Effects of Flibanserin on the Pre- and Post-menopausal Female Brain

IRB16-0087

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Protocol Version 3/20/2019

HSDD, EEG, and Flibanserin Study Detailed Protocol Narrative

1. Background:

Hypoactive sexual desire disorder (HSDD) is the most common sexual complaint in women. Over the past 8 years, Dr. Stephanie Cacioppo (née Ortigue) Ph.D. has developed and validated the Desire Intention task (DIT; e.g., Bolmont et al., 2014; Cacioppo et al., 2013; Ortigue & Bianchi-Demicheli, 2008), in which individuals are instructed to indicate as rapidly and as accurately as possible whether or not each visually presented stimulus (e.g., attractive persons of the opposite sex) is sexually desirable to them at the moment of the experiment. This task has been IRB approved previously (IRB#12-2229). In a functional magnetic resonance imaging (fMRI) study Dr. Stephanie Cacioppo discovered that women with HSDD, compared to normal controls, show a hypoactivation of the neural network known to sustain sexual desire in healthy non-HSDD individuals (Bianchi-Demicheli et al., 2011; Cacioppo & Hatfield, 2013; Cacioppo et al., 2012), including dopamine-rich limbic regions associated with reward processing, and a hyperactivation of brain regions involved when people view themselves from a third-person perspective ("spectatoring") rather than from a first person perspective when viewing sexually desirable stimuli (Bianchi-Demicheli et al., 2011; Cacioppo and Cacioppo, 2013).). A caveat with fMRI is that it does not inform us about the temporal dynamics between these brain areas. In 2008, Dr. Stephanie Cacioppo was also the first to identify the brain microstate underlying sexual desire in healthy non-HSDD subjects (Ortigue & Bianchi-Demicheli, 2008). The proposed study will be the first to address this question in patients with HSDD pre- and post-flibanserin.

Flibanserin (Addyi) is a new medication approved by the FDA for the treatment of pre-menopausal women with HSDD. We propose a study using the DIT to determine the extent to which flibanserin normalizes brain activity in women with HSDD and the extent to which regional brain activation is associated with changes in symptoms and behavior (as measures with self-report measures of sexual desire and eye-tracking movements).

2. Purpose:

The research question of this double-blind randomized outpatient clinical trial is to determine the pre-post change in the Flibanserin group and investigate the extent to which Flibanserin normalizes brain activity in premenopausal and postmenopausal women with HSDD and the extent to which regional brain activation is associated with changes in symptoms and behavior (as measured with self-report measures of sexual desire and/or eye-tracking movements).

3. Aims:

Aim 1: By targeting deficits in subjective desire in postmenopausal women with hypoactive sexual desire disorder, flibanserin may offer a unique mechanism to address HSDD. Because of the pharmacology of flibanserin and its effects on the brain circuitry of emotion and its positive and already accepted effects on premenopausal women with HSDD, we hypothesize that subjective feelings and neurobehavioral responses to sexually desirable stimuli are improved after an 8-week intake of flibanserin versus placebo.

Aim 2: All women, independent of hormonal phase, should demonstrate similar responses. We hypothesize that similar changes should be observed in premenopausal and postmenopausal women after an 8-week intake of flibanserin versus placebo.

4. Primary Outcome Measure:

EEG Results: Evoked Brain Potentials (measured brain response that is the direct result of a specific cognitive event). We will be analyzing change from baseline EEG results at 8 weeks (before and after the subject takes the flibanserin or placebo). We will average the electrical brain activity evoked by each type of stimuli to calculate the evoked brain potentials (any stereotyped electrophysical response to a stimulus).

Evoked brain potentials in response to sexually desired stimuli compared to:

1. Non sexually desired stimuli
2. Basic visual non-sexual stimuli (reversal checkerboard) will be our proposed endpoints, as they will allow us to measure electric brain signals specific to cognitive

mechanisms underlying sexual stimuli processing rather than any other non-cognitive processes or basic visual processes. Amplitude of the signal, latency, and brain topography across 128 recorded vectors will be measured.

Secondary Outcome Measures:

-Eye movement tracking: movements to first saccades. We will be analyzing change from baseline eye movement tracking results at 8 weeks.

-Female Sexual Function Index: change from baseline to final score at 8 weeks.

-UCLA Loneliness Scale: change from baseline to final score at 8 weeks.

-Life Satisfaction Scale: change from baseline to final score at 8 weeks.

