International Journal of Impotence Research (2006) 18, 164–169
 0955-9930/06 $30.00
www.nature.com/ijir

ORIGINAL ARTICLE

Safety and efficacy of citalopram in the treatment of premature ejaculation: a double-blind placebo-controlled, fixed dose, randomized study

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We evaluate the efficacy and safety of citalopram, a potent and highly selective serotonin reuptake inhibitor (SSRI) antidepressant, in patients with premature ejaculation (PE). In total, 58 potent men with PE were included in the study. Patients were randomly assigned to receive 20 mg oral daily citalopram (group 1, $n = 29$) or placebo (group 2, $n = 29$), during a 12-week period for each agent. Pretreatment evaluation included history and physical examination, intravaginal ejaculatory latency time (IVELT) evaluation, International Index of Erectile Function (IIEF) and Meares–Stamey test. The efficacy of two treatments was assessed every 2 weeks during treatment, at the end of study and in 3- and 6-month follow-up after cessation of treatment, using responses to IIEF, IVELT evaluation, mean intercourse satisfaction domain, mean weekly coitus episodes and adverse drug effects. The trial was completed by 51 (88%) men. Analysis revealed a difference in the evolution of IVELT delay over time ($P < 0.001$). The IVELT after citalopram and placebo gradually increased from 32 and 28 s to approximately 268 and 38 s, respectively. The mean weekly intercourse episodes increased from pretreatment values of 1.3 and 1.2 to 2.4 and 1.4, for citalopram and placebo, respectively ($P < 0.05$). Baseline mean intercourse satisfaction domain values of IIEF 10 and 11 reached to 16 and 10 at 12-week treatment in groups 1 and 2, respectively ($P < 0.05$). Mean IVELT in group 1 was 210 and 198 s at 3- and 6-month follow-up, while in group 2 it was 27 and 25 s ($P < 0.001$), respectively. At 3- and six-month intercourse satisfaction domain values of IIEF were 15 and 14 in group 1 and 10 and 10 ($P < 0.05$) in group 2, respectively. Group 1 patients reported a significantly higher number of intercourse episodes per week ($P < 0.05$). Mean number of adverse events was 12 for citalopram and 4 for placebo ($P < 0.05$). In conclusion, these results indicate that citalopram has significantly better results in terms of IVELT and intercourse satisfaction versus placebo. Further studies with different dosages and treatment regimens are necessary to draw final conclusions on the efficacy of this drug in PE and to prolong the efficacy.
International Journal of Impotence Research (2006) **18,** 164–169. doi:10.1038/sj.ijir.3901384; published online 18 August 2005

Keywords: premature ejaculation; treatment; citalopram; serotonin; sexual dysfunction

Introduction

In general, the prevalence of premature ejaculation (PE) is reported as being between 22 and 38% in the adult male population,[1,2] and up to almost 40% of men experience the problem on a recurring basis.[3,4]

It is generally assumed that selective serotonin reuptake inhibitors (SSRIs) sexual side effects are related to increased central 5-hydroxytryptamine (5-HT, serotonin) neurotransmission and activation of postsynaptic 5-HT receptors.[5,6] Selective SSRIs (paroxetine, fluoxetine, sertraline) are reported to be effective for treating PE.[7,8] In addition, selective noradrenaline reuptake inhibitors, nortriptyline and protriptyline, have been found to be associated with delayed ejaculation.[9] SSRIs are selective for inhibition of 5-HT uptake, with selectivity over noradrenaline uptake ranging from 54 nm (fluoxetine) to 3400 nm (citalopram).[10] Work on citalopram has been inconsistent. For example, in a randomized, double-blind study, 31 men with PE were randomly assigned to receive paroxetine (20 mg/day) and citalopram (20 mg/day) for 5 weeks. Paroxetine exerted a strong delay (8.9-fold) increase, whereas

