Without Sexual Dysfunction


Psychosocial-Neurobiology of Sexual Response
Neural Pathways Regulating Sexual Desire in the Brain

Key regions of the brain:
- Solid green - main excitatory pathways
- Dashed red - inhibitory pathways
- Black pathways - known connections that can be both excitatory & inhibitory

Each neurotransmitter is highlighted to denote excitatory (green) or inhibitory (red) effect on specific pathways or at specific sites

Effect neuroplasticity daily vs prn?
Changes in Neural Activity in Response to Viewing an Erotic Video in Women

No HSDD | HSDD | No HSDD | HSDD

Deactivation *(decreased blood flow)*
Left brain

Activation *(increased blood flow)*
Right brain
Daily vs. PRN

HSDD causes neuroplasticity of the brain
If a goal of treatment is to reverse this....

*Effect neuroplasticity daily vs prn?*
Experiencing HSDD: Sexual Activity

Difficult to stay in the moment during sexual activity
Result may be poor arousal/lubrication, muted orgasm
Loss of positive anticipation for future sexual activity

Don’t you think you would want to combat this with a daily medication?
HSDD Associated With:

Negative emotional and psychological states
Medical conditions including depression
Decreased quality of life including
  ◦ impaired body image
  ◦ self-confidence
  ◦ self-worth
Feel less connected to their partners
Complaints of Women with HSDD

Do not feel like a woman
Do not feel whole
Feel “beige”
Women with HSDD Want Their “Normal” Back

- **69%**
  Want to feel like a “normal” person again in terms of sexual desire

- **52%**
  Don’t want their relationship with their partner to suffer

- **43%**
  Want to restore their sense of femininity

For women, it’s not about the number of Satisfying Sexual Events (SSEs)
Improvement with Flibanserin QHS

The only daily FDA-approved treatment for HSDD is flibanserin
(Testosterone is used off label for postmenopausal women)

Patient experience is that they feel whole, feel like a woman, no longer feel beige.
Many patients report return of desire, arousal, orgasm
Neuroplasticity results in women having positive anticipation for sex.

*How can you do that with a prn drug, dispensed 4/month.*
Premenopausal Flibanserin Pivotal Trials: Efficacy Endpoints

Study 147
Monthly Frequency, Mean ± SE

Study 71
Monthly Frequency, Mean ± SE

Study 75
Monthly Frequency, Mean ± SE

SSEs
FSFI-Desire
FSDS-R13 (Distress)

* p < 0.05; ** p < 0.01
LS = least squares.
Postmenopausal Flibanserin Trial: Mean Change from Baseline Across Key Endpoints at Week 24

Primary endpoints

- SSEs
  - Placebo: 0.6
  - Flibanserin: 1.0
  - Difference: 0.4
  - P = 0.0040

- FSFI-Desire Score
  - Placebo: 0.0
  - Flibanserin: 0.7
  - Difference: 0.7
  - P < 0.0001

Secondary endpoint

- FSDS-R Item 13
  - Placebo: 0.6
  - Flibanserin 100 mg qhs: 0.8
  - Difference: 0.2
  - P = 0.0083

Data on File, Sprout Pharmaceuticals, Inc.
Daily Dosing Increases in Sexual Responses

**HSDD**: sexual responsiveness, sexual thoughts/dreams, initiation of sexual activity, positive anticipation, articulation of sexual desires, and decreased inhibition from sexual Post Traumatic Stress Disorders (PTSD) related to physical and emotional abuse, trauma and previous sexual pain experiences.

**Non-HSDD**: intensified and/or faster lubrication/arousal, clitoral engorgement, stronger or increased number of orgasms, and enhanced sexual satisfaction.
Daily Dosing Improves Non-Sexual Responses

Improved relationships including partners being more attentive, and mood changes such as having fun, feeling more alive, feeling less stressed and general happiness

One woman reported having “reignited her sexual self”

Most respondents lost several pounds of weight, and most slept better
Daily vs PRN

- Daily: Flibanserin - take nightly with water
  ◦ Skip if you binge drink

- PRN: Bremelanotide - inject into abdomen and thigh
  ◦ Causes nausea in 40% of women (take odansetron to counteract this)
  ◦ Raises blood pressure
  ◦ Causes hyperpigmentation
PRN Dosing