-Body Dysmorphic Disorder Questionnaire: change in answers from baseline to final visit at 8 weeks.

-Hamilton Anxiety and Depression Scale: change from baseline to final score at 8 weeks.

-Rosenberg Self-Esteem Scale: change from baseline to final score at 8 weeks.

-Hostility Measure: change from baseline to final score at 8 weeks.

Female Sexual Distress Scale-Revised: change from baseline to final score at 8 weeks.

IOS Scale with Partner: change in answers from baseline to final answers at 8 weeks.

Body image measure: change in baseline to final score at 8 weeks.

Sexual Desire Inventory: change in baseline to final score at 8 weeks.

Marital Satisfaction Scale: change in baseline to final score at 8 weeks.

5. Methodology:

The proposed study aims to test 60 pre-menopausal heterosexual or bisexual women (i.e., women who are menstruating) and 60 postmenopausal heterosexual or bisexual women (women who are no longer menstruating for at least 6 months) with hypoactive sexual desire disorder (HSDD) and investigate how their brain activity (as measured by non-invasive surface electroencephalogram, EEG) responds to desirable stimuli (photographs of models in business suits) before and after the administration of an FDA approved drug, Addyi (ingredient Flibanserin, NDA# 022526) for sexual desire disorder. The goal of this experiment is to investigate how the subjects' brain waves and their subjective desire for sexual activity change after an 8-week intake of Addyi

(Flibanserin; 100mg **at bedtime**)—an FDA approved drug for the treatment of hypoactive sexual desire disorder (HSDD) in **premenopausal women (but not FDA approved in postmenopausal women) or** after an 8-week intake of a placebo. The pharmacist will randomly assign once the subject to the treatment group (group with Flibanserin) or to the control group (group with placebo). Before and then again after the 8-week regimen, the patient will be asked to fill-out a series of questionnaires (e.g., demographics, body image; sexual desire) and do a behavioral visual task on a computer while the patient's brain activity (brain waves) and eye-movement will be recorded using a non-invasive high-density electroencephalogram (EEG) system and a non-invasive eye-tracking system, respectively. At mid-term (at 4 weeks), the patient will be also asked to fill-out the same series of questionnaires (e.g., demographics, body image; sexual desire) and do the same behavioral visual task on a computer while the patient's brain activity (brain waves) and eye-movement will be recorded using a non-invasive high-density electroencephalogram (EEG) system and a non-invasive eye-tracking system, respectively.

Subjects will be recruited via Flyers posted on Campus and/or in Obstetrics and Gynecology practices and/or via ads posted on Craigslist by research coordinator, Sarah Redden. From these ads, interested individuals will be asked to go on Survey Monkey (https://www.surveymonkey.com/r/HPENlabresearch) and complete a survey that will help us determine whether they meet our selection criteria or email Dr. Cacioppo at hpen@uchicago.edu or call the research team. Research coordinator will then contact individuals who may meet selection criteria. She and Dr. Grant and/or Dr. Lee will meet with them and give them the informed consent to read and go through it with the subjects. Upon receipt of a signed informed consent, participants will meet with Dr. Grant or Dr. Lee who will diagnose them with HSDD. If the subject does not have HSDD, she is not eligible to participate in the study. Subjects with a confirmed diagnosis of HSDD by Dr. Grant or Dr. Lee will then be randomly assigned by the UChicago Pharmacy/Investigational Drug Service to either Addyi (100 mg once daily at bedtime for 8 weeks, n = 60 subjects) or placebo (100 mg once daily at bedtime for 8 weeks, n = 60 subjects). The research question of this double-blind randomized outpatient clinical trial is to determine the pre-post change in the Flibanserin group and investigate the

extent to which Flibanserin normalizes brain activity in women with HSDD and the extent to which regional brain activation is associated with changes in symptoms and behavior (as measured with self-report measures of sexual desire and/or eye-tracking movements).
The study is registered on clinicaltrials.gov.

