Adjunctive Treatment with Lodenafil Carbonate for Erectile Dysfunction in Outpatients with Schizophrenia and Spectrum: A Randomized, Double-Blind, Crossover, Placebo-Controlled Trial

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ABSTRACT

Introduction. Evidence is accumulating to support the presence of erectile dysfunction in patients with schizophrenia. This dysregulation may be amenable to therapeutic intervention to improve adherence and quality of life of patients who suffer from schizophrenia and schizoaffective disorders.

Aim. We aimed to evaluate the use of adjunctive medication lodenafil for the treatment of erectile dysfunction in outpatients with schizophrenia and spectrum.

Methods. The design was a randomized, double-blind, crossover, placebo-controlled trial with lodenafil and it was carried at the Schizophrenia Outpatients Program.

Main Outcome Measures. The measures used to assess sexual dysfunction were Arizona Sexual Experiences Scale (ASEX) and International Index of Erectile Function (IIEF). The Positive and Negative Syndrome Scale (PANSS) and the Quality of Life Scale (QLS) were also used. The measures included the levels of prolactin, estradiol, luteinizing hormone, sex hormone-binding globulin, free testosterone, and total testosterone at baseline and end point. Lodenafil and placebo pills were used by the patients for 16 weeks.

Results. Fifty male outpatients fulfilled the criteria and 94% of the participants completed the study. Lodenafil and placebo produced improvement in ASEX, IIEF scale, PANSS, and QLS, and there was no statistical difference between lodenafil and placebo groups in all sexual domains in the results of PANSS and QLS and in the results of hormone levels.

Conclusion. These results indicate that both lodenafil and placebo were effective in the treatment of erectile dysfunction for schizophrenia. Placebo effect is very important in patients with schizophrenia and this study showed the importance of discussing sexuality and trying to treat these patients. Further studies designed to test treatments of erectile dysfunction in patients who suffer from schizophrenia are necessary. **Nunes LVA, Lacaz FS, Bressan RA, Nunes SOVA, and Mari JJ. Adjunctive treatment with lodenafil carbonate for erectile dysfunction in outpatients with schizophrenia and spectrum: A randomized, double-blind, crossover, placebo-controlled trial. J Sex Med **;**:**–**.**

Key Words. Schizophrenia; Erectile Dysfunction; Treatment; Crossover Trial; Placebo; Lodenafil Carbonate; Antipsychotic

Introduction

Sexual dysfunction is common in the general population, with estimates of 43% of women and 31% of men reporting some types of sexual dysfunction [1]. The prevalence of sexual dysfunction in patients with schizophrenia has been considered to be higher than in the general population, with reported rates averaging 50–75% [2,3], and the use of antipsychotic drugs is frequently associated with sexual dysfunction [4]. Symptoms may concern penile erection,

lubrification, orgasm, libido, sexual arousal, or overall sexual satisfaction [5,6]. Antipsychotics can cause sexual dysfunction through multiple mechanisms, including sedation, hyperprolactinemia (which can cause sexual dysfunction directly and indirectly by causing secondary hypogonadism), and antagonism of α-adrenergic, dopaminergic, histaminic, and muscarinic receptors [7]. Moreover, there are many other factors that may cause sexual problems for patients with schizophrenia, including concomitant medications, the effect of the disease itself, comorbidity with other psychiatric disorders, and various endocrine, vascular, or genitourinary diseases [8]. Negative symptoms of the disorder, such as anhedonia, avolition, and blunted effect related to hypodopaminergic activity in the frontal cortex, severely harm the ability to enjoy sexual life. Moreover, these patients face difficulties in establishing relationships due to recurrent psychotic episodes, obesity, and low self-esteem [9].