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Received 25 April 2005; revised 23 June 2005; accepted 28 June 2005; published online 18 August 2005

citalopram mildly delayed ejaculation (1.8-fold).[11] However, a later study showed clear benefit.[12] In addition, real long-term efficiency of different selective SSRIs in treating PE has not yet been defined. In most published studies, treatment and follow-up times have been only weeks and these studies have been concentrated mainly on short-term effects. Although the therapeutic effect of a drug is seen within weeks, alleviation of problem for a much longer time is required. Citalopram is a potent and highly SSRIs antidepressant, which has been introduced in therapy as a racemic drug.[13] Ranking SSRIs regarding their selectivity reveals citalopram, sertraline, paroxetine, flavoxamine and fluoxetine, in decreasing order.[11] If selectivity for the serotonergic system over other systems would be the determining factor for the inhibitor process on ejaculation, it would be expected that citalopram would cause considerable delay in ejaculation. For physiological PE pharmacological management, various agents have been used with variable success rates. In some reports, after the end of therapy, the PE recurs in as much as 90% of patients.[14] We need a safe and effective drug launched specifically for the treatment of PE, especially if it induces long-term benefit for the patient after it is withdrawn. In this study we compared placebo with citalopram, the most selective SSRI known. This is the first controlled long-term study with citalopram in regard to PE.

Materials and methods

This study comprised 58 married men (aged 21–49 years) with PE and their wives. All patients gave their written informed consent to participate in the study after procedures and possible side effects were explained to them. Patients and their wives were interviewed separately. All couples were in a stable relationship for at least 6 months. PE was defined as an intravaginal ejaculatory latency time (IVELT) of less than 2 min that occurred in more than 90% of coitus. The IVELT was the time between the start of vaginal insertion and the start of intravaginal ejaculation. All patients underwent preliminary assessment, including a medical and sexual history, physical examination, and structured interview diagnostic of mental and physical disorders and self-administration of International Index of Erectile Function (IIEF)[15] (Table 1). The efficacy of the placebo and citalopram was assessed using responses to the questions 6–11. Meares–Stamey test was also carried out to exclude genital tract infection. To be able to exclude organic sexual dysfunctions, fasting blood glucose level, urine analysis, complete blood count, sex hormones and prolactin levels were measured. Only patients without any obvious organic cause of PE and possible sexual intercourse equal or greater than 1 per week were included. Those with erectile dysfunction according to IIEF were excluded (Table 1); an organic cause of PE including anatomical abnormalities, genital infection and neurological disorder; low libido; chronic depression, psychiatric or physical illness; alcohol, drug or substance abuse; organic illness causing limitation in SSRI use; use of psychotropic and antidepressant medication; and serious relationship problems. All patients were free of all medications for at least the previous 4 weeks.

Table 1 International index of erectile function questionnaire

1. How often were you able to get an erection during sexual activity?
2. When you had erection with sexual stimulation, how were your erections hard enough for penetration?
3. When you attempted sexual intercourse, how often were able to penetrate your partner?
4. During sexual intercourse, how often were able to maintain your erection to completion of intercourse?
5. During sexual intercourse, how difficult were to maintain your erection to completion of intercourse?
6. How many times have you attempted sexual intercourse?
7. When you attempted sexual intercourse, how often was it satisfactory for you?
8. How much have you enjoyed sexual intercourse?
9. When you had sexual intercourse, how often did you ejaculate?
10. When you had sexual intercourse, how often did you have the feeling of orgasm or climax?
11. How often have you felt sexual desire?
12. How would you rate your level of sexual desire?
13. How satisfied have you been with your overall sex life?
14. How satisfied have you been with your sexual relationship?
15. How do you rate your confidence that you could get and keep an erection?

Pretreatment IVELT was measured during a 4-week baseline period, during which patients were requested to experience coitus at least four times. Pretreatment frequency of sexual intercourse was the mean number of attempts per week during the previous 4 weeks.