6. Duration of Protocol:

The total duration of the entire study on campus is 4.5 hours maximum. **Visit 1's duration:** 2 hours. Upon receipt of the subject's written consent, the subject will meet with Dr. Grant or Dr. Lee to have a diagnosis of HSDD confirmed, take a urine pregnancy test, and be asked to fill out questionnaires (duration 45 minutes maximum). Then, an IRB-approved member of the HPEN laboratory will walk the subject to the laboratory where the subject will be completing other questionnaires and performing the behavioral visual task while the subject's brain activity and eye movements are recorded (1h15 minutes maximum, including breaks and time to walk to the laboratory). At the end of Visit 1, a member of the HPEN laboratory will walk the subject to the pharmacy where they will receive either Flibanserin or Placebo. The HPEN member will not know what the patient receives (placebo or Flibanserin). One week after visit 1, a member of the study staff will contact the subject via telephone to see if the subject has experienced any side effects or if the subject has any questions. If any side effects are reported, the study staff will immediately contact Dr. Grant or Dr. Lee to confirm that any appropriate follow up is provided. **Phone call 2's duration:** 30 minutes. Two weeks after visit 1, the subject will be asked about any side effects she has experienced or is currently experiencing. The subject will also be asked to fill out some of the same questionnaires as visit 1 and answer questions about mood and sexual desire. **Visit 2's duration:** 1 hour. The subject will go directly to the HPEN laboratory, where the subject will perform the behavioral visual task again while the subject's brain activity and eye movements are recorded and fill out the same questionnaires the subject filled out during Visit 1. **Visit 3's duration**: 1 hour. The subject will again go directly to the HPEN laboratory to perform the behavioral visual task while the subject's brain activity and eye movements are recorded and fill out the same questionnaires as Visits 1 and 3.

7. Location of Study:

Visit 1 part A and visit 2 will take place in the Department of Psychiatry and Behavioral Neuroscience, 5841 S. Maryland Avenue, Chicago, IL, 60637), and visit 1 part B (behavioral task, self-report questionnaires, EEG recordings, and eye-movement recordings), visit 2, and visit 3 will take place in the High-Performance Electrical Neuroimaging Laboratory. 940 E. 57th Street, 4th Floor, Chicago, IL 60637.

8. Special Precautions:

Precautions related to the contradictions of Addyi (Flibanserin) will be followed. This will occur in the survey monkey pre-screening survey and again in the consent form.

9. Experimental Controls:

We will recruit 60 pre-menopausal women and 60 postmenopausal women who have HSDD, as determined by one of the MDs on the research team (using the DSM 5 criteria), during Visit 1. Then, the pharmacist will randomly assign the subjects to the treatment group (group with Flibanserin) or to the control group (group with placebo).

10. Type and Number of Experimental Subjects:

We expect to collect data from a total of 120 subjects between the age of 21 and 74 years. We will be testing premenopausal and postmenopausal women with hypoactive sexual desire disorder. Flibanserin is FDA approved for premenopausal but not postmenopausal women with HSDD. Women who are pregnant (or think they are pregnant), or who are nursing (or breastfeeding), or women who report not being able to stop drinking alcohol during the duration of the study will NOT be tested.

Power: Using G* power calculation software (Version 3.1.9.2) for a within-between interaction in repeated measures ANOVA, a total sample size of 120 will yield 95% power to detect a significance, with alpha = .05 and an effect size of 0.14.

11. Statistical Analyses:

EEG data will be analyzed using an established Matlab toolbox, CENA (The Chicago Electrical Neuroimaging Analytics). Standard statistical analyses will be performed using SPSS. Compared to fMRI, which has a very low temporal resolution, high-density EEG/ERP has a very high temporal resolution (Ortigue & Bianchi-Demicheli, 2008). When combined with brain source localization algorithms, high-density EEG-ERP is called electrical neuroimaging. Electrical neuroimaging can identify dynamical patterns of communication between brain regions that contrast analyses, such as fMRI, may not detect. This proposal takes advantage of electrical neuroimaging and a new suite of tools (i.e., the Chicago Electrical Neuroimaging Analytics, CENA), that Dr. Stephanie Cacioppo developed and validated recently for segmenting high-density electrical brain activity (Cacioppo et al., 2014, 2015). Compared to the standard waveform analysis of event-related potentials (ERP) components that provide local information about amplitude and latency of the brain electric signal collected from one electrode in response to a stimulus, CENA provides general information about the stable momentary configuration of the global scalp electric potential over a high-density multi-channel electrode array. This approach provides information about the temporal sequence of discrete information processing operations evoked by the presentation of a stimulus within the context of a particular experimental task. That temporal sequence of information processing includes a series of stable brain microstates, each of which is characterized by specific cognitive computations and a relatively stable spatial distribution of brain activity. Combined with brain source localization algorithms, this method can then provide a video-clip of the potential brain sources that sustain every electrical brain state recorded from the surface of the scalp –without having to perform an fMRI scan (see attached example). The brain microstate approach complements the traditional approach of ERP peaks and troughs at specific electrode positions, but with more comprehensive analyses of time-varying activity across the entire scalp (Cacioppo et al., 2014, 2015).