Phosphodiesterase type 5 (PDE5) inhibitors are currently the first-line treatment for erectile dysfunction [10]. Lodenafil carbonate is a novel PDE5 inhibitor developed in Brazil. It was tested first in 72 men over the age of 18, with erectile dysfunction for at least 6 months, within a stable sexual relationship. The study showed that lodenafil carbonate was well tolerated and the dosage of 80 mg was significantly more efficacious than placebo for erectile dysfunction [11]. Lodenafil carbonate had shown efficacy, safety, and tolerability in another study with men without psychiatric condition: a phase III, prospective, randomized, double-blind, placebo-controlled study that involved 350 men with erectile dysfunction [12]. Lodenafil is a low-cost medication, making it affordable for the majority of the population, especially for patients with schizophrenia, who are either unemployed or living on a small welfare stipend. There is a lack of large, well-designed, controlled longitudinal trials for the treatment of erectile dysfunction in patients with schizophrenia [13]. Sildenafil has been used in schizophrenia in one double-blind, placebo-controlled, crossover study composed of 32 male patients who were living with spouses and it was superior to placebo in all measures, including erections and satisfaction with sexual intercourse [14]. There are two open-label trials with sildenafil that showed improvements in all sexual scales [15,16]. There is an open-label trial with vardenafil that was associated with significant improvements in orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction, and improvement in quality of life [17], and it was carried out with 21 patients in a stable relationship. There is a case report of a man suffering from schizophrenia who was successfully treated with sildenafil for 6 months [18]. Another case report described the use of tadalafil in the treatment of erectile dysfunction in a married male schizophrenic outpatient with a good response [19].

The aim of this study is to test the use of lodenafil carbonate as adjunctive medication in the treatment of erectile dysfunction in a double-blind crossover trial with stable outpatients with schizophrenia and spectrum.

Methods

Study Population

The subjects were male outpatients with schizophrenia and schizoaffective disorder, recruited from two outpatient programs of the Universidade Federal de São Paulo (The Schizophrenia Program-PROESQ and The Itapeva Psychosocial Outprogram Center—CAPS Itapeva). The study was conducted from May 2009 to May 2010. The following inclusion criteria were employed to recruit outpatients with schizophrenia and schizoaffective disorder: (i) diagnosis of schizophrenia and schizoaffective disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), axis I (Structured Clinical Interview for DSM IV Disorders [SCID-IV]) translated into the Portuguese language [20] and (ii) men aged between 18 and 60 years receiving a stable dose of antipsychotic for at least 4 weeks. All patients had to present normal blood values in the following laboratory tests: hemogram, glucose, aspartate transaminase, alanine transaminase, gamma glutamyl transferase, urea, creatinine, and a normal electrocardiogram. Patients were excluded when the sexual dysfunction could be associated with a medical condition such as diabetes, multiple sclerosis, recent stroke, severe arterial hypertension, coronary arterial disease, peripheral vascular disease, central nervous system (CNS) tumors, falciform anemia, and leukemia. The other reasons to exclude patients were as follows: (i) patients with delirium, dementia, amnestic disorders, and mental retardation; (ii) presence of erectile dysfunction due to surgery; (iii) patients under regular use of nitrate, alpha block, or anticoagulants; (iv) patients presenting a comorbidity with severe major depressive disorder and alcohol- and other substance-related disorder; and (v)

patients with previous use of lodenafil, sildenafil, tadalafil, vardenafil, or other PDE5 inhibitors. All the physicians from the schizophrenia program and Caps Itapeva were asked to select potential stabilized psychotic patients who might benefit from the intervention and to fulfill the inclusion criteria of the randomized controlled trial (RCT). Then, the relative or the main patient caregiver was contacted to explain the reasons for the study so as to obtain the authorized approval for participation.

Instruments

The *Arizona Sexual Experiences Scale* (ASEX) is a five-item questionnaire designed to measure sexual functioning on the areas of sexual drive, arousal, and penile erection, ability to reach orgasm, and satisfaction with orgasm over the last week [21]. The instrument has been adapted for the Brazilian context to be used by patients with schizophrenia spectrum [22].