The patients were randomly assigned to either group of 29 subjects each. Randomization was determined by a computer-generated schedule. Group 1 was given 20 mg citalopram (Cipram, Lundbeck Inc.) orally daily for 12 weeks. Group 2 received a similar regimen of placebo. The placebo tablets were a starch compound of the same color and size of citalopram. All the men were asked not to consume alcoholic drinks within 6 h of sexual activity. There were no statistical differences in IVELT, IIEF, and mean coitus attempts per week in the two groups (Table 2). Treatment was administered in a randomized sequence that remained unknown to the patient and to the physicians. The effect of treatment was assessed every 2 weeks during treatment, at the end of study and 3 and 6 months after the cessation of treatment. For the analysis of efficacy and safety, all patients were

assessed in each visit evaluating changes in IVELT, mean intercourse satisfaction domain, mean weekly coitus episodes and adverse drug effects. All patients were asked to indicate their sexual satisfaction on a scale of 0–5 as proposed by Kim and Paick, with 0 being extremely dissatisfied and 5 extremely satisfied.[16]

None of the patients underwent formal psychosexual counseling. Patients were given a diary to record the frequency of coitus and adverse drug-related effects and were requested to measure IVELT using a stopwatch. Subjective estimation and questionnaire assessments of ejaculation latency may lead to higher variability in clinical outcome measures;[17] therefore, for the most accurate determination of ejaculation latency the best method is the use of a stopwatch. Couples were also instructed not to use condoms or topical anesthetic cream, not to pause during intercourse or to have interrupted intromission. Furthermore, they were requested not to increase their intercourse frequency and if intercourse took place more than once in a single session, only the first intercourse was measured. Sexual satisfaction rates of patients and their partners and comparison of the incidence of side effects were tested using the χ^2 test. A paired *t*-test was used for the evaluation of IVELT between baseline and after treatment. A *P*-value <0.05 was considered statistically significant. Statistical analysis was performed using the computer statistical package SPSS/4.0 (SPSS, Chicago, IL, USA) and SAS/6.4 (SAS Institute Cary, NC, USA).

Results

All patients were seen with their partners and interviewed about their sexual activity and patient's ejaculation function. In total, 58 patients were recruited, but only 51 (88%) completed the whole randomized trial study (26 of 29 in the citalopram group and 25 of 29 in the placebo group) (Figure 1).

Seven patients were noncompleters. Reasons for noncompletion included one adverse effect (citalopram group), three lack of effect on ejaculation (placebo group) and three lost for follow-up (two from the citalopram group and one from the placebo group). The difference in dropout rates was not significant between the groups. There were no statistical differences in patients' characteristics in the two groups (Table 2). Mean patient age was 32 years (range 21–50) in group 1 and 34 (range 21–48) in group 2 ($P=0.01$ not significant).

After 12 weeks of treatment, the IVELT differed significantly between two treatment groups. During the study, from week one onward and at the study end point (week 12), there were significant differences between the treatment groups ($P<0.001$) (Table 3). The mean pretreatment IVELT was markedly increased from baseline 32 s in the citalopram group to 268 s compared with only a gradual and mild increase in the placebo group (from 28 to 38 s) (Table 4).

The mean pretreatment intercourse frequency was 1.3 per week for citalopram compared to 1.2 per week for placebo. The citalopram demonstrated superiority in increasing mean pretreatment inter-

Table 2 Patient characteristics

Variables	*Citalopram* (n = *26*)	*Placebo* (n = *25*)	P-*value*
Mean age, years (range)			
Patients	32 (21–50)	34 (21–48)	NS
Partners	28 (20–48)	29 (21–50)	NS
Duration of marriage, years (range)	12 (2–21)	12 (2–22)	NS
Education level (no)			
Patients			
Lower	6	5	NS
Middle	8	8	NS
Higher	12	12	NS
Partners			
Lower	4	4	NS
Middle	10	10	NS
Higher	12	11	NS
Premature ejaculation (no)			
Primary	10	11	NS
Secondary	16	14	NS
Never ejaculated intravaginally	4	4	NS

NS = not significant.