Subjects who do not adhere to the recommended dosing regimen will not be discontinued from the study. Rather, data from these subjects should be included in an intent-to-treat analysis.

Statistical Hypotheses:

a. The research questions of this double-blind randomized study are: (a) to determine the pre-post change in the Flibanserin group vs. Placebo group in women with hypoactive sexual desire disorder (HSDD), (b) to compare the effect is Flibanserin (vs. placebo) on behavioral and brain changes between pre-menopausal women and postmenopausal women, (c) to investigate the extent to which post-Flibanserin's regional brain activations (compared to pre-Flibanserin's regional brain activations) are associated with changes in symptoms and behavior (as measured with self-report measures of sexual desire and/or eye-tracking movements), and (d) to investigate the extent to which Flibanserin normalizes brain activity in women with HSDD compared to matched healthy controls. The statistical hypotheses include the following:

i. Demographics: Statistical analyses for demographic and self-report measures will be computed using SPSS software. Prior to inferential analyses, descriptive statistics, including distributions, means, standard deviations, skewness, and kurtosis will be generated. Data will also be examined for the pattern and mechanism of missing data. Continuous data will be tested for normality and homogeneity of variance. Potential differences between the treatment and placebo groups in terms of demographic and behavioral measures will be explored using multivariate analysis of variance (MANOVA) or appropriate non-parametric tests as appropriate. Similar analyses will be performed to detect potential differences between the pre-menopausal subjects and the post-menopausal subjects. The overall significance level for these analyses will be at 5%, and effect sizes and confidence intervals will also be performed to test hypotheses about correlations.

ii. Behavioral data: Statistical analyses will be computed using SPSS software. Reaction times and performance data (ratings) will be screened. Prior to inferential analyses, descriptive statistics, including distributions, means, standard deviations, skewness, and kurtosis will be generated. Data will also be examined for the pattern

and mechanism of missing data. A 2 (Treatment Type: Addyi or Placebo) x 2 (Group Type: pre- or post-menopausal) X 2 (type of stimuli: desired, nondesired) x 3 time (Visit 1, Visit 2, Visit 3) repeated-measures ANOVA will be performed on the reaction times and ratings to assess for main effects and interaction effects. P values, confidence interval, and effect sizes will be reported.

iii. Eye-tracking Data: A similar ANOVA will be performed for the following dependent variables: onset to first fixation and duration of fixation. As in our 2014's paper (Bolmont, Cacioppo, & Cacioppo), we will also analyzed include the subjects' visual area of interest (face vs. body) as a within-subject factors in our ANOVA.

iiii. Electrophysiological Data: EEG data will be analyzed using an established Matlab toolbox, CENA (The Chicago Electrical Neuroimaging Analytics). Standard statistical analyses will be performed using SPSS. Compared to fMRI, which has a very low temporal resolution, high-density EEG/ERP has a very high temporal resolution (Ortigue & Bianchi-Demicheli, 2008). When combined with brain source localization algorithms, high-density EEG-ERP is called electrical neuroimaging. Electrical neuroimaging can identify dynamical patterns of communication between brain regions that contrast analyses, such as fMRI, may not detect. This proposal takes advantage of electrical neuroimaging and a new suite of tools (i.e., the Chicago Electrical Neuroimaging Analytics, CENA), that Dr. Stephanie Cacioppo developed and validated recently for segmenting high-density electrical brain activity (Cacioppo et al., 2014, 2015). Compared to the standard waveform analysis of event-related potentials (ERP) components that provide local information about amplitude and latency of the brain electric signal collected from one electrode in response to a stimulus, CENA provides general information about the stable momentary configuration of the global scalp electric potential over a high-density multi-channel electrode array. This approach provides information about the temporal sequence of discrete information processing operations evoked by the presentation of a stimulus within the context of a particular experimental task. That temporal sequence of information processing includes a series of stable brain microstates, each of which is characterized by specific cognitive computations and a relatively stable spatial distribution of brain activity. Combined with brain source localization algorithms, this method can then provide a video-clip of the

potential brain sources that sustain every electrical brain state recorded from the surface of the scalp –without having to perform an fMRI scan (see attached example). The brain microstate approach complements the traditional approach of ERP peaks and troughs at specific electrode positions, but with more comprehensive analyses of time-varying activity across the entire scalp (Cacioppo et al., 2014, 2015).