Woman has to make a decision she wants to have desire on that day

Will that make her feel like a woman?
HSDD Treatment Debate: Daily vs. On-Demand

Brooke Faught, DNP, WHNP-BC, NCMP, IF
Brooke Faught
DNP, WHNP-BC, NCMP, IF

Director
• Women’s Institute for Sexual Health (WISH)
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• Nashville, TN

Secretary
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Disclosures

- Speaker/Consultant
  - AMAG, Therapeutics MD, Lupin, JDS Therapeutics, Trophikos

- Principal Investigator
  - IPSEN Innovation
WHO WILL WIN?
Hypoactive Sexual Desire Disorder

HSDD is defined as persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity accompanied by clinically significant distress, and is not otherwise accounted for by a general medical or psychiatric condition.

- **HSDD subtypes**: lifelong or acquired, generalized or situational

Female Sexual Arousal Disorder (DSM-IV)  
ICD-10 F52.22

Female Sexual Interest/Arousal Disorder  
(DSM-5)
Norepinephrine and dopamine increase sexual arousal
Serotonin sexual satiety signal and arousal inhibition
Oxytocin/melanocortins: role in attachment/bonding - ++arousal effects
Hormones (E,T) influence synthesis and storage of neurotransmitters and Declining levels contribute to decrease in sexual arousal as well as sexual comfort

Patterns of Cortical Activation and Deactivation by Erotic Visual Cues

- Increased blood flow = activation
- Decreased blood flow = deactivation

Bremelanotide (BMT)

- BMT is a recently-approved novel cyclic 7-amino acid melanocortin-receptor agonist, with high affinity for the type-4 melanocortin receptor, and an analog of α-melanocyte-stimulating hormone (α-MSH)
- Melanocortin 4 receptors have influence on sexual response
- Melanocortin analogs studied for >40y
  - BMT patented ~20y ago
- FDA-approved for the treatment of HSDD in premenopausal women
- BMT is delivered via a pre-filled auto-injector on an “as desired” basis

All data presented at ISSWSH annual meeting Feb 2017 by Simon, J.
Bremelanotide (BMT)

- BMT is NOT “female Viagra”
- Rapid onset, although acts on CNS, not the NO pathway.
- Onset of action 45m, effect lasts up to 16h with 2.7h half-life
- Presumed long-term benefit from the reduction of distress and memory of increased receptivity and positive sexual encounter.
Bremelanotide: Mechanism of Action

HSDD-related dopamine release

Treatment of HSDD with bremelanotide

In pre-clinical animal studies, efficacy was blocked by dopamine antagonist

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1 Pre-clinical animal studies conducted by Palatin.

Open access: https://doi.org/10.1016/j.mayocp.2016.09.018
Bremelanotide vs. Flibanserin

Happy

- Flibanserin
- Bupropion
- Testosterone
<table>
<thead>
<tr>
<th><strong>Bremelanotide</strong></th>
<th><strong>Flibanserin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset of action:</strong> 45 min</td>
<td><strong>Onset of action:</strong> 8 weeks</td>
</tr>
<tr>
<td>Metabolized via hydrolysis of its peptide bonds</td>
<td>Metabolized via CYP3A4 &amp; CYP2C9*</td>
</tr>
<tr>
<td>Contraindicated <em>uncontrolled</em> hypertension or known cardiovascular disease</td>
<td>Contraindicated in concomitant use with moderate or strong CYP3A4 inhibitors as well as patients with hepatic impairment</td>
</tr>
<tr>
<td>Studied in same-sex couples</td>
<td>Studied only in heterosexual couples</td>
</tr>
<tr>
<td>No etoh restriction</td>
<td>Do not take if recent consumption of 3 etoh beverages or any etoh within past 2h</td>
</tr>
<tr>
<td>1st Rx free, flexible dosing</td>
<td>1st Rx free, regimented dosing</td>
</tr>
<tr>
<td>Top SE: nausea, flushing, inj site reactions</td>
<td>Top SE: dizziness, somnolence, nausea</td>
</tr>
<tr>
<td>No interaction with antidepressants, hormonal and nonhormonal contraceptives agents</td>
<td>OCPs incr AEs of flibanserin through CYP3A4 inhibition. No PK data on antidepressants.</td>
</tr>
<tr>
<td>Improved potential compliance with PRN dosing</td>
<td>Decreased potential compliance with chronic dosing</td>
</tr>
</tbody>
</table>

