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Efficacy of testosterone combined with a PDE5 inhibitor and testosterone combined with a serotonin $_{1A}$ receptor agonist in women with SSRI-induced sexual dysfunction. A preliminary study

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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are known to cause sexual dysfunction, such as decreased sexual motivation, desire, arousal, and orgasm difficulties. These SSRI-induced sexual complaints have a high prevalence rate, while there is no approved pharmacological treatment for SSRI-induced sexual dysfunction. It is hypothesized that a polymorphisms in the androgen receptor gene, encoded by the nucleotides cysteine, adenine, and guanine (CAG), influence the effect of testosterone on sexual functioning. In an explorative, randomized, double-blind, placebo-controlled, crossover study we investigated the possible effects of sublingual testosterone combined with a serotonin (5-HT)$_{1A}$ receptor agonist, and of sublingual testosterone combined with a phosphodiesterase type 5 inhibitor (PDE5-i) on sexual functioning in women with SSRI-induced sexual dysfunction. Furthermore, we did an exploratory analysis to assess if the CAG polymorphism influences this effect. 21 pre- and postmenopausal women with SSRI-induced sexual dysfunction participated and underwent the following interventions: a combination of testosterone (0.5 mg) sublingually and the PDE5-i sildenafil (50 mg) and a combination of testosterone (0.5 mg) sublingually and the 5-HT$_{1A}$ receptor agonist buspirone (10 mg). The results show that women who use a low dose of SSRI and have relatively long CAG repeats report a marked improvement in sexual function in response to both treatments compared to placebo. This explorative study and preliminary results indicate that in women with SSRI-induced sexual dysfunction, a combination of testosterone sublingually and a PDE5-i or testosterone sublingually and a 5-HT$_{1A}$ receptor agonist might be promising treatments for certain subgroups of women with this condition.

1. Introduction

Antidepressant therapy has been frequently associated with negative sexual side effects, such as decreased sexual motivation, desire, arousal, and orgasm difficulties (Rosen et al., 1999; Montgomery et al., 2002). These negative sexual side effects can produce psychological distress and an impaired quality of life. Selective serotonin reuptake inhibitors (SSRIs) are the most notorious for causing sexual dysfunction (SD) with an estimated prevalence rate of 20–70% (Serretti and Chiesa, 2009; Montejo et al., 2001). Although some beneficial effects have been reported with the use of buspirone (Landen et al., 1999; Norden, 1994), bupropion (Labbate and Pollack, 1994; Safarinejad, 2011; Clayton et al., 2004) or type 5 phosphopdiesterase (PDE5) inhibitors (e.g., sildenafil) (Nurnberg et al., 2008, 2003; Fava et al., 1998), to date no FDA approved pharmacological treatment for SSRI-induced SD is available.

Of the different serotonin (5-HT) receptors, 5-HT$_{1A}$ and 5-HT$_2$ receptors are well accepted to be involved in sexual functioning (Clayton and Hamilton, 2009; Berger et al., 2009). The SSRI-induced elevated synaptic serotonin levels, and by inference the increased serotonergic neurotransmission, are thought to inhibit the sexual excitatory effects of dopamine and norepinephrine in the mesolimbic reward system (Clayton and Hamilton, 2009;

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Meltzer et al., 1979; Done and Sharp, 1992) via a tonic increased serotonergic activity in the prefrontal cortex (PFC) (Evers et al., 2005; Goldapple et al., 2004). 5-HT_{1A} receptor agonists, e.g., buspirone, decrease serotonergic activity for a short time after a single dose administration via activation of the somatodendritic autoreceptor (Liu et al., 2004; Sprouse and Aghajanian, 1987; Hamon et al., 1988). Accordingly, acute treatment with a 5-HT_{1A} receptor agonist might decrease, during a relatively short period of time, the serotonergic inhibitory control in the PFC, which might lead to an increased activity in the mesolimbic system involved in sexual motivation. Therefore, the use of a 5-HT_{1A} receptor agonist could be part of treatment in patients with SSRI-induced SD.

