A double-blind, randomized, placebo-controlled, proof of concept study to investigate the differences between the combined administration of 0.5 mg sublingual testosterone and 10 mg buspirone and 10 mg buspirone administration alone in women with hypoactive sexual desire disorder

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To investigate the differences between the combined administration of 0.5 mg sublingual testosterone and 10 mg buspirone and 10 mg buspirone administration alone in increasing sexual satisfaction during sexual activity in the domestic setting in…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sexual dysfunctions, disturbances and gender identity disorders
Study type	Interventional

Summary

ID

NL-OMON37080

Source
ToetsingOnline

Brief title
EB93 PoC

Condition

- Sexual dysfunctions, disturbances and gender identity disorders

Synonym
low sexual desire, sexual dysfunction

Research involving
Human

Sponsors and support

Primary sponsor: Emotional Brain
Source(s) of monetary or material Support: Emotional Brain BV

Intervention

Keyword: decreased sexual arousal, decreased sexual interest, HSDD, Sexual desire

Outcome measures

Primary outcome

Sexual satisfaction (SSEQ)

Secondary outcome

VPA

CBV

SARSAQ

Study description

Background summary

Lybridos (0.5 mg testosterone + 10 mg buspirone) is under development by Emotional Brain BV as an on-demand treatment for (the subset of) women with hypoactive sexual desire disorder (HSDD) characterized by maladaptive activity of sexual inhibitory systems. Lybridos is intended for use on a per need (i.e., not continuous) basis before proposed sexual activity. The cause of maladaptive activity of sexual inhibitory systems is not well elucidated, but both physiological and psychological factors are believed to be involved. Thus a combined treatment targeting the motivational sensitivity for sexual stimuli (testosterone) and enhancing a potential genital sexual response by decreasing possible inhibitory factors (buspirone) may increase genital arousal, as well as the frequency and quality of sexual encounters.

Our previous studies have shown that women with HSDD can be subdivided on the base of their pre-attentional bias for sexual stimuli (1,2). Although these women may be diagnosed with Female Sexual Dysfunction (FSD) according to the Diagnostic and Statistical Manual of Mental disorders, fourth edition (text revision) (DSM IV-TR), they appear to process sexual stimuli differently. When women with low sensitivity for sexual cues receive testosterone, alterations in pre-attentional bias for sexual stimuli occur, which could be an important condition for the induction of sexual motivation and sexual desire. Several studies have demonstrated that for women suffering from HSDD whose low initial sensitivity to sexual cues was boosted by sublingual testosterone, the combination of testosterone and a PDE-5 inhibitor (Lybrido) induced higher levels of vaginal blood flow when exposed to sexual stimuli (1,2), coupled with subjective reports of more intense genital sensations and sexual lust (1). It was also shown that neither testosterone nor a PDE-5 inhibitor produced these effects in women with HSDD when administered separately (1,2). In these same studies, subjects who did show an increased pre-attentional bias for sexual stimuli before testosterone administration, showed a decrease in pre-attentional bias after testosterone administration. Since these women showed no increase in vaginal blood flow or subjective reports of genital sensations in any of the drug conditions, and because most of them had a history of negative sexual experiences, it was hypothesized that this group suffered from maladaptive activity of sexual inhibitory systems. Acute 5HT1a agonism decreases serotonergic activity (3,4), an important mediator of inhibitory mechanisms (5). It was postulated that these individuals might benefit from the inhibition of these inhibitory mechanisms through acute 5HT1a agonism, especially in conjunction with testosterone-induced intensified sexual stimulation. In a study investigating the efficacy of the combination of testosterone and a PDE-5 inhibitor and of the combination of testosterone and a 5HT1a agonist it was indeed shown that women with HSDD who did not respond to the combination of testosterone and a PDE-5 inhibitor, responded positively to the combination of testosterone and a 5HT1a agonist (Lybridos), as measured by event logs and week diaries pertaining to their sexual activities at home (Tuiten et al., 2012 in preparation).