The *International Index of Erectile Function* (IIEF) [23] is a self-administered questionnaire for assessing sexual function and it is composed of 15 questions (IIEF-15) arranged into five domains including erectile function (questions 1–5 and 15; possible score 1–30), orgasmic function (questions 9 and 10; possible score 1–10), sexual desire (questions 11 and 12; possible score 2–10), intercourse satisfaction (questions 6–8; possible score 0–15), and overall satisfaction (questions 13 and 14; possible score 2–10). The IIEF with a score ≤ 25 in the erectile function domain was indicative of erectile dysfunction. As the majority of patients with schizophrenia or schizoaffective disorder are single, it was decided to adapt the IIEF with questions that included the word masturbation. In all the questions where there was the word sexual activity, the following question was added: or masturbation? This was regarded here as a *Modified IIEF*.

The *Quality of Life Scale* (QLS) is an instrument for rating deficit syndrome among patients with schizophrenia spectrum [24], and the Portuguese version adapted to the Brazilian cultural context was applied [25].

The *Positive and Negative Syndrome Scale* (PANSS) was designed to measure severity of psychopathology, positive and negative symptoms of patients with schizophrenia and schizoaffective disorder. The PANSS was translated into Portuguese [26].

All the questionnaires were translated and translated back into the Portuguese language.

Procedures

Sexual dysfunction was regarded as clinically important in the following situations: (i) for those scoring ≥ 18 in the ASEX; (ii) each individual item of ASEX with score ≥ 5; (iii) one of the three items with individual score ≥ 4; and (iv) scoring ≤ 25 in the IIEF. Patients who fulfilled the inclusion and exclusion criteria were asked to sign a written informed consent approved by the Ethics Research Committee of the Universidade Federal de São Paulo. Those who agreed to participate were randomly and sequentially allocated in a double-blind, crossover trial to receive lodenafil or placebo treatment. Placebo and lodenafil pills were identical in appearance and both were manufactured by Cristalia Laboratory. The random assignment schedule was derived with a random-number table. The allocation code was broken after 16 weeks at the end point of the study and when all data were completed. The trial was conducted over 16 weeks and in two phases. The first phase lasted 8 weeks and patients received lodenafil carbonate or placebo. In the following 8 weeks, patients were crossed over: patients who were taking lodenafil carbonate shifted to placebo and patients under placebo received lodenafil carbonate. There was no washout period in between the two treatment periods because the half-life of lodenafil is only 4 hours. Figure 1 illustrates the design of the study.

A self-reported questionnaire was used to gather information on sociodemographic characteristics such as age, marital status, race, religion, and educational background, time of disease onset, prior treatments, psychiatric admissions, current pharmacologic treatment, substance use disorders, sexual function, and presence of partner. Patients were also instructed to keep a detailed daily diary of sexual activity. The following scales were administered at baseline, at week 4, at week 8, at week 12, and at week 16: ASEX, IIEF, Modified IIEF, and PANSS. The QLS was administered at baseline and at the end of study. It is well known that patients who suffer from schizophrenia may have difficulties in replying routinely to questionnaires. Patients with cognitive impairments such as those with dementia, mental retardation, delirium, and other amnestic disorders were excluded from the study. Thus, recruited patients were clinically stable and researchers were trained to explain each item of the scales in case of any doubt to make sure that patients were able to understand the meaning of the questions. The research team assessing outcomes were blinded to the intervention status.