In sexual functioning it is well recognized that testosterone plays an important role (Auger, 2004; Hull and Dominguez, 2007). Tuiten et al. (2000, 2002) reported that a single dose of 0.50 mg sublingual testosterone increased genital arousal and experiences of sexual lust and genital sensation in premenopausal sexually functional women 3–4 h after the induced testosterone peak. This delay in effect of sublingual testosterone has been frequently replicated in several studies regarding cognitive and affective functions, including sexual functioning and social behavior (Postma et al., 2000; Aleman et al., 2004; Schutter and van Honk, 2004; van Honk et al., 2004, 2005, 2001; van Honk and Schutter, 2007; Hermans et al., 2006, 2007, 2008 Bos et al., 2010, 2013; Eisenegger et al., 2010). In addition, it has been demonstrated that the combined use of sublingual testosterone with a PDE5-inhibitor (PDE5-i), and of sublingual testosterone with a 5-HT_{1A} receptor agonist are two treatments which are effective in different subgroups of women with Hypoactive Sexual Desire Disorder (HSDD). The first combination increased sexual satisfaction in women who have a relatively insensitive brain system for sexual cues (Poels et al., 2013), while the second combination was most suitable for women with enhanced activity of sexual inhibitory mechanisms (van Rooij et al., 2013). The sequence and timeframe of the delivery of the compounds in both combination-treatments were such that the pharmacological effects of the PDE5-i and 5-HT_{1A}ra coincide with the time-window of the testosterone-induced behavioral effects (Poels et al., 2013; van Rooij et al., 2013). The behavioral effects of sublingual testosterone are mediated, at least in part, by binding to the androgen receptor (AR). It is our hypothesis that polymorphisms in the AR gene are of influence in this behavioral effect. The polymorphic polyglutamine stretch in the aminoterminal domain of the AR, encoded by the nucleotides cysteine, adenine, and guanine (CAG), is known to influence the function of the receptor as a transcription factor, so that relatively long CAG repeat lengths are associated with a low level of receptor function (Chamberlain et al., 1994; Kazemi-Esfarjani et al., 1995; Tut et al., 1997). It can be hypothesized that women with relatively long CAG repeat lengths are less sensitive to sexual cues because their AR has a low level of receptor functioning. These women may need higher levels of circulating testosterone to activate intracellular processes after binding to the AR. Therefore, they could benefit more from sublingual testosterone in increasing their brain's sensitivity compared to women with relatively shorter CAG repeats.

In this explorative study we investigated the possible effects of sublingual testosterone combined with a 5-HT_{1A} receptor agonist, and of sublingual testosterone combined with a PDE5-i on sexual functioning in pre- and postmenopausal women with SSRI-induced SD.

2. Methods

2.1. Study subjects

Twenty-one women, aged ≥ 21, pre- or postmenopausal with a diagnosis of SSRI-induced SD (comorbidity with other SDs was allowed) according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (Text Revision) (DSM-IV-TR) criteria (American Psychiatric Association, 2000) were randomized (the diagnosis SSRI-induced SD falls under the diagnosis substance-induced SD). This diagnosis was made by a trained psychologist. In order to meet the criteria of this diagnosis it was evaluated to what extend depressive or anxious feeling contributed to the sexual complaints and it was assessed how these subjects experienced sex prior to the start of the SSRI. Participants used an SSRI for at least 3 months and were on a stable dose for a minimum of 6 weeks. Participants used the following SSRIs: citalopram ($n=5$), paroxetine ($n=11$), venlafaxine ($n=3$), fluvoxamine ($n=1$) and sertraline ($n=1$).

Exclusion criteria included a history of serotonin syndrome, endocrine disease, neurological problems, a current serious psychiatric disorder (e.g., schizophrenia, psychosis or treatment for obsessive compulsive disorder, anorexia nervosa, bulimia nervosa and/or social anxiety neurosis), cardiovascular condition, hypertension, and abnormal liver or renal function.

Blood samples for determination of baseline levels of total testosterone, Sex Hormone Binding Globulin (SHBG), albumin, Thyroid Stimulating Hormone (TSH), Follicle Stimulating Hormone (FSH), estrogen and CAG repeat length were collected at the screening visit. A urine pregnancy test was applied to all premenopausal women.

