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

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Primary ObjectiveTo investigate the possible efficacy of combined administration of 0.5 mg sublingual testosterone and 10 mg tadalafil in increasing sexual satisfaction during sexual activity in the domestic setting in healthy female subjects with...

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

Summary

ID

NL-OMON36064

Source
ToetsingOnline

Brief title
Tadalafil Proof of Concept

Condition

- Sexual dysfunctions, disturbances and gender identity disorders

Synonym
problems with sexual functioning, Sexual dysfunction

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Proof of Concept, Tadalafil, Testosterone

Outcome measures

Primary outcome

The primary endpoint is the increase in sexual satisfaction of a single coital event, measured using the Sexual Satisfaction of an Event Questionnaire (SSEQ), and through a psychological interview discussing in depth (at follow up but whilst still blinded) the difference between two sexual events experienced at home whilst using study medication.

Secondary outcome

The secondary endpoints are as follows:

• Physiological sexual response

o VPA in response to erotic film clips

o CBV in response to erotic film clips

• Subjective sexual response

o Subjective rating of sexual desire and arousal in response to an erotic film clip (SARSAQ)

• Safety assessments

Study description

Background summary

Female sexual dysfunction (FSD) refers to various disturbances or impairments of sexual function, including a lack of interest in sexual activity, repeated failure to attain or maintain sexual excitement, and inability to attain an orgasm following sufficient arousal. A recent study estimated that 43% of women suffer from sexual dysfunction in the United States (US).1 Low sexual desire (22% prevalence) and sexual arousal problems (14% prevalence) belong to the most common categories of sexual dysfunction of women. These categories are convenient in providing working definitions and an accepted lexicon for researchers and therapists. However, it may be incorrect to assume that these disorders are fully independent of each other. Both case studies and epidemiological studies demonstrate that these disorders can overlap and may be interdependent. In some cases, it may be possible to identify the primary disorder that led to the others, but in many cases, this may be impossible. In view of the recognition that sexual desire and arousal problems often coexist, it has recently been recommended that a new combined diagnosis of Sexual Interest/Arousal Disorder replace the separate diagnoses of hypoactive sexual desire disorder (HSDD) and female sexual arousal disorder (FSAD) in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), scheduled for publication in 2013.
The 3 (transitional and overlapping) phases of the human sexual response can each be disrupted, leading to low sexual desire, sexual arousal problems, and hampered orgasm. The phases are regulated by relatively independent neurotransmitter functions, and dysfunctions are candidates for psychopharmacological treatment. Traditionally, motivated behaviors have been divided into appetitive and consummatory components. Activities aimed at obtaining reward and satisfactions belong to the appetitive component. The fundamental appetitive motivational process is an intrinsic brain function and is especially related to the predictive value of stimuli for reward.
Processing of motivationally relevant information (ie, stimuli predicting reward) causes an increase in activity of the meso accumbens dopaminergic system (ie, dopamine neurons of the ventral tegmental area [VTA] innervating the nucleus accumbens). The activity of this system is increased during flexible approach behavior when anticipating reward related to copulation.2 Increasing activity in these dopaminergic pathways facilitates sexual motivation, in particular anticipatory sexual behavior.3
Anticipating sexual reward will produce arousal of the genitals, in which at least 2 key neurotransmitters are involved: acetylcholine and nitric oxide (NO). Acetylcholine and NO both promote erections in men and lubrication and swelling in women. Orgasm, the consummatory phase of human sexual response, is facilitated by descending spinal noradrenergic fibers and innervation of the genitals, and inhibited by descending spinal serotonergic fibers.
In many mammalian species, female sex steroids are necessary for the expression

of female sexual behavior. As a result, the capability for copulation in these animals is limited to the period of ovulation.4,5 Humans (as well as higher primates) show sexual intercourse outside the periovulatory period. In humans, testosterone is clearly involved in female sexual behavior.6 The disappearance of testosterone following ovariectomy and adrenalectomy is accompanied by a complete loss of libido,7,8 while substitution of this steroid maintains sexual desire and fantasies after surgical menopause.9

