

SELECTIVE SEROTONIN RE-UPTAKE INHIBITOR IN THE TREATMENT OF PREMATURE EJACULATION

JOSÉ P.T. NOVARETTI, ANTONIO C.L. POMPEO, SAMI ARAP

Division of Urology, School of Medicine, University of São Paulo (USP), São Paulo, SP, Brazil

ABSTRACT

Introduction and Objectives: This prospective, double-blind, randomized, cross-over, placebo-controlled study was designed to investigate the efficacy and side effects of the selective serotonin re-uptake inhibitors, fluoxetine hydrochloride, on postponing ejaculation in patients with premature ejaculation (PE).

Patients and Methods: A total of 55 men with PE were scheduled to begin this study, but 5 dropped out. All patients were heterosexual, ages 19 to 65 who experienced primary premature ejaculation (lifelong rapid ejaculation). They were evaluated at the start and at the end of the study to evaluate the degree of anxiety and depression using the Hamilton Anxiety Scale and Beck et al. Partners were asked to determine the time between vaginal penetration and ejaculation (latency time), by using a clock marking the seconds. Treatment phases consisted of an 8-week administration period of placebo or fluoxetine capsules, 4 weeks of wash-out and an additional 8-week cross-over treatment. All patients were interviewed before and 8, 12 and 20 weeks after beginning the treatment.

Results: Baseline mean ejaculatory latency time was 60.6 s; 20 mg/day of fluoxetine increased it to 199.3 s ($p < 0.001$). This resulted in significantly greater sexual satisfaction for men: 68% ($p < 0.001$). Generally, fluoxetine was well tolerated and there were no major side effects. None of the patients discontinued therapy due to adverse effects. No significant alterations in the Hamilton Anxiety Scale and Beck et al. Scale for Depression scores at the beginning and at the end of the study were observed. Anxiety and depression showed no influence in the improvement of PE treated with Fluoxetina hydrochloride.

Conclusion: Fluoxetina hydrochloride may be regarded as a safe and effective option in the treatment of premature ejaculation.

Key words: ejaculation; fluoxetine; antidepressant drugs; sexual dysfunction

Braz J Urol, 28: 116-122, 2002

INTRODUCTION

Premature Ejaculation (PE) is the most common sexual dysfunction, which, according to some authors (1), affects almost 50% of men. Because the ejaculation occurs much sooner than desired, it causes a significant suffering for the patient, as it impedes a satisfactory sexual intercourse.

There are many definitions of PE in the medical literature; however, there is no consensus.

A quantitative definition is being formulated to obtain parameters to be used in scientific studies. The most used parameter has been the latency time, which is the