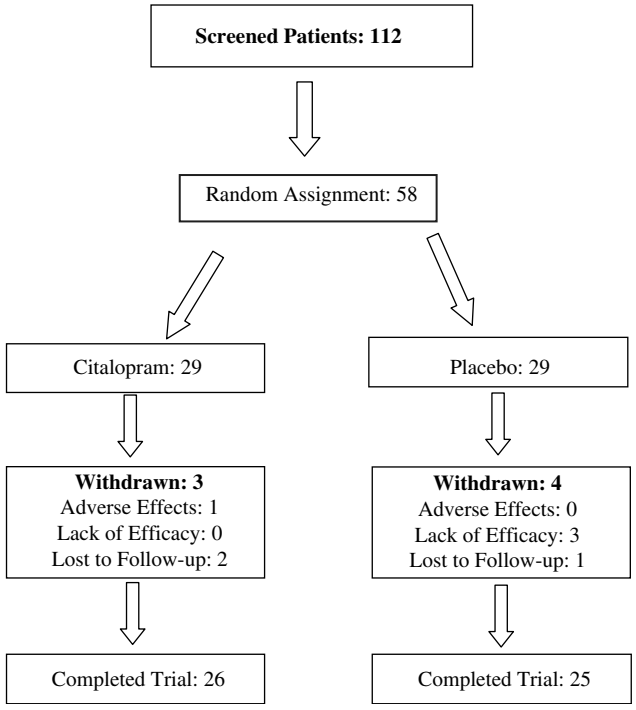

Figure 1 Study design.

Table 3 Mean intravaginal ejaculatory latency time in men with PE in various assessment points

Group	*Baseline*	*2 weeks*	P-*value*	*4 weeks*	P-*value*	*6 weeks*	P-*value*	*8 weeks*	P-*value*	*10 weeks*	P-*value*	*12 weeks*	P-*value*
Citalopram	32	181	<0.001	242	<0.001	248	<0.001	250	<0.001	268	<0.001	268	<0.001
Placebo	28	31	NS	33	NS	33	NS	35	NS	38	NS	38	NS

NS = not significant; PE = premature ejaculation.

Table 4 Mean IVELT, frequency of coitus and mean intercourse satisfaction domain values of the IIEF

	Baseline	*12 week*	P-*value*	*3 month*	P-*value*	*6 month*	P-*value*
Group 1							
Mean IVELT (s)	32	268	<0.001	210	<0.001	198	<0.01
Mean no. coitus/week	1.3	2.4	<0.05	2.2	<0.05	2	<0.05
Mean intercourse satisfaction domain values of the IIEF	10	16	<0.05	15	<0.05	14	<0.05
Sexual satisfaction score	1.3	3.6	<0.05	3.6	<0.05	3.3	<0.05
Group 2							
Mean IVELT (s)	28	38	NS	27	NS	25	NS
Mean no. coitus/week	1.2	1.4	NS	1.1	NS	1.2	NS
Mean intercourse satisfaction domain values of the IIEF	11	10	NS	10	NS	10	NS
Sexual satisfaction score	1.4	1.8	NS	1.5	NS	1.6	NS

IVELT = intravaginal ejaculatory latency time; IIEF = International Index of Erectile Function.