A significant and clinically meaningful change from baseline for each subject pre- and post-treatment with flibanserin is as follows:

Median effective doses of flibanserin on increase in SD level will demonstrate at least a medium effect size (e.g., Coden's d > 0.48) relative to placebo (PBO); and at least a medium effect size (Coden's d > 0.48) between flibanserin and PBO conditions in SD levels; and relationship between change in SD self-report levels and change in behavioral responses (reaction times) during SD paradigm in flibanserin (vs PBO) is of at least a medium effect size (r > 0.48); or relationship between change in flibanserin and change in electrophysiological responses during SD paradigms in flibanserin (vs. PBO) is of at least a medium effect size (r > 0.48); Relationship between change in Flibanserin and change in eye movement responses during SD paradigms in Flibanserin(vs. PBO) is of at least a medium effect size (r > 0.48). There will be no adverse events of more than mild severity which are rated as possibly, probably, or definitely related to acute, oral administration of flibanserin to a greater extent than PBO in HSDD participants.

12. Potential Risks and Benefits:

The study will offer no direct benefits (besides monetary benefits and potential improvement of sexual desire) to participants. The questionnaires, tracking eye-movement, and EEG behavioral task also present minimal risks, which may include boredom and fatigue from looking at pictures for a few minutes during EEG collection and anxiety or discomfort or distress related to responding to questionnaires.
Addyi risks: Addyi (flibanserin) is a multifunctional serotonin agonist and antagonist (MSAA) indicated for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual

desire that causes marked distress or interpersonal difficulty and is NOT due to: a co-existing medical or psychiatric condition, problems within the relationship, or the effects of a medication or other drug substance. The recommended dosage of Addyi is 100 mg taken once daily at bedtime.

CONTRAINDICATIONS: Alcohol; Moderate or strong cytochrome P450 3A4 inhibitors; Hepatic impairment.

IF THE SUBJECTS ARE A NURSING MOTHER, THEIR PARTICIPATION IS NOT RECOMMENDED.

IF THE SUBJECTS ARE PREGNANT, YOUR PARTICIPATION CANNOT BE ACCEPTED.

DRUG INTERACTIONS: Oral contraceptives increase Flibanserin exposures and incidence of adverse effects.

FDA-approved Flibanserin has known sides effects we want you to be aware of, such as syncope and Central Nervous System (CNS) depression.

Other common side effects of Addyi (Flibanserin) include: dizziness, sleepiness, nausea, fatigue, insomnia, and dry mouth. Other side effects of Addyi include anxiety, constipation, abdominal pain, menstrual spotting, rash, sedation, and spinning sensation (vertigo).

Addyi may interact with alcohol, CNS depressants (such as diphenhydramine, opioids, hypnotics, benzodiazepines), antifungals, antiviral drugs, grapefruit juice, oral contraceptives, cimetidine, fluoxetine, ginkgo, ranitidine, proton pump inhibitors, selective serotonin reuptake inhibitors (SSRIs), some antibiotics, nefazodone, , ketoconazole, itraconazole, posaconazole, clarithromycin, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin, conivaptan, amprenavir,

atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil, paroxetine, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapetine, St. Johns Wort, digoxin, sirolimus, and some medicines used to treat high blood pressure, chest pain (angina), or other heart problems.

Drug interactions can be found in all tables including CYP3A4 inhibitors and CYP2C19 on:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
Note: The use of moderate or strong CYP3A4 inhibitors is contraindicated in patients taking flibanserin, and flibanserin may interact with other medications (weak CYP3A4 inhibitors, strong CYP219 inhibitors, CYP3A4 inducers, and digoxin.

Addyi is only available through the Addyi risk evaluation and mitigation strategy (REMS) Program because of the increased risk of severe low blood pressure and fainting (loss of consciousness) with alcohol use. **By agreeing to participate in the present study and by signing the present consent form, the subject also agrees NOT to drink alcohol or beverages including alcohol while taking Addyi (Flibanserin), that is for a period of 8 weeks.**
If the subject feels that they won't be able to follow a non-alcoholic diet for 8 weeks, they will be asked to tell the research team. We will compensate them for their time spent with us.