Sublingually administered testosterone (0.5mg) has been shown to have a delay in effect of about 4 hours on subjective and peripheral sexual arousal (6,7) in sexually functional women, but not in women with HSDD (1,2). If this central effect of testosterone administration is coupled with the use of buspirone, an increase in subjective and peripheral sexual arousal may be observed in women with HSDD. However, the peak effect of buspirone must coincide with the peak effect of the 4 hour delay effect of testosterone. So for buspirone (Tmax approx. 60 minutes), one would have to administer the sublingual testosterone first, and after 2-3 hours the buspirone.

The present small exploratory study is directed at investigating the efficacy of the combination of a single dose of 0.5 mg sublingual testosterone with 10 mg buspirone compared to placebo and buspirone (10 mg) alone, as part of the

ongoing drug development program for Lybridos.

Study objective

To investigate the differences between the combined administration of 0.5 mg sublingual testosterone and 10 mg buspirone and 10 mg buspirone administration alone in increasing sexual satisfaction during sexual activity in the domestic setting in healthy female subjects with hypoactive sexual desire disorder (HSDD).
To investigate the differences between the combined administration of 0.5 mg sublingual testosterone and 10 mg buspirone and 10 mg buspirone administration alone in increasing vaginal pulse amplitude (VPA), clitoral blood volume (CBV) and subjective ratings of sexual desire and arousal in the laboratory, in healthy female subjects with hypoactive sexual desire disorder (HSDD).

Study design

This is a double blind, randomized, placebo controlled proof of concept (small exploratory) study, with 3 psychophysiological laboratory measurement sessions (placebo, buspirone administration, combined testosterone and buspirone administration) separated by at least 1 day, followed by a 3-week at home period where subjects have 3 coital events after using the study medication, separated by at least 1 day.
Subjects will visit the study site a total of 5 times: 1 screening visit, 3 visits for psychophysiological measurement and 1 follow up visit. During the psychophysiological measurement visits, VPA, CBV and subjective desire and arousal will be measured, and the subject*s health will also be monitored. At the end of the last psychophysiological measurement visit, study medication for the 3-week at home period will be dispensed. Subject receive 1 dose of each study medication and are instructed to have an coital event following each medication intake. After each coital event at home, sexual satisfaction will be measured using a sexual satisfaction questionnaire (which will be distributed at the last psychophysiological measurement visit).

Intervention

Three interventions will be performed on all participants:
sublingual testosterone (0.5mg) and a tablet buspirone (10mg)
placebo solution and a tablet buspiron (10mg)
placebo solution and aplacebo tablet.

Study burden and risks

The main adverse reactions to exogenous androgens given chronically in physiological to slightly supraphysiological concentrations are androgenic side effects, primarily hirsutism and acne. We consider it to be highly unlikely

that testosterone administration in the doses and frequency to be used in this study will give rise to any serious health risks. In our previous studies, no serious health risks/adverse reactions were observed. Within 15 minutes of testosterone (0.5 mg, sublingually) intake plasma testosterone concentration increased 10-fold, and returned to baseline levels within 150 minutes Testosterone is administered over two admission periods with a 7 day wash-out between the admission periods. The dosing regimen regarding testosterone is therefore considered to be safe.
The combined use of sublingual testosterone and buspirone is considered safe because buspirone efficacy is not influenced when testosterone is given concomitantly. Moreover, the dose of buspirone in one dose of Lybridos is at most two thirds of the starting daily dose and less than a half (2/5) of the lightest weekly dose of buspirone prescribed for use as an anxiolytic drug. A previous home study (EB70) showed that Lybridos is well tolerated on long term, see the Investigator*s Brochure for Lybridos for additional information. Data on the effect of buspirone and testosterone on oral contraceptives is lacking. For this reason, participants on oral contraceptives will be instructed to use a second anti-conception method (double barrier). All participants will be instructed not to become pregnant during the study.
Clinically relevant abnormalities in ECG or chemistry may be noticed, in which case a medical specialist may be asked for advice, upon decision of the research team. If the specialist confirms that medical treatment is necessary, the participant*s GP physician will be informed. This procedure is mandatory and explained to the subject in the Informed Consent form.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provision of written informed consent.
2. Female 21 - 45 years of age with Hypoactive Sexual Desire Disorder (comorbidity with other sexual dysfunctions e.g Female Sexual Arousal Disorder (FSAD) is allowed). The diagnosis will be made by an experienced psychologist/sexologist.;3. Healthy according to normal results of medical history, physical examination, laboratory values and vital signs, unless the investigator considers an abnormality to be clinically irrelevant.;4. Subjects must have a heterosexual relationship.;5. Be involved in a stable relationship and have a partner who will be accessible during the 3-week at home period.