Twenty-one women participated after providing written informed consent. This study was approved by the local medical ethics committee and carried out in agreement with the International Conference on Harmonisation—Good Clinical Practice (ICH-GCP).

2.2. Study design

Study setting and design are the same as described in Poels et al. (2013) and van Rooij et al. (2013). In this manuscript only the results of the event questionnaire (see further on), which was filled out after following each sexual events, will be reported.

In a randomized, double-blind, placebo-controlled, crossover design, 21 women underwent three different medication regimes: (i) **placebo**: placebo for testosterone (cyclodextrin solution without testosterone) and placebo for the PDE5 inhibitor (PDE5i = sildenafil)/5-HT_{1A} receptor agonist (5-HT_{1A}ra = buspirone) (powder-filled gelatine capsule without sildenafil/buspirone); (ii) **T + PDE5i:** the combination of testosterone (0.5 mg) sublingually with cyclodextrin as carrier and sildenafil (50 mg, hidden in a powder-filled gelatine capsule); (iii) **T + 5-HT_{1A}ra**; the combination of testosterone (0.5 mg) sublingually with cyclodextrin as carrier and buspirone (10 mg, hidden in a powder-filled gelatin capsule). Each medication regime lasted four weeks and the order of the three medication regimes was randomized (Poels et al., 2013; van Rooij et al., 2013).

Participants were instructed to take the cyclodextrin solution (testosterone or placebo) sublingually 4 h prior to each measurement session or sexual event and rinse it under the tongue for 1 min. They were instructed to ingest the capsule (sildenafil, buspirone or placebo) 2.5 h later. When they had experienced a sexual event they were asked to fill out a secure web-based event questionnaire (EQ) within 24 h following the sexual event. The EQ comprised of 10 questions (one open-ended, four multiple-choice, five 5-point Likert scale items) concerning the type, duration, pleasantness and intensity of the sexual event.

In order to monitor changes in psychological wellbeing, the Beck Depression Inventory-II (BDI-II) and the State-Trait Anxiety Inventory—Disposition 2 (Trait) version Y (STAI-DY2) questionnaires were filled out at baseline and final follow up visit as well as after each treatment period.

2.3. Statistical analysis

Based on high Cronbach's alpha's of 5 items measuring desire and intensity of the sexual events (measured by the EQ) during the

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different drug conditions (Placebo: α=0.92; T+PDE5i: α=0.90; T+5-HT$_{1A}$ra: α=0.92) the mean of these items were calculated as a qualitative measure of "sexual satisfaction".

Two participants did not fill out their EQs in the placebo treatment period, however they did report sexual events in the T+PDE5i and T+5-HT$_{1A}$ra period. Because of the small study population their missing placebo data was imputed in the following manner: the correlation between placebo and the mean of both drug conditions (((T+PDE5i)+(T+5-HT$_{1A}$ra))/2) was high (r=.617, p=0.005). Because all participants had (T+PDE5i) and (T+5-HT$_{1A}$ra) data, z-scores were made of the ((T+PDE5i)+(T+5-HT$_{1A}$ra))/2 variable. The two subjects with the missing placebo data comprised of one subject with a negative z-score and one subject with a positive z-score based on the ((T+PDE5i)+(T+5-HT$_{1A}$ra))/2 variable. The mean of sexual satisfaction during placebo of the subjects with a negative z-score in the ((T+PDE5i)+(T+5-HT$_{1A}$ra))/2 condition was imputed in the placebo condition for one subject and the mean of sexual satisfaction during placebo of the subjects with a positive z-score in the ((T+PDE5i)+(T+5-HT$_{1A}$ra))/2 condition was imputed in the placebo condition for the other subject.

Regarding the comparability of dosages of the SSRI use, the dosing classification of Gartlehner et al. (2007) was used in this study. We divided the subjects into two subgroups on the basis of their SSRI dose: a low and medium-high dose group. SSRI dosages that were classified as low (n=16) were: citalopram $<$30 mg, fluvoxamine $<$75 mg, paroxetine $<$30 mg, sertraline $<$75 mg and venlafaxine $<$156.3 mg. Higher dosages of each SSRI (n=5) were classified as medium-high dosages.