Data from Five 24-Week, Randomized, Double-Blind Placebo-Controlled Trials in Premenopausal Women with HSDD

The data presented below are derived from five 24-week randomized, double-blind, placebo-controlled trials in premenopausal women with acquired, generalized HSDD. In these five trials, the frequency and quantity of alcohol use was not recorded. Three of these trials (Studies 1 through 3) also provided efficacy data [see **Clinical Studies**]. One of these trials (Study 5) did not evaluate the 100 mg bedtime dose.

In four trials, 100 mg ADDYI at bedtime was administered to 1543 premenopausal women with HSDD, of whom 1060 completed 24 weeks of treatment. The clinical trial population was generally healthy without significant comorbid medical conditions or concomitant medications. The age range was 18-56 years old with a mean age of 36 years old, and 88% were Caucasian and 9% were Black.

Serious adverse reactions were reported in 0.9% and 0.5% of ADDYI-treated patients and placebo-treated patients, respectively.

Adverse Reactions Leading to Discontinuation

The discontinuation rate due to adverse reactions was 13% among patients treated with 100 mg ADDYI at bedtime and 6% among patients treated with placebo. Table 1 displays the most common adverse reactions leading to discontinuation in four trials of premenopausal women with HSDD.

Table 1: Adverse Reactions* Leading to Discontinuation in Randomized, Double-blind, Placebo-controlled Trials in Premenopausal Women with HSDD

	PLACEBO (N=1556)	ADDYI (N=1543)
Dizziness	0.1%	1.7%
Nausea	0.1%	1.2%
Insomnia	0.2%	1.1%
Somnolence	0.3%	1.1%
Anxiety	0.3%	1%
*Adverse reactions leading to discontinuation of > 1% of patients receiving 100 mg ADDYI at bedtime and at a higher incidence than placebo-treated patients.		

Most Common Adverse Reactions

Table 2 summarizes the most common adverse reactions reported in four trials of premenopausal women with HSDD. This table shows adverse reactions reported in at least 2% of patients treated with ADDYI and at a higher incidence than with placebo [see **WARNINGS AND PRECAUTIONS**]. The majority of these adverse reactions began within the first 14 days of treatment.

Table 2: Common Adverse Reactions* in Randomized, Double-blind, Placebo-controlled Trials in Premenopausal Women with HSDD

	PLACEBO (N=1556)	ADDYI (N=1543)
Dizziness	2.2%	11.4%
Somnolence	2.9%	11.2%
Nausea	3.9%	10.4%
Fatigue	5.5%	9.2%
Insomnia	2.8%	4.9%
Dry mouth	1.0%	2.4%
* Adverse reactions reported in ≥ 2% of patients receiving 100 mg ADDYI at bedtime and at a higher incidence than placebo-treated patients.		

Less Common Adverse Reactions

In four trials in premenopausal women with HSDD treated with 100 mg ADDYI at bedtime, less common adverse reactions (reported in ≥ 1% but < 2% of ADDYI-treated patients and at a higher incidence than with placebo) included:

- Anxiety (ADDYI 1.8%; placebo 1.0%),
- Constipation (ADDYI 1.6%; placebo 0.4%),
- Abdominal pain (ADDYI 1.5%; placebo 0.9%),
- Metrorrhagia (ADDYI 1.4%; placebo 1.4%),
- Rash (ADDYI 1.3%; placebo 0.8%),
- Sedation (ADDYI 1.3%; placebo 0.2%), and
- Vertigo (ADDYI 1%; placebo 0.3%).

Appendicitis

In the five trials of premenopausal women with HSDD, appendicitis was reported in 6/3973 (0.2%) flibanserin-treated patients, while there were no reports of appendicitis in the 1905 placebo-treated patients.

Accidental Injury

In five trials of premenopausal women with HSDD, accidental injury was reported in 42/1543 (2.7%) ADDYI-treated patients and 47/1905 (2.5%) placebo-treated patients. Among these 89 patients who experienced injuries,9/42 (21%) ADDYI-treated patients and 3/47 (6%) placebo-treated patients reported adverse reactions consistent with CNS depression (e.g.,somnolence, fatigue, or sedation) within the preceding 24 hours.