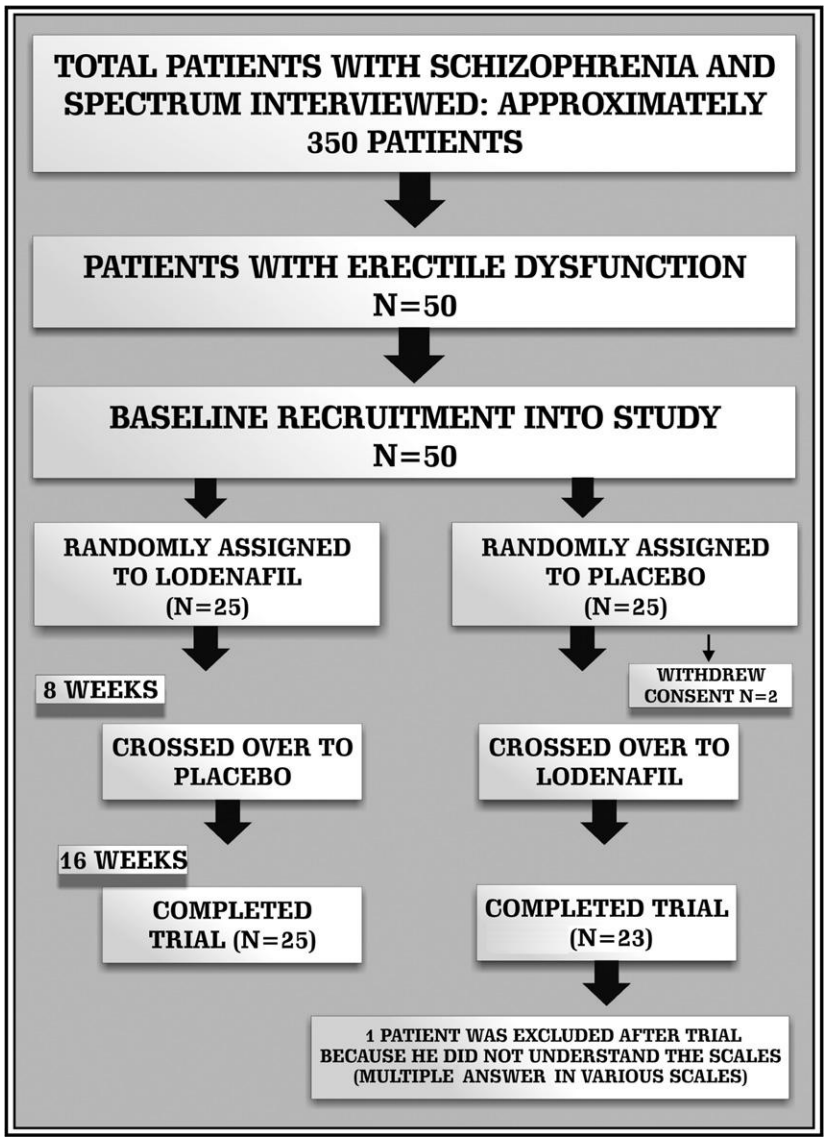

Figure 1 A randomized, double-blind, crossover, placebo-controlled trial with lodenafil

Blood laboratory tests were performed at baseline and at the end point of the study for the following measures: prolactin, estradiol, luteinizing hormone (LH), sex hormone-binding globulin (SHBG), free testosterone, and total testosterone. The Brazilian company that manufactures lodenafil supplied the drug and placebo pills free of charge and funded the fieldwork (laboratory tests, the application of the questionnaires, and transport for the patients).

The patients were instructed to take a maximum of one capsule of lodenafil (80 mg) per day 1 hour before sexual intercourse or masturbation. The patients could use one capsule whenever they feel sexual desire; the use was free. The sexual arousal was determined by the patients and it could include erotic movies, magazines, partner stimulation, or others. They could use a maximum of two capsules per week whenever they wished. No other psychosexual treatment was provided during the study period.

Statistical Analyses

Statistical analyses were performed using Statistics Software (Washington, DC, USA), considering a significance level of 5%. The parametric tests paired *t*-test and analysis of variance (*F*) were applied to assess quantitative variables that presented normal distribution. The nonparametric tests—Wilcoxon (*T*) and Mann–Whitney (*U*)—were used in the quantitative variables without

normal distribution. The qualitative variables were assessed by using chi-square test (χ^2). The sample size was estimated from previous studies [27], assuming the independence of response in each patient with an anticipated proportion of discordant pairs being 0.34 and an anticipated odds ratio of 7.5 at a 5% level of significance and 80% power; the group size required was 26 at each group.

Results

There were 350 patients screened, but only 50 were eligible for the study (25 patients were assigned to receive lodenafil and 25 patients to placebo). After 8 weeks, the order of medication was reversed. Forty-seven patients concluded the study, a completion rate of 94%. Two patients from the placebo group withdrew consent and one patient was excluded because he did not understand the scales and gave multiple answers for the same question.