For the CAG repeat length, we divided the subjects into two subgroups based on the mean of the CAG repeat length: subject with a relative short CAG repeat length (CAG $\leq$22 repeats) and subjects with relative long CAG repeat length (CAG length $>$22 repeats). This cut-off point corresponds to other studies with CAG repeats in women (e.g., the comparison between women with breast cancer and controls) (Spurdle et al., 1999; Haiman et al., 2002). Unfortunately, the CAG results of two subjects are missing due to an error in the laboratory analysis. In total, the mean of the CAGs of 19 subjects were used for the analysis: 8 subjects with relatively short CAG repeats and 11 subjects with relatively long CAG repeats.

Demographic data were analyzed to investigate possible group differences (low versus medium-high SSRI dose and short versus long CAG repeat length) with an independent t-test if the data were normally distributed. For non-normally distributed data, the Mann–Whitney test was used. Categorical data was compared between the groups with a Chi-square test. For each of the dependent variables, separate 2 × 2 × 2 repeated measures analyses of variance (repeated measures ANOVA) were carried out. The within-subject factor was drug response, and had two levels (T+PDE5i versus Placebo, and T+5-HT$_{1A}$ra response versus placebo). The between subject factor was SSRI dosage (low SSRI dose versus medium-high SSRI dose) and CAG repeat length (short CAG repeat length versus long CAG repeat length). To calculate the relative increase in sexual satisfaction, placebo was subtracted from the T+PDE5-i treatment and this was divided by placebo and multiplied by 100%. The same calculation was done for the relative increase in sexual satisfaction after T+5-HT$_{1A}$ra treatment. An alpha level of 0.05 was set for all analyses.

3. Results

Twenty-one women completed the study. All baseline hormonal values were in the normal female reproductive and/or postmenopausal range. There were no clinical significant changes in the scores of the BDI-II and STAI-DY2 questionnaires during the study.

The baseline characteristics and hormone levels of the 21 women are outlined in Table 1.

Table 1
Demographics and baseline hormonal values of the participating women.

	Subjects	Low dose SSRI	Medium-high dose SSRI	P
N	***21***	***16***	***5***	
Age, years	**38.81 ± 11.9**	**40.38 ± 12.5**	**33.80 ± 9.4**	**n.s.**[a]
Body mass index (kg/m²)	**24.4 ± 3.3**	**23.91 ± 3.5**	**26.12 ± 2.9**	**n.s.**[a]
Race, no (%)				
Caucasian	**21 (100)**	**16**	**5**	
SSRI-antidepressant, no (%)				**n.s.**[b]
Citalopram	**5 (24)**	**4**	**1**	
Paroxetine	**11 (52)**	**8**	**3**	
Venlafaxine	**3 (14)**	**3**	**0**	
Fluvoxamine	**1 (5)**	**1**	**0**	
Sertraline	**1 (5)**	**0**	**1**	
				n.s.[b]
Menopausal status, no (%)				
Premenopausal	**16 (76)**	**11**	**5**	
Postmenopausal	**5 (24)**	**5**	**0**	
				n.s.[b]
Contraception, no (%)				
Hormonal	**12 (57)**	**9**	**3**	
Non-hormonal	**5 (24)**	**3**	**2**	
None	**4 (19)**	**4**	**0**	
Total testosterone (ng/mL)	**0.34 ± 0.5**	**0.31 ± 0.5**	**0.45 ± 0.6**	**n.s.**[c]
SHBG (nmol/L)	**98.7 ± 66.2**	**100.6 ± 67.5**	**92.8 ± 69.2**	**n.s.**[a]
Mean CAG length	**22.4 ± 2.3**	**22.1 ± 2.4**	**23.2 ± 2.4**	**n.s.**[a]

Age and relationship duration are represented in means ± standard deviation. The body mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
Testosterone values $<$0.7 ng/mL are analysed as 0.01 ng/mL, the SHBG levels values $>$200 nmol/L are analysed as 200 nmol/L.