An important aspect of sexual motivation is physiological sexual responding. Measured as an increase in vaginal vasocongestion elicited by sexual stimuli, this responding is considered to be preparatory for copulatory behavior.10 In hypogonadotropic, hypogonadal females, substitution with testosterone undecanoate 40 mg orally per day during an 8 week period enhanced vaginal responsiveness.10 This effect was not found in another group of hypogonadotropic, hypogonadal patients (unpublished data). In both studies, subjects received testosterone each morning, but subjects in the first study were tested in the afternoon, and subjects in the second study were tested in the morning. The different outcomes on physiological responding between these experiments may be caused by a time dependent effect of testosterone on vaginal arousal. A third study was conducted to determine the effect of a single dose of testosterone sublingually, as compared with placebo, on vasocongestion during presentation of visual erotic stimuli.11 On treatment days, 8 sexually functional women were exposed, at intervals of 1.5 hours, to 6 erotic films depicting intercourse. The intake of testosterone caused a sharp increase in plasma levels of testosterone of short duration. About 3 to 4.5 hours after this testosterone peak, a striking increase in vaginal responsiveness was observed when the subjects were exposed to the visual sexual stimuli. These findings demonstrate a time lag in the effect of sublingually administered testosterone on genital arousal in sexually functional women. This study was replicated 2 years later, with the same results.12

The results of the above mentioned studies demonstrate that testosterone is involved in female sexual motivation in a time dependent fashion. The influence of sex steroids on sexual behavior might be explained by the existence of a steroid responsive neural network, a highly interconnected group of sex hormone receptor-containing neurons in the brain.13 This network is not a closed circuit, but serves reproductive aims by functioning as an integrating and activating center between external sensory cues, hormonal processes, and reproductive behavior. This is partly accomplished by selective filtering of sensory input and amplification of signals that may facilitate sexual behavior. It is assumed that an increase in vaginal vasocongestion induced by sexual stimuli is preparatory for copulatory behavior. Visual exposure to sexual intercourse between members of the species of the onlooker is a potent releasing stimulus for such a preparatory motivational response. Both men and women have a marked capacity to respond to erotic films with a genital response.14 The increased motivational sensitivity for sexual cues induced by testosterone presumably results from an altered brain state in which dopaminergic, serotonergic, and noradrenergic pathways are involved. Indeed, the VTA,15 the dorsal raphe nucleus (serotonergic),16 and the nucleus coeruleus

(noradrenergic)17 are all modulated by androgen activity in rats.
In several studies, it has been shown that selective type 5 phosphodiesterase (PDE 5) inhibitors improve erectile function in men with erectile dysfunction, on average close to normal function.18 In the penis, NO released from nerves and endothelium, induces production of cyclic guanosine monophosphate (cGMP); cGMP plays a key role in relaxing smooth muscle, necessary for the induction of an erection. This nucleotide is hydrolyzed by phosphodiesterases, of which PDE 5 exerts the main activity in the corpora cavernosa. Therefore, PDE 5 inhibitors will, during sexual stimulation, enhance the action of NO/cGMP on erectile function.19 The genitals of both sexes have common embryological origins. Recently, it has been shown that the clitoris consists of an erectile tissue complex, which embeds the anterior vaginal wall. Clitoral erection and the anterior wall of the vagina are highly involved in female sexual arousal and response. Sildenafil, a PDE 5 inhibitor, has been shown to improve sexual performance in sexually functional women.14 Two recent studies showed increased genital sensation in subsets of postmenopausal women with arousal disorder.20,21 Data on tadalafil is lacking. Only one study has been described investigating effects of tadalafil in women.22In this study, 3 women using serotonin enhancing agents reported improved sexual functioning following 20 mg tadalafil use. These studies suggest that a PDE 5 inhibitor might be beneficial for women with sexual dysfunction. However, most studies show that the use of a PDE5 inhibitor in female sexual dysfunction (mostly HSDD or FSAD) is not efficacious, possibly because central mechanisms of sexual arousal are not targeted. 23,24
Sexual functions are the result of an interaction between central and peripheral processes. Combining medications in such a way that both central and peripheral processes are enhanced - for example by combining testosterone and a PDE 5 inhibitor - is theorized to have a synergistic effect, because enhancement of central processes alone should enhance peripheral processes and vice versa. Enhanced central and peripheral mechanisms then receive enhanced feedback stimulation from each other, increasing each process in a cumulative manner. Indeed, in previous studies,23,24 the combination treatment of sublingual testosterone (0.5 mg) and vardenafil (10 mg) induced a very strong and significant increase in vaginal pulse amplitude, coupled with subjective reports of more intense genital sensations and sexual lust in women suffering from FSD, whereas neither substance alone had an effect. In an experiment on the efficacy of on demand use of sublingual testosterone (0.5 mg) combined with sildenafil (50 mg), physiological and subjective sexual responses were evaluated in an ambulatory psychophysiology laboratory at home for 1 week. Subsequently, sexual improvement and satisfaction during use of the this combination was measured (in the bedroom) for 3 weeks. The combination significantly improved sexual functioning in both phases (manuscript submitted). The findings that sublingual testosterone combined with sildenafil or combined with vardenafil can increase measures of sexual arousal in women with HSDD, suggests that combining 0.5 mg sublingual testosterone with tadalafil may also have such an effect. Sublingual testosterone has a delay in effect of approximately 4 hours.11,12 A single dose can thus induce increased sexual