Demographic and clinical characteristics at baseline are presented in Table 1. The control and experimental groups showed no statistically significant differences for age, education, marital status, the average number of years of illness, body mass index, use of alcohol, drugs, and tobacco, baseline mean scores, and standard deviations (SDs) of ASEX, IIEF, Modified IIEF, QLS, and PANSS questionnaires (Table 1).

Table 1 The sociodemographic and clinical characteristics of male patients taking lodenafil or placebo at baseline

Variables	Lodenafil (N = 25)	Placebo (N = 23)	
Age (years)			
Mean ± SD (median)	38.7 ± 8.9 (38.0)	35.7 ± 8.8 (34.0)	$P = 0.25$
Years of education			
Mean ± SD	12.5 ± 2.8 (12.0)	11.4 ± 4.0 (11.0)	$P = 0.28$
Marital status			
Single	20 (80.0%)	15 (62.2%)	$P = 0.41$
Years of disease			
Mean ± SD (median)	13.8 ± 7.9 (12.0)	12.9 ± 8.3 (12.0)	$P = 0.71$
Body mass index (kg/m^2)			
Mean ± SD (median)	29.6 ± 6.3 (28.4)	28.2 ± 4.7 (28.1)	$P = 0.40$
Current smokers	15 (60%)	8 (34.8%)	$P = 0.15$
Current alcohol use	4 (16.0%)	4 (17.4%)	$P = 0.80$
Current drug abuse	1 (4.0%)	0 (0.0%)	$P = 1.00$
Total PANSS			
Mean ± SD	60.2 ± 8.9	59.2 ± 13.8	$P = 0.79$
Modified IIEF (total)			
Mean ± SD	33.1 ± 12.0	32.0 ± 16.0	$P = 0.87$
IIEF (total)			
Mean ± SD	24.6 ± 10.4	28.2 ± 16.6	$P = 0.61$
ASEX (total)			
Mean ± SD	17.2 ± 5.4	15.1 ± 4.7	$P = 0.17$
QLS (total)			
Mean ± SD	2.8 ± 0.8	3.1 ± 1.1	$P = 0.56$

Chi-square test (χ^2); U = Mann–Whitney test
PANSS = Positive and Negative Syndrome Scale; IIEF = International Index of Erectile Function; ASEX = Arizona Sexual Experiences Scale; QLS = Quality of Life Scale; SD = standard deviation

The rates of sexual functioning in the two groups at baseline, first phase, and second phase of the study are displayed in Table 2. Lodenafil and placebo produced improvement in ASEX, IIEF scale, PANSS, and QLS. ASEX and IIEF scale did not show statistical difference between lodenafil and placebo groups in all sexual domains and total scores.

The PANSS and the QLS scores are displayed in Table 3. Patients showed a reduction of psychotic symptoms as measured by PANSS in both groups and presented a better quality of life in the experimental and control groups. These changes were not statistically significant between the two groups.

In the results summarized in Table 4, no statistically significant changes in levels of prolactin, total testosterone, SHBG, estradiol, and LH in treatment with lodenafil and placebo from baseline to end point were observed. However, the free testosterone level in the lodenafil group had changed from baseline to end point (mean SD = 9.3 ± 3.3; SD = 7.6 ± 2.0), and in the placebo group, it had changed from baseline to end point, respectively (mean SD = 12.0 ± 4.4; mean SD = 8.2 ± 2.5), and this was statistically significant.

Lodenafil carbonate was well tolerated by all the patients and no one discontinued the trial as a result of adverse drug reactions. The most common side effects were headache, nauseas, and dizziness. No adverse drug interactions were reported.