[a] T-test.
[b] Chi-square test.
[c] Mann–Whitney test.

3.1. Sexual satisfaction during sexual events

Overall, treatment with T+PDE5i or treatment with T+5-HT$_{1A}$ra produced no statistically significant increase in sexual satisfaction as compared with placebo. Subsequently, the participants were divided on the basis of their SSRI dose (in low SSRI dose (n=16) and medium-high SSRI dose (n=5)) and CAG repeat length (n=8 with short repeat length and n=11 with long repeat length), the results showed that there was a highly significant interaction effect between placebo versus T+PDE5i and these groups. The interaction between placebo and T+5-HT$_{1A}$ra and the two groups (SSRI dose and CAG repeat length) was also statistically significant. In the following sections each effect for the different drugs will be described separately.

3.2. Placebo versus T+PDE5i

The interaction between drug (placebo versus T+PDE5i) and the two groups (SSRI dose and CAG repeat length) was statistically significant F(1,15)=14.17, P=0.002. In Fig. 1 it is shown in which group there is an increase or decrease in sexual satisfaction (relative increase in sexual satisfaction compared to placebo).

As shown in Fig. 1, only women with relatively long CAG repeats and using relatively low SSRI doses (n=8) reported statistically significant more sexual satisfaction in the T+PDE5i (M=3.53, SE=0.26) condition compared to placebo (M=2.92, SE=0.21 [F(1,7)=−4.67, P=0.002]).

3.3. Placebo versus T+5-HT$_{1A}$ra

The interaction between drug (placebo versus T+5-HT$_{1A}$ra) and the two groups (SSRI dose and CAG repeat length) was

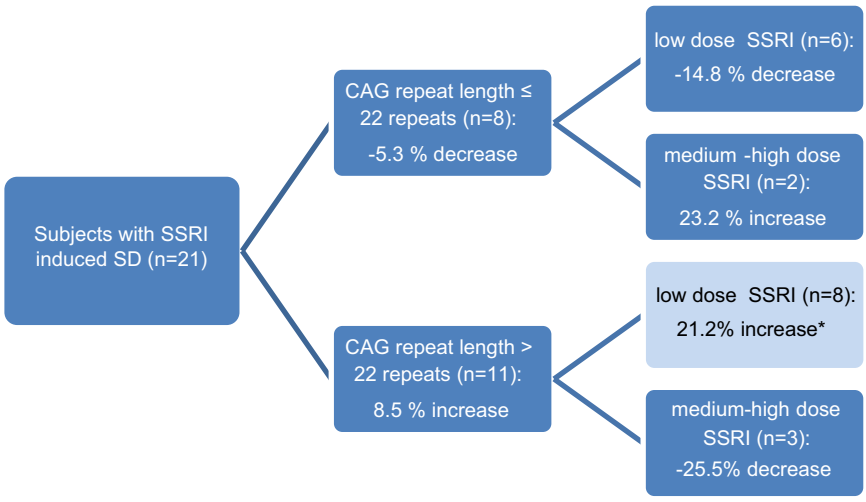

Fig. 1. Overview of subjects in the different groups and the relative increase or decrease after T+PDE5i treatment compared to placebo. Relative increase is calculated as T+PDE5i-placebo/placebo × 100%. *$p < 0.05$.

statistically significant $F(1,15)=13.37$, $P=0.002$. In Fig. 2 it is shown in which group there is an increase or decrease in sexual satisfaction (relative increase in sexual satisfaction compared to placebo).

As shown in Fig. 2 and comparable with the results after T+PDE5i administration, only women with relatively long CAG repeats and using relatively low SSRI doses ($n=8$) reported statistically significant more sexual satisfaction in the T+5-HT_{1A}ra ($M=3.58$, SE=0.27) condition compared to placebo ($M=2.92$, SE=0.21 [$F(1,7)=-3.50$, $P=0.010$]).

Two women with short CAG repeat length and a medium-high SSRI dose seem to respond more to T+5-HT_{1A}ra (31% increase in sexual satisfaction), although not significant.