Table 5 Sexual satisfaction rates of the patients and wives

	Satisfied (%)		*Moderate satisfied (%)*		*Dissatisfied (%)*	
	Patients	*Wives*	*Patients*	*Wives*	*Patients*	*Wives*
Baseline	—	—	—	8	100	92
Group 1						
12 week	72*	71*	18**	19***	10*	10*
3 month	68*	68*	20**	21***	12*	11*
6 month	62*	63*	24**	25***	16*	12*
Group 2						
12 week	16	6	22	13	62	81
3 month	15	6	20	12	65	82
6 month	14	6	24	13	62	81

*$P \leqslant 0.001$ versus group 2.
**P = not significant versus group 2.
***$P \leqslant 0.05$ versus group 2.

course frequency. The mean intercourse frequency at 12-week treatment was 2.4 and 1.4 for citalopram and placebo, respectively ($P<0.05$). Baseline and 12-week mean intercourse satisfaction domain values of the IIEF were 10, 11 and 16, 10 in groups 1 and 2, respectively. Citalopram group reported significantly greater intercourse satisfaction than those in the placebo group ($P<0.05$).

Eight of the 58 patients reported never having experienced intravaginal ejaculation before treatment. Intravaginal ejaculation was achieved by three of the four patients (mean age 27.4 years) who had never achieved it at the end of treatment with citalopram. Intravaginal ejaculation was not achieved in four patients (mean age 26.1 years) with placebo. Citalopram also increased statistically significant sexual satisfaction scores ($P<0.05$) (Table 5).

In 3- and 6-month follow-up of treatment, patients receiving citalopram demonstrated significantly improved IVELT compared to those receiving placebo (Table 4). The mean IVELT was 210, 198 and 27, 25 s in 3- and 6-months follow-up for citalopram and placebo, respectively. At the 3- and 6-month follow-up, sexual satisfaction rates demonstrated significant improvement among patients receiving citalopram compared with those receiving placebo ($P<0.05$). Also, group 1 patients reported a significantly higher number of intercourse episodes weekly ($P<0.05$) in 3- and 6-month follow-up.

Table 6 Drug-related side effects

	No. group 1 (Pts %)	*No. group 2 (Pts %)*	P-*value*
Dry mouth	3 (10)	—	<0.05
Nausea	6 (20)	—	<0.05
Loss of appetite	3 (10)	—	<0.05
Erectile dysfunction	—	2	NS
Headache	—	1	NS
Insomnia	—	1	NS

NS = not significant.

Generally the two drugs were well tolerated. An ejaculation did not occur in our patients. More adverse effects were associated with citalopram treatment ($P<0.05$) (Table 6). Erectile dysfunction was not noted with citalopram but was noted with placebo in two patients. Of patients in the citalopram group, three (10%), six (20%) and three (10%) developed dry mouth, nausea and loss of appetite, respectively. These were episodic and mild to moderate in severity. One patient in the citalopram group was dropped out of the study because of side effect. He developed gastrointestinal upset.

Data analysis did not show any statistically significant difference in men with primary and secondary PE in terms of average baseline, 3- or 6-month IVELT. Similarly, data did not show significant differences in men with primary and secondary PE regarding IVELT, IIEF domain, mean weekly coitus episodes and adverse effects profiles.

Discussion

This study demonstrated that citalopram 20 mg daily significantly delay ejaculation in men. Furthermore, mean weekly intercourse episodes for patients treated with citalopram compared to placebo were significantly superior. We also used an inventory for analysis of satisfaction scores for the men or their wives. Satisfaction scores significantly improved with citalopram.

While the pathophysiology of PE has not been fully elucidated, dysfunction in serotonergic system has been implicated. Of the SSRIs, paroxetine, sertraline, fluoxetine and tricyclic antidepressants (clomipramine) have all been shown to be effective in the treatment of PE.[18–20] In a study, 30 patients with PE were randomly assigned to two groups. In total, 15 of them (group I) received 8 weeks of citalopram treatment, but the remaining (group II) did not. IVELT considerably elevated after 8 weeks of citalopram treatment in group I with a mean of 209 ± 72.1 s but not in group II. The mean dose of citalopram received in group I was 30.7 ± 9.3 mg/day.[12] Other studies have suggested that citalopram is ineffective[21] or mildly increases IVELT.[22]