Exclusion criteria

Cardiovascular conditions;1. Any underlying cardiovascular condition, including unstable angina pectoris;2. Systolic blood pressure >= 140 mmHg and/or diastolic blood pressure >= 90 mmHg. ;3. Systolic blood pressure < 90 mmHg and/or diastolic blood pressure <50 mmHg;Gynecological and obstetric conditions;4. Use of oral contraceptive containing anti-androgens (e.g. Crypteron acetate) or (anti)androgenic progestogens (drospirone, dienogest, chlormadinone acetate and norgestrel);5. Use of oral contraceptive containing 50 µg estrogen or more;6. Pregnancy or intention to become pregnant during this study (Note: An urine pregnancy test will be performed in all women prior to the administration of study medications.);7. Lactating or delivery in the previous 6 months ;8. Unexplained gynecological complaints, such as clinically relevant abnormal uterine bleeding patterns;9. Subjects with a perimenopausal or postmenopausal hormonal status (follicle-stimulating hormone>40);Other medical conditions;10. Liver- and/or renal insufficiency;11. Current clinically relevant endocrine disease ;12. Current clinically relevant neurological disease which, in the opinion of investigator, would compromise the validity of study results, or which could form a contraindication for buspirone and/or testosterone use;13. (A history of) hormone-dependant malignancy;14. Vision impairment, such as partial or complete blindness or color blindness;15. Dyslexia;16. Positive test result for immunodeficiency virus, hepatitis B, or hepatitis C (acute and chronic hepatitis infection);Psychological/psychiatric factors;17. History of (childhood) sexual abuse that, in the opinion of the investigator, could result in negative psychological effects when testosterone is administered;18. (Psychotherapeutic and/or

pharmacological treatment for) a psychiatric disorder that, in the opinion of the investigator, would compromise the validity of study results or which could be a contraindication for buspirone and/or testosterone use;19. Current psychotherapeutic treatment for female sexual dysfunction;20. Current sexual disorder of vaginismus or dyspareunia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (text revision (DSM IV TR));21. A substance abuse disorder that, in the opinion of the investigator, is likely to affect the subject's ability to complete the study or precludes the subject*s participation in the study (mild or moderate alcohol consumption is allowed but must be stopped 12 hours before the Stroop task).;22. Positive test result for illicit drugs;Concomitant medication;23. Subjects who are taking CYP3A4-inhibitors (eg, ritonavir, ketoconazol, itraconazol claritromycine, erytromycine and saquinavir);24. Subjects who are taking CYP3A4-inducers (eg, carbamazepine, fenytoïne, fenobarbital, st Johns Wort, rifampicine);25. Use of serotonergic drugs (eg, trazodon, fluvoxamine), tricyclic antidepressants or other antidepressants;26. Use of testosterone therapy within 6 months before study entry;27. Use of any other medication that interferes with study medication (eg, monoamine oxidase (MAO) inhibitors (includes classic MAO inhibitors and linezolid), calcium channel blockers (eg, diltiazem and verapamil), triptans);General;28. Illiteracy, unwillingness, or inability to follow study procedures;29. Any other clinically significant abnormality or condition which, in the opinion of investigator, might interfere with the participant*s ability to provide informed consent or comply with study instructions, compromise the validity of study results, or be a contraindication for buspirone and/or testosterone use.;30. Participation in any other clinical drug study in the previous 3 months.&#xD

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-08-2012

Enrollment:	9
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	buspar
Generic name:	buspirone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	testosteron
Generic name:	testosterone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-08-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-08-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-003543-30-NL
CCMO	NL41678.056.12