*CYP3A4: clarithromycin, erythromycin, diltiazem,itraconazole, ketoconazole, ritonavir, verapamil, goldenseal and grapefruit. CYP2C9: 100+ drugs incl warfarin, phenytoin, acenocoumarol, tolbutamide, losartan, glipizide, and some nonsteroidal anti-inflammatory drugs*
Randomized ~1,200 women with HSDD
- 1:1 ratio bremelanotide or placebo

Patients self-administered bremelanotide 1.75 mg or placebo using the auto-injector as needed in anticipation of sexual activity
- Dose selection based on positive Phase 2 data

The double blind efficacy portion consisted of a 24-week treatment evaluation period

80% of women completing the Phase 3 studies choose to participate in the rollover safety study
Efficacy

Results: FSFI-D (Completers)

Relative to placebo, the FSFI-D score increased in women using BMT 1.75 mg from the first month of double-blind treatment.

Following a sensitivity analysis that assumed all dropouts were treatment failures, the effect size decreased but results still showed statistically significant improvement in comparison to placebo.

Error bars are standard error of the mean.
BMT, bremelanotide; FSFI-D, Female Sexual Function Index desire domain.

All data presented at ISSWSH annual meeting Feb 2017 by Simon, J.
Efficacy

Results: FSFI-D (Completers)

Compared with those taking placebo, women taking BMT had significantly increased scores on the desire domain of the FSFI at 6 months, indicating an increase in desire.

\[ P < 0.0001 \]

\[ n = 190 \]

\[ n = 274 \]

\[ n = 173 \]

\[ n = 219 \]

*P* values determined by unadjusted Wilcoxon rank-sum test. Error bars are standard error of the mean.

BMT, bremelanotide; FSFI-D, Female Sexual Function Index desire domain.

All data presented at ISSWSH annual meeting Feb 2017 by Simon, J.
Efficacy Results: FSDS-DAO Item 13 (Completers)

Relative to placebo, FSDS-DAO Item 13 score decreased in women taking BMT 1.75 mg from the first month of double-blind treatment.

Change in FSDS-DAO Item 13 from Baseline to End of Core (Double-Blind) Phase

Error bars are standard error of the mean.
BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm.

All data presented at ISSWSH annual meeting Feb 2017 by Simon, J.
Efficacy Results: FSDS-DAO Item 13 (Completers)

Compared with those taking placebo, women using BMT had a significant reduction in their FSDS-DAO Item 13 score at 6 months, indicating a reduction in distress related to low sexual desire.

Figure 4. Change in FSDS-DAO Item 13 from Baseline to End of Core (Double Blind) Phase

*P* < 0.0001

*P* = 0.0007

All data presented at ISSWSH annual meeting Feb 2017 by Simon, J.
• Both core studies demonstrated a trend in improved desire and arousal compared to baseline as well as improved patient satisfaction related to the desire and arousal domains.
Rebuttal:

Daily vs PRN

DAILY

SUE GOLDSTEIN, CSE, CCRC, IF
SAN DIEGO SEXUAL MEDICINE
Only PRN medication is Bremelanotide

Causes nausea in 40% of women although you can take a medication for this

◦ Does your patient want to take a medication to counteract the side effect of another medication?

Raises blood pressure

◦ Does the thought of raising your patient’s blood pressure give you hypertension?

Trypanophobia

   Fear of needles....
Only PRN medication is Bremelanotide

Causes hyperpigmentation

*Women who may already have body issues have to worry about brown spots if they inject too often*
Hypoactive Sexual Desire Disorder

Who wants to be a whole women half of the time (or 4 days a month)?
Hypoactive Sexual Desire Disorder

OR

a whole women
all of the time?
Daily vs. PRN

Generalized, acquired HSDD – the disease state for which these medications are indicated – affects women 24/7.

We should provide a treatment that helps 24/7—returns each woman to her “normal” 24/7 — not just when she makes the conscious decision to inject herself.