Discussion

The study was carried out to examine the safety and efficacy of lodenafil carbonate, a novel PDE5 inhibitor fully developed in Brazil, in patients with schizophrenia and spectrum with erectile dysfunction. In this randomized, double-blind, placebo-controlled trial, lodenafil showed significant improvement in erectile dysfunction in men with schizophrenia and schizoaffective disorder as showed in scores of ASEX, IIEF scale, Modified IIEF scale, PANSS, and the QLS but not statistically significant when compared with positive changes in the placebo group. However, lodenafil was well tolerated with no discontinuations due to adverse events, and there was no major adverse drug interaction noted during the randomized, double-blind, placebo-controlled trial. It can be assumed that lodenafil can be safely combined with antipsychotics as adjunctive treatment of sexual

Table 2 Rates of sexual functioning among male patients with lodenafil or placebo in the mean baseline and end-point changes in ASEX, IIEF, and modified IIEF

Total ASEX	Lodenafil (mean ± SD)	Placebo (mean ± SD)	Lodenafil vs. placebo*
First phase			
Baseline	17.2 ± 5.4	15.1 ± 4.7	$F = 0.54$
End point	14.9 ± 4.9	15.1 ± 4.5	$P = 0.4678$
Crossover	$F = 3.42$—$P = 0.0711$		
Baseline	15.1 ± 4.7	17.2 ± 5.4	$F = 1.34$
End point	13.9 ± 4.1	14.8 ± 5.8	$P = 0.2532$
Baseline vs. end point*	$F = 7.24$—$P = 0.0099$		
Penile erection (ASEX)			
First phase			
Baseline	3.8 ± 1.2	3.2 ± 1.2	$F = 0.4$
End point	2.9 ± 1.2	3.1 ± 1.1	$P = 0.5286$
Crossover	$F = 7.25$—$P = 0.0099$		
Baseline	3.2 ± 1.2	3.8 ± 1.2	$F = 1.35$
End point	2.9 ± 1.0	3.0 ± 1.4	$P = 0.2510$
Baseline vs. end point*	$F = 7.93$—$P = 0.0072$		
Total IIEF			
First phase			
Baseline	24.6 ± 10.4	28.2 ± 16.6	$U = 250.5$—$P = 0.6014$
End point	38.2 ± 17.4	39.4 ± 16.5	$U = 267.5$—$P = 0.8730$
Crossover	$T = 30.5$—$P = 0.0004$	$T = 18.5$—$P = 0.0007$	
Baseline	28.2 ± 16.6	24.6 ± 10.4	$U = 250.5$—$P = 0.6014$
End point	42.9 ± 15.8	39.9 ± 16.4	$U = 242.5$—$P = 0.4884$
Baseline vs. end point†	$T = 1.5$—$P < 0.0001$	$T = 31.0$—$P = 0.0004$	
Erectile function (IIEF)			
First phase			
Baseline	9.4 ± 5.8	10.4 ± 7.6	$U = 263.5$—$P = 0.8063$
End point	14.7 ± 8.6	15.1 ± 7.3	$U = 263.5$—$P = 0.8063$
Crossover	$T = 46.0$—$P = 0.0051$	$T = 21$—$P = 0.0006$	
Baseline	10.4 ± 7.6	9.4 ± 5.8	$U = 263.5$—$P = 0.8063$
End point	16.7 ± 7.0	15.2 ± 8.5	$U = 250.0$—$P = 0.5940$
Baseline vs. end point†	$T = 6.0$—$P < 0.0001$	$T = 38.0$—$P = 0.0014$	
Total Modified IIEF			
First phase			
Baseline	33.1 ± 12.0	32.0 ± 16.0	$U = 267.0$—$P = 0.8646$
End point	45.4 ± 13.3	42.0 ± 16.5	$U = 251.0$—$P = 0.6089$
Crossover	$T = 31.5$—$P < 0.001$	$T = 23.5$—$P = 0.0014$	
Baseline	32.0 ± 16.0	33.1 ± 12.0	$U = 267.0$—$P = 0.8646$
End point	48.9 ± 13.8	46.0 ± 15.9	$U = 231.5$—$P = 0.3537$
Baseline vs. end point†	$T = 2.0$—$P < 0.0001$	$T = 48.0$—$P = 0.0021$	
Erectile function (M IIEF)			
First phase			
Baseline	12.4 ± 5.5	11.8 ± 7.3	$U = 268.0$—$P = 0.8814$
End point	18.9 ± 5.8	15.1 ± 7.3	$U = 247.0$—$P = 0.5505$
Crossover	$T = 23.5$—$P < 0.001$	$T = 25.5$—$P = 0.0018$	
Baseline	11.8 ± 7.3	12.4 ± 5.5	$U = 268.0$—$P = 0.8814$
End point	20.0 ± 6.4	18.8 ± 7.8	$U = 252.0$—$P = 0.6239$
Baseline vs. end point†	$T = 4.0$—$P = 0.0002$	$T = 45.0$—$P = 0.0081$	