The notable findings of our study first include the superiority of citalopram over placebo in increasing all of the measured parameters (IVELT, IIEF and mean number of coitus episodes weekly). Second, significant improvement in the above-mentioned parameters was observed in 3 and 6 months after cessation of therapy. We must consider that most patients experience a return of symptoms following cessation of any drug treatment for PE. We noted better and statistically significant improvement in ejaculatory control after the discontinuation of citalopram. Patients continued to show therapeutic effect with improved IVELT. This provides additional evidence that citalopram may offer a favorable balance of serotonergic neurotransmissions in patients with PE.

The reasons for the different effects of the various SSRIs on IVELT are not clear. Potency, 5-HT selectivity and effects on other neurotransmitters such as noradrenaline may play a pivotal role in the differences between SSRIs in delaying ejaculation. As inhibition of 5-HT reuptake after acute SSRI administration leads to increased synaptic levels of 5-HT,[23] it could be suggested delaying IVELT may be that the various SSRIs differentially inhibit 5-HT transporter populations and result in different postsynaptic 5-HT receptors activity. Citalopram is a bicyclic phthalane derivative with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram is the most selective SSRI currently available.[24] It has only minimal effects on norepinephrine and dopamine neurotransmission with 3400 times more serotonin (5-HT) activity than norepinephrine. Various SSRIs have differential enhancing effects on 5-HT release in different brain areas; in some areas (e.g. median raphe nucleus), 5-HT release can be increased by 10-fold and in other areas (e.g. dorsal hippocampus) by only 2-fold, for example, by citalopram administration.[25] Citalopram follows first-order kinetics and therefore the plasma concentration is proportional to the daily maintenance dose for doses in the range of 20–60 mg. Citalopram differs from other SSRIs (such as fluoxetine, fluvoxamine, or paroxetine) because it does not inhibit any CYP450 isoform and shows linear kinetics throughout the duration of the treatment.[13] Absorption of citalopram is not affected by food.[26] Steady-state concentrations are reached in 1–2 weeks with once daily dosing.[27] Desensitization of 5-HT_{1a} autoreceptors is thought to occur after a long-term treatment, and gradually the firing of the 5-HT neurons will normalize. However, there will be no tolerance to the 5-HT-reuptake inhibition by CIT.[28]

Citalopram also provides significant improvements on the overall sexual functions of the patients with PE, suggesting that the overall sexual functions of patients with PE including sexual desire and partner's satisfaction have improved. Citalopram was well tolerated with only one patient discontinuing on account of an adverse event. The major concern seems to regard be time of administration.

In many cases, SSRIs are clinically effective only after 30 days of administration in depressed patients. Thus, it may happen in patients with PE, and 3–4 week administration of SSRIs may not be enough for clinical efficacy. In this respect, our study may be accepted as a reliable study on long-term administration of an anti-depressant drug. Waldinger *et al.*[29] described the rapid onset of action (<1 week) of the SSRIs on ejaculation delay, in contrast to the relatively long period before the antidepressant efficacy of the SSRIs is revealed (4–6 weeks), as a manifestation of different underlying neurobiological substrates in depression and sexual function. Therefore, we think that long-term administration of SSRIs is required for long-term efficacy.

A limitation of our study is that we were unable to assess economic status and other psychosocial factors that might affect treatment results.

From the above we can conclude that the differences between SSRIs in delaying IVELT probably cannot be fully explained only by their actions on the central 5-HT system. Probably there are other mechanisms, neurotransmitter, neuropeptide, or hormonal effects, that cause these differences.

Conclusions

Citalopram administered on a chronic daily basis is safe and effective in patients with PE. Improved IVELT was also associated with objective improvement in overall sexual satisfaction. In addition, the real long-term efficiency of citalopram was also proved after treatment cessation. Larger randomized double-blind studies would be the next logical step in further confirming the efficacy of this drug.

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