PRN dosing allows for spontaneity — whenever a woman wants!
Daily Dosing vs PRN

Which would you want?
REBUTTAL
• 29 gauge needle
  • Epipen and Epipen Jr are 22 gauge

• Reconnect Study Core Phase Quantitative Exit Interview
  • N = 242 completed interview
  • Most participants reported “excellent” or “very good” re: ease of use of the autoinjector (86.8%) and not needing daily medication (79.3%)
The majority of common adverse reactions were reported to be mild to moderate in intensity and transient.

18% of women discontinued use of Vyleesi due to adverse reactions.
Safety of BMT

- Bremelanotide has a favorable safety profile
- Most AEs were mild or moderate in nature
- TEAEs led to treatment discontinuation/interruption in approximately 18% of women taking bremelanotide (vs. 2% in placebo)
- Most of the bremelanotide AEs causing withdrawal were gastrointestinal (11.1% in Study 301 and 7.6% in Study 302)
- Bremelanotide’s safety profile was consistent with prior clinical experience; no new or unusual safety issues were identified

All data presented at ISSWSH annual meeting Feb 2017 by Simon, J.
Discontinuation rate due to adverse reactions was 13% for flibanserin 100 mg and 6% for placebo.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Flibanserin (n=1543)</th>
<th>Placebo (n=1556)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>11.4%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>11.2%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10.4%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9.2%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2.4%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>
Understanding Nausea for Patients With Vyleesi™

Nausea improved for most patients by the second dose.

+ The highest incidence of nausea was after the first Vyleesi dose (21% of patients)
+ After subsequent Vyleesi doses, incidence of nausea declined (~3% of patients)

The median onset of nausea was within 1 hour postdose and lasted about 2 hours in duration.

Patients treated with Vyleesi in the clinical trials

+ 40% experienced nausea
+ 13% required antiemetic therapy
+ 8% discontinued due to nausea

If your patient experiences persistent or severe nausea or is bothered by nausea but wishes to continue therapy, consider prescribing an antiemetic.

1. VYLEESI™ (bremelanotide injection) Prescribing Information. AMAG Pharmaceuticals, Inc; 2019.
In the pivotal trials, hyperpigmentation of the face, gingiva, and breasts was reported in 1% of patients who received up to 8 doses per month of Vyleesi compared with 0% of patients on placebo.

- Patients with dark skin were more likely to develop focal hyperpigmentation
- Hyperpigmentation did not always resolve following discontinuation of Vyleesi

In another clinical study:

- 38% of patients developed hyperpigmentation after receiving Vyleesi daily for 8 consecutive days
- An additional 14% developed new pigmentary changes after 8 more consecutive days of treatment

- Consider discontinuing Vyleesi if hyperpigmentation develops and advise patients to take no more than 8 doses per month.

1. VYLEESI™ (bremelanotide injection) Prescribing Information. AMAG Pharmaceuticals, Inc; 2019.
• Blood pressure increases peaked between 2-4 hours postdose
• There was a corresponding reduction in heart rate up to 5 beats per minute
• Blood pressure and heart rate usually returned to baseline within 12 hours postdose

Vyleesi is contraindicated in women who have uncontrolled hypertension or known cardiovascular disease. Before initiating Vyleesi, consider the patient’s baseline cardiovascular risk, ensure blood pressure is well controlled, and advise patients not to administer more than 1 Vyleesi dose within 24 hours.

1. VYLEESI™ (bremelanotide injection) Prescribing Information. AMAG Pharmaceuticals, Inc; 2019.
SSEs

- SSEs and frequency of sexual activity not components of HSDD dx
- FDA no longer requires # of SSEs as co-primary endpoint
Flibanserin is Safe and Effective, HOWEVER:

BMT gives everyone the opportunity to be an active, willing, and desirous participant in a sexual encounter, not just a passive vehicle.
Can’t we all just get along?

- Both meds approved only for premenopausal women with HSDD
- Both meds offer free starter Rx
- Both meds safe and effective in appropriate patients.
- Neither med significantly increases frequency of sexual activity, but rather increases quality of sexual encounters
  - Women with HSDD still having sex
- Why not consider concurrent usage of BMT and flibanserin?