*Analysis of variance
†Wilcoxon test
IIEF = International Index of Erectile Function; ASEX = Arizona Sexual Experiences Scale; M IIEF = Modified International Index of Erectile Function; SD = standard deviation

dysfunction for patients with schizophrenia spectrum. This finding was consistent with another study that used sildenafil as an adjunctive treatment for antipsychotic-induced erectile dysfunction. In this randomized, double-blind, placebo-controlled, flexible-dose, two-way crossover trial, the results showed that the use of sildenafil was associated with significant improvement in sexual

Table 3 The PANSS and QLS scores for male patients taking lodenafil or placebo

Total PANSS	Lodenafil (mean ± SD)	Placebo (mean ± SD)	Lodenafil vs. placebo†
First phase			
Baseline	60.2 ± 8.9	59.2 ± 13.8	$U = 274.5$—$P = 0.7885$
End point	53.3 ± 8.3	55.5 ± 13.5	$U = 270.5$—$P = 0.7257$
Baseline vs. end point*	$T = 6.0$—$P < 0.001$	$T = 31.0$—$P = 0.0176$	
Crossover			
Baseline	60.2 ± 8.9	59.2 ± 13.8	$U = 274.5$—$P = 0.7885$
End point	50.8 ± 12.3	49.4 ± 8.3	$U = 279.0$—$P = 0.8607$
Baseline vs. end point*	$T = 31.0$—$P = 0.0011$	$T = 2.5$—$P < 0.0001$	
Total QLS	**Lodenafil (mean ± SD)**	**Placebo (mean ± SD)**	**Lodenafil vs. placebo†**
Baseline	2.8 ± 0.8	3.1 ± 1.1	$U = 259.0$—$P = 0.5564$
End point	3.2 ± 0.9	3.3 ± 1.1	$U = 279.5$—$P = 0.8689$
Baseline vs. end point*	$T = 23.5$—$P = 0.0003$	$T = 39.0$—$P = 0.0137$	

*Wilcoxon test
†Mann–Whitney test
PANSS = Positive and Negative Syndrome Scale; QLS = Quality of Life Scale; SD = standard deviation

function for a variety of parameters. The number of grade 3 or 4 erections increased from baseline in both treatments (placebo and sildenafil) [14]. However, in the sildenafil study, different from this RCT, patients showed improvements in the number of adequate erections, satisfaction with sexual intercourse, and the duration of erections that were significantly different from the placebo. The majority of patients were single in the lodenafil study and the study was carried out in a period of 16 weeks. Recruited patients for the sildenafil study had stable relationships and the follow-up took 2 weeks, a shorter period than the lodenafil study.

The fact that both groups showed improvements in sexual activities raises the possibility of the importance of the positive effect of placebo to improve erectile dysfunction in patients with schizophrenia spectrum. It is noteworthy, as this is a special population, and medical attention may play an important role for these patients. Patients with schizophrenia can be very suggestible; the existing evidence suggests that placebo response in schizophrenia trials may be similar in magnitude, quality, and impact to that observed in depression trials [28]. The Hawthorne effect, that is, a tendency that patients have to change their behavior when they receive special attention [29], cannot be excluded. Studies addressing sexual issues have generally concluded that patients with schizophrenia are prepared and open to discuss issues relating to sexual activity, and the majority of patients with schizophrenia believe that it can be beneficial for their lives [30].