responses in women without FSD,11,12 but not with HSDD.23,24 To allow the pharmacodynamic effect of a single dose of sublingual testosterone to optimally overlap with the pharmacodynamic effect of sildenafil or vardenafil, these two PDE5 inhibitors have to be administered approximately 2 hours after the testosterone administration. Tadalafil has maximum concentration 2 hours after ingestion, and a terminal half life of approximately 18 hours. Thus, when sublingual testosterone and tadalafil are combined, both compounds can be taken simultaneously. Simultaneous administration of two drugs is easier and could improve protocol adherence. The present small exploratory study is directed at investigating the possible efficacy of the combination of a single dose of 0.5 mg sublingual testosterone with 10 mg oral tadalafil, administered simultaneously.

Study objective

Primary Objective
To investigate the possible efficacy of combined administration of 0.5 mg sublingual testosterone and 10 mg tadalafil in increasing sexual satisfaction during sexual activity in the domestic setting in healthy female subjects with hypoactive sexual desire disorder (HSDD).

Secondary Objectives
The secondary objectives are as follows:

To investigate the possible efficacy of combined administration of 0.5 mg sublingual testosterone and 10 mg tadalafil 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).

To evaluate the safety of combined administration of 0.5 mg sublingual testosterone and 10 mg tadalafil

Study design

This is a double blind, randomized, placebo controlled proof of concept (small exploratory) study, with 2 psychophysiological laboratory measurement sessions (placebo & active) separated by at least 4 days, and a 1 week at home period where subjects have 2 coital events, separated by at least 4 days.
Subjects will visit the study site a total of 4 times: 1 screening visit, 2 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 1-week at home period will be dispensed. After a coital event at home, sexual satisfaction will be measured using a sexual satisfaction questionnaire.

At follow up (whilst still blinded), an in depth psychological interview is given in order to further investigate possible drug dependent differences between sexual events.

Intervention

administration of sublingual testosterone (0.5 mg) and an oral tablet containing tadalafil (10 mg)

Study burden and risks

Use of T+Tad is expected to improve the level of sexual satisfaction for a single sexual event.
Dosed separately, testosterone and tadalafil administration at the doses and frequency proposed for this study are not known to result in any serious health risks.
Testosterone and sildenafil(a shorter acting PDE5 inhibitor) have been dosed together in several studies (A total of 172 subjects have been dosed with testosterone and sildenafil). No significant adverse events (AEs) have been observed when testosterone and sildenafil was administered together. Because the combination of T+Tad is roughly equivalent, we also expect this combination to be safe.
The amount of testosterone (0.5 mg) used roughly corresponds to what women produce endogenously per day.25 After sublingual administration of 0.5 mg T, circulating testosterone increases to supraphysiological levels for only a very short period of time and quickly returns to baseline levels within 3 hours. In contrast to this, continuous androgen administration chronically raises testosterone levels to supraphysiological levels, which can result in masculinization effects such as hirsutism; it has also been linked to an increased risk of developing specific types of cancer and adverse cardiovascular effects. Sublingual T (0.5 mg) however, only contains a very modest amount of testosterone, and in this study, the maximum amount of testosterone administered will be twice 0.5 mg; this level of testosterone exposure is significantly less than levels that have been associated with the above mentioned side effects. Hence, the suggested dose and dosing regimen for testosterone, as a component of T+Tad, is considered to be safe.
Tadalafil has been approved for use in men by the FDA and the EMA (amongst others) for erectile dysfunction and pulmonary hypertension. In men it is well tolerated, the most frequent AEs (>10%) being headache and dyspepsia. In the here used dosis (10 mg) it is considered to be safe.
Data on the effect of tadalafil and testosterone on oral contraceptives are lacking. For this reason, participants on oral contraceptives will be instructed to use a second contraceptive method (double barrier). All participants will be instructed not to become pregnant during the study.