In Fig. 3 the relative increase of sexual satisfaction for both treatments compared to placebo is shown in the women with long CAG repeats and a relatively low dose of SSRI ($n=8$).

Treatment with T+PDE5i and T+5-HT_{1A}ra was well tolerated.

4. Discussion

This is the first study in which a combination of testosterone with either a PDE5i (sildenafil) or a 5-HT_{1A} receptor agonist (buspirone) are used in women with SSRI-induced Sexual Dysfunction. Although both individual treatments showed no significant main effects on sexual functioning compared to placebo, our analyses revealed a significant interaction effect between SSRI dosage (low and medium-high SSRI dose, CAG repeat length (short and long length), and treatment response (placebo versus drug), on sexual satisfaction. Subsequent analyses showed that women with relatively long CAG repeat lengths and who use a low dose of SSRI, experienced an increase in sexual satisfaction after T+PDE5i administration compared to placebo (the relative increase in sexual satisfaction was approximately 22%). Moreover, for this subgroup of women our analyses revealed also an increase in sexual satisfaction after T+5-HT_{1A}ra administration compared to placebo (approximately 24%). In this study an increase in sexual satisfaction is found only in women with relatively long CAG repeat length and who use a low dose of SSRI. Here we will discuss possible hypotheses for the observed drug response patterns although they only can be considered as very preliminary.

It may be hypothesized that women with relatively long CAG repeat lengths are less sensitive to sexual cues because their AR has a low level of receptor functioning and would therefore benefit more from sublingual testosterone in increasing their brain's sensitivity compared to women with relatively shorter CAG repeats.

In this study statistically significant differences are only found in women with relatively long CAG repeat lengths using a low dose of SSRI. It can be hypothesized that women who use a low SSRI dose have a relatively modest elevation of synaptic serotonin levels and therefore treatment with sublingual testosterone is sufficient to increase the sensitivity of the brain, thereby increasing sexual motivation. Under this condition of increased sexual motivation, the PDE5i enhances physiological sexual responding. In case of the T+5-HT_{1A}ra treatment, the on-demand intake of the 5-HT_{1A}ra component lowers the serotonin firing activity for a relatively short period and thereby allows the sublingual testosterone component to increase the sensitivity of the brain for sexual cues, thereby increasing sexual satisfaction.

It was expected that for women who use a medium-high SSRI dose, T+5-HT_{1A}ra administration would be beneficial in increasing sexual satisfaction since acute 5-HT_{1A}ra administration will lower tonic serotonin levels and thereby decreases the sexual complaints during its active behavioral window. However, there was no statistically significant increase in sexual satisfaction after T+PDE5i and T+5-HT_{1A}ra administration, irrespective of CAG repeat length in these women. One possibility is that this non-significant difference is due to the small numbers of subjects in this study. Only 5 women used a medium-high SSRI dose, of which two women with relatively long CAG repeats report an increase in sexual satisfaction of 31% although not significant. Another explanation is that in women who use a medium-high SSRI dose, synaptic serotonin levels and serotonergic neurotransmission are more profoundly increased resulting in higher tonic activity of serotonin, at which level the buspirone dosage studied might be too low.

In earlier studies we have shown that women with HSDD can be divided in two groups: women who have a relative insensitive brain system for sexual cues (who responded on T+PDE5i) and women with enhanced activity of sexual inhibitory mechanisms (who responded on T+5-HT_{1A}ra). In the present study population, women who use a low SSRI dose and have relatively long CAG repeats respond to T+PDE5i and T+5-HT_{1A}ra treatment, however it is not known which women can be subtyped into women who have a relative insensitive brain system for sexual cues or women with enhanced activity of sexual inhibitory mechanisms. There are many factors that could influence the brain's sensitivity in this population; the use and dosage of an SSRI, genetic factors such as serotonin receptor polymorphisms, and other polymorphisms. Furthermore, an individual's response to certain psychological factors (e.g., a negative sexual experience) is influenced by their brain's sensitivity and therefore these factors should also be taken