Table 4 The comparison between hormone levels in the baseline and end point of the trial for male patients taking lodenafil or placebo

ANOVA	Lodenafil vs. placebo*	Baseline vs. end point*
SHBG	$F = 2.27$	$F = 0.08$
	$P = 0.1388$	$P = 0.7723$
Prolactin	$F = 0.52$	$F = 0.22$
	$P = 0.4755$	$P = 0.6402$
Total testosterone	$F = 0.007$	$F = 2.21$
	$P = 0.9335$	$P = 0.1437$
Free testosterone	$F = 5.37$	$F = 22.45$
	$P = 0.0249$	$P < 0.001$
Estradiol	$F = 0.27$	$F = 0.84$
	$P = 0.6069$	$P = 0.3643$
LH	$F = 0.07$	$F = 0.03$
	$P = 0.7889$	$P = 0.8735$

*ANOVA (F)
ANOVA = analysis of variance; SHBG = sex hormone-binding globulin; LH = luteinizing hormone

On the other hand, concern about sexual dysfunction may exacerbate psychiatric symptoms [31]. Therefore, the management of patients with sexual dysfunction receiving antipsychotic agents should be addressed carefully as different compounds impose dissimilar risks for sexual dysfunction [32–37]. Quetiapine was associated with less severe sexual dysfunction than olanzapine and risperidone [38]. Other studies have found no differences between first- and second-generation antipsychotics [39–41]. For men with schizophrenia taking antipsychotic medication and experiencing erectile dysfunction, the use of PDE5 inhibitors may be useful treatment options as additional medication [42].

The frequencies of adverse events were similar to those from previous published trials with PDE5 inhibitor therapy [15,18]. In the laboratory blood tests, there were no significant differences at

baseline and at the end of the study in prolactin, estradiol, LH, SHBG, free testosterone, and total testosterone.

These findings should be interpreted in the context of a number of limitations. First, the questions of ASEX, IIEF scale, Modified IIEF scale, PANSS, and QLS are self-reported, and sexual function may not be accurate in men presenting a schizophrenia spectrum disorder. Second, as the majority of patients were single, it was decided to adapt the IIEF with questions that included the word masturbation and this was regarded here as a *Modified IIEF*. The sample was heterogeneous with respect to marital status; they could be single, married, or presenting a stable heterosexual relationship. It would be better if all patients were in a stable relationship. Patients were not separated if they masturbate or had sexual activities with a partner. Lodenafil had shown efficacy and tolerability in erectile dysfunction in three studies with men without psychiatric condition and in all studies with men with sexual partners [11,12,43]. Third, the information about sexual dysfunction during the prodromal phase and the remission periods prior to the study was not available and it is not certain that the sexual dysfunction was really induced by the antipsychotic medication. Many patients had to be excluded for several reasons: (i) medical condition associated with sexual dysfunction, such as diabetes; (ii) the regular use of nitrate, alpha block, or anticoagulants; (iii) comorbidity with severe major depressive disorder and alcohol- and other substance-related disorder; and (iv) patients that used other PDE5 inhibitors in the past. Finally, it was a crossover study and it is plausible to suppose a carryover effect: patients perhaps felt that they were still taking the medication but the placebo helped them to feel safe and more likely to have an erection.

Conclusion

Nevertheless, despite these limitations, it is important to mention that sexual dysfunction is a frequently occurring problem in clinical practice in patients with schizophrenia, and this new drug is safe and can be useful to treat sexual dysfunction for patients taking antipsychotics. Erection is an important event for male patients and the use of lodenafil carbonate may help to improve adherence to treatment. There is a lack of RCTs on the clinical management of antipsychotic-induced sexual dysfunction in the literature, there are no proper comparisons for efficacy of agents, and it is important to emphasize the positive impact that this study had on erection. As far as we know, no other drug was tested in a well-conducted trial in a satisfactory period of time for this population. It would be important to run a RCT to compare the efficacy of lodenafil with other drugs available to treat sexual dysfunction in patients with schizophrenia.

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Statement of Authorship

Category 1

(a) Conception and Design
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