Source: http://www.rxlist.com/addyi-side-effects-drug-center.htm

13. Monitoring of Safety:

A researcher will be present with participants during the duration of the experiment. While participants are in a separate room sheltered from electrical interference for EEG recording, researchers will monitor participants' well-being via cameras and microphones within this room. Participants will have the ability to communicate with researchers through these microphones and may opt out of participation at any time. Participants will also be provided with the IRB's contact information on the consent form, and we will contact IRB should any adverse effects occur.

Participants will be advised not to drive, operate machinery, or do things that require clear thinking until at least 6 hours after taking flibanserin and until they know how flibanserin affects them. This has been addressed in the informed consent and will be discussed with participants.

Regarding Addyi's side effects: Subjects will be directed to call a member of the study team if they believe they are experiencing any side effects.

Vital signs (blood pressure, pulse, respiratory rate, temperature, height, weight) will be obtained at every visit. Orthostatic vital signs will be used in terms of blood pressure and pulse.

No baseline laboratory testing will be done.

14. Payment:

Participants will receive a parking voucher or $ 5 for public transportation at the end of every visit. At the end of each visit, participants will also receive $20 monetary compensation for their participation in the study. At the end of visit 3, participants will receive also receive $50 monetary compensation for completing the entire study.

15. Informed Consent:

Participants will be provided with the consent form attached in this IRB application. Participants must acknowledge understanding of procedures, risks, and benefits by signing this consent form before the study can proceed.

16. Confidentiality:

De-identified data will be stored in locked drawers or cabinets or on password-protected computers within the HPEN laboratory or on password protected University of Chicago server, such as UChicago Box. Data may be used in publications, but no personally identifiable information will be disseminated outside of researchers included in this protocol.

17. References to Justify Study:

Bianchi-Demicheli, F., Cojan, Y., Waber, L., Recordon, N., Vuilleumier, P., Ortigue, S. (2011). Neural bases of hypoactive sexual desire disorder in women: an event-related fMRI study. Journal of Sexual Medicine, 8, 2546-2559.

Bolmont, M., Cacioppo, J.T., & Cacioppo, S. (2014). Love is in the gaze: An eye-tracking study of love and sexual desire. Psychological Science. July 16. pii: 0956797614539706.

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Cacioppo, S., & Cacioppo, J.T. (2013). Lust for life. Scientific American Mind, 24, 56-63.

Cacioppo, S., & Cacioppo, J. T. (2015). Dynamic spatiotemporal brain analyses using high-performance electrical neuroimaging, Part II: A Step-by-Step Tutorial. Journal of Neuroscience Methods, 256: 184-197. pii: S0165-0270(15)00337-4. Doi: 10.1016/j.jneumeth.2015.09.004.

Cacioppo S., Couto B., Bolmont M., Sedeno L., Frum C., Lewis, J. W., Manes F., Ibanez A., Cacioppo, J. T. (2013) Selective decision-making deficit in love following damage to the anterior insula. Current Trends in Neurology, 7, 15-19.

Cacioppo, S. & Hatfield, E. (2013). From desire to love: New advances from social neuroscience. In L. Bormans (Eds). “The World Book of Love" (pp. 116-119). Tielt, Belgium: Lannoo Publishers.

Cacioppo, S., Weiss, R. M. Runesha, H. B., & Cacioppo, J. T. (2014). Dynamic Spatiotemporal Brain Analyses using High Performance Electrical NeuroImaging: Theoretical Framework and Validation. Journal of Neuroscience Methods, 238, 11-34. doi: 10.1016/j.jneumeth.2014.09.009.

Ortigue, S. & Bianchi-Demicheli, F. (2008). The chronoarchitecture of human sexual desire: a high-density electrical mapping study. NeuroImage 43, 337-345.

18. Recruiting Methods:

Subjects will be recruited via Flyers posted on Campus or Obstetrics and Gynecology practices or via ads posted on Craigslist.

19. Primary Physician Notification:

Dr. Jon Grant, M.D.

20. Anticipated Coordination between Inter-Departmental Faculty:

Stephanie Cacioppo, Ph.D., Jon Grant, M.D., and Royce Lee, M.D. are all members of the Department of Psychiatry and Behavioral Neuroscience. These researchers will coordinate extensively on this project.

21. Pregnancy Test: Conducted at screening visit.

22. Acceptable forms of birth control: oral contraceptives (e.g., combined pill or progestin only pill), intrauterine device, shot/injection, partner uses a male condom, vaginal ring, birth control patch, and abstinence.