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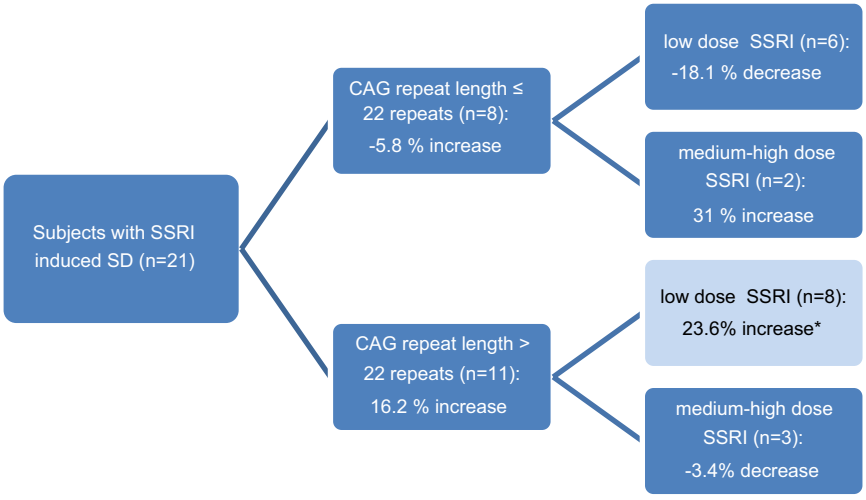

Fig. 2. Overview of subjects in the different groups and the relative increase or decrease after T+5-HT_{1A}ra treatment compared to placebo. Relative increase is calculated as T+5-HT_{1A}ra-placebo/placebo × 100%. *$p < 0.05$.

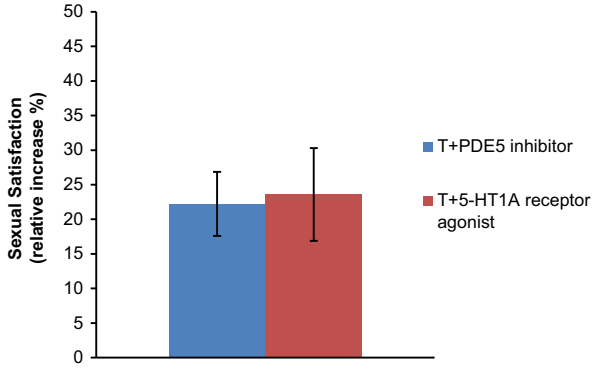

Fig. 3. The increase in sexual satisfaction following T+PDE5i and T+5-HT_{1A}ra treatment in subjects with long CAG repeat length who use a low dose of SSRI ($n=8$). Treatment with T+PDE5-i increased sexual satisfaction with 22%, relative to placebo and sexual satisfaction was increased by 24% after T+5-HT_{1A}ra administration. Relative increase is calculated as T+5-HT_{1A}ra-placebo/placebo × 100% and as T+PDE5i-placebo/placebo*100%.

into account. Also, it is not known if CAG repeat length itself influences the risk of developing SSRI induced female sexual dysfunction. To identify specific subgroups in this population that could benefit from treatment with T+PDE5i and T+5-HT_{1A}ra, future research will focus on a personalized medicine approach through knowledge of more genetic polymorphisms, other biological markers, and other dosages of the compounds. In the present study a small number of women was included with a variety of SSRI molecules and dosages, therefore future studies on a larger scale are warranted.

Conclusively, this explorative study and preliminary results indicate that in women with SSRI-induced SD, T+PDE5i or T+5-HT_{1A} might be promising treatments for certain subgroups of women with this condition, depending on genetics, SSRI dose, and psychological factors.

Contributors

KvR, SP, PW, JB, HK, AG, BO and AT wrote the manuscript; KvR, SP, PW, JB, HK and AT designed at executed the research; KvR, HK and AT analysed the data. All authors have approved the final article.

Role of the funding source

Funding for this study was provided by Emotional Brain B.V. Emotional Brain B.V. had a role in study design, collection, analysis and interpretation of the data, writing of the report and the decision to submit the paper for publication. Data were monitored by an independent/external contract research organisation (PSR Group BV, Hoofddorp, The Netherlands.

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