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 to 45 years of age, inclusive, premenopausal, with HSDD (comorbidity with female sexual arousal disorder and/or female orgasmic disorder [FOD; only as secondary diagnosis] is allowed). The diagnosis of HSDD will be established by a trained professional.
3.Heterosexual orientation
4.Be involved in a stable relationship
5.Healthy according to normal results of medical history, physical examination, laboratory values, and vital signs; exceptions may be made if the investigator considers an abnormality to be clinically irrelevant

Exclusion criteria

Cardiovascular Conditions
1.Any underlying cardiovascular condition, including unstable angina pectoris, that would preclude sexual activity
2.History of myocardial infarction, stroke, transient ischemic attack or life threatening arrhythmia within the prior 6 months
3.Uncontrolled atrial fibrillation/flutter at screening or other significant abnormality observed on electrocardiogram (ECG)
4.Systolic blood pressure >= 140 mmHg and/or diastolic blood pressure > 90 mmHg
5.Systolic blood pressure < 90 mmHg and/or diastolic blood pressure < 50 mmHg;Gynecological and Obstetric Conditions
6.Use of oral contraceptive containing anti androgens
7.Use of oral contraceptive containing 50 µg estrogen or more
8.Pregnancy or intention to become pregnant during this study (Note: A urine pregnancy test will be performed in all women prior to the administration of study medications.)
9.Lactating or delivery in the previous 6 months
10.Significant abnormal pap smear in the previous 12 months
11.History of bilateral oophorectomy
12.Other unexplained gynecological complaints, such as clinically relevant abnormal uterine bleeding patterns;Other Medical Conditions
13.Liver and/or renal insufficiency (aspartate aminotransferase and alanine aminotransferase > 3 times the upper limit of normal and/or glomerular filtration rate < 29 mL/min based on the Cockcroft and Gault formula)
14.Current clinically relevant endocrine disease or uncontrolled diabetes mellitus
15.Current clinically relevant neurological disease which, in the opinion of the investigator, would compromise the validity of study results, or which could form a contraindication for tadalafil and/or testosterone use
16.History of hormone dependent malignancy
17.Vision impairment, such as partial or complete blindness or color blindness
18.Dyslexia
19.Positive test result for human immunodeficiency virus, hepatitis B, or hepatitis C (acute and chronic hepatitis infection);Psychological/Psychiatric Factors
20.History of (childhood) sexual abuse that, in the opinion of the investigator, could have negative psychological effects when testosterone is administered
21.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 tadalafil and/or testosterone use
22.Current psychotherapeutic treatment for female sexual dysfunction
23.Current sexual disorder of vaginismus or dyspareunia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (text revision).
24.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.
25.Positive test result for illicit drugs;Concomitant Medications
26.Use of potent CYP3A4 inhibitors (eg, ritonavir, ketoconazol, itraconazol claritromycine, erytromycine, saquinavir and grapefruitjuice)

27.Use of potent CYP3A4 inducers (eg, carbamazepine, phenytoin, phenobarbital, St Johns Wort, rifampicin)
28.Use of nitrates or nitric oxide donor compounds
29.Use of SSRIs
30.Use of any other medication that interferes with study medication (eg, monoamine oxidase [MAO] inhibitors [includes classic MAO inhibitors and linezolid)
31.Use of medication (including herbs) that would compromise the validity of study results
32.Use of testosterone therapy within 6 months before study entry;General
33.Illiteracy, unwillingness, or inability to follow study procedures
34.Participation in other clinical trials within the last 90 days
35.Any other clinically significant abnormality or condition which, in the opinion of the 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 tadalafil and/or testosterone use

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-07-2011
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cialis

Generic name:	tadalafil
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	testosterone
Generic name:	testosterone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-06-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-07-2011
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	EUCTR2011-002770-23-NL
CCMO	NL37237.056.11