Any pregnancy conceived during this study will be followed and its outcome (both maternal and neonatal) will be reported.

23. Inclusion/Exclusion Criteria:

Inclusion:

- Female
- Between 21 and 74 years old
- Menstruating for pre-menopausal and not mensutrating for at least 6 months for the post-menopausal women. **The FDA defines postmenopausal as:** 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy (U.S. Department of Health and Human Services, 2003).
  Premenopausal is defined as the period in a woman's life preceding menopause.
- DSM-5 diagnosis of hypoactive sexual desire disorder (HSDD) (also called disorder in sexual thoughts or interests)

Exclusion:

- Male
- < 21 years-old or > 74 years-old
- Hairstyles that induce artifacts to the EEG recording (i.e. braids, weave, extensions)
- Currently taking psychotropic medication
- Currently pregnant or lactating
- Women who report not being able to stop drinking alcohol during the duration of the study
- History of seizures or neurological disorders
- Under hormonal therapy
- Current or past diagnosis of cancer
- Any unstable medical illnesses
- Lifetime history of bipolar disorder, schizophrenia, or psychotic disorder
- Current or recent (past 3 months) substance abuse or dependence
- Current or recent (past 3 months) clinical depression
- Currently taking any medications that have/may have unfavorable interactions with Flibanserin
- Uncorrected vision
- Hepatic impairment

24. Study Drug Compliance:

In order to assess study drug compliance, we will ask subjects to bring back any unused medication at their next visit. Any missed doses will be accounted for by counting the number of pills the subject returns.

25. Study Drug Dispensation:

During the first visit, after Dr. Jon Grant or Dr. Royce Lee meet with the subject and determine if the subject is eligible to participate in the study, one of them will send a prescription to the investigational drug services (IDS) pharmacy at the University of Chicago Medical Center. The prescription is based on a randomization chart, so the physicians will order the drug by placing a coded patient number on the prescription sheet. When sent to the IDS pharmacy, they will know if that specific ID number is randomized to the flibanserin or the placebo, thus keeping it blinded to the physicians. Shortly after the study drug is ordered, a member of the study staff will pick it up from the IDS pharmacy and deliver it to the EEG lab where the subject will be doing the EEG procedures. After the subject is finished with all visit procedures, she will be given the study drug and instructions on how to take it.

All tablets will be dispensed at one time during the first visit. The total number of tablets each subject will receive is 56 tablets (8 weeks x 1 tablet/day).

26. Institutional Review Board (IRB):

The supervisory role of the IRB includes reviewing, approving, and monitoring all aspects of this research. All changes that are made to the study are always approved by the IRB before being implemented. The University of Chicago IRB follows the ethical principles consistent with the Declaration of Helsinki of the World Health Organization and the Belmont Report. It follows the policies of the FDA, the protection of human subjects, and others. Please follow link to read more:
http://bsdirb.bsd.uchicago.edu/policies-procedures/index.html

27. Prohibited Medications
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (refer to section 12 for more information)

The following medications are not to be taken by eligible subjects:

atazanavir; azamulin; buspirone; Clarithromycin; darunavir; dextromethorphan N-demethylation; digoxin; eletriptan; erythromycin N-demethylation; felodipine; indinavir; itraconazole; ketoconazole; lopinavir; lovastatin; midazolam 1-hydroxylation; midazolam; nefazodone; nelfinavir; nifedipine oxidation; Nootkatone; rifampin; ritonavir; saquinavir; sildenafil; simvastatin; telithromycin; terfenadine C-hydroxylation; testosterone 6 b –hydroxylation; ticlopidine; tipranavir; triazolam 4-hydroxylation triazolam; troleandomycin; verapamil.

28. Adverse Events:

Dr. Stephanie Cacioppo, Dr. Jon Grant, and Dr. Royce Lee will be responsible for the detection, documentation, classification, reporting, and follow-up of adverse events, including events meeting the definition of a serious adverse event (SAE). An adverse event (AE) us any undesirable experience associated with the use of a medical product in a patient. For the regulatory definitions of SAEs, refer to http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm.

All AEs will be recorded regardless of causality or severity. At the minimum, information collected concerning AEs should include the following: onset date, resolution date, severity (i.e., mild, moderate, or severe), relationship to study drug, intervention (if needed), seriousness of the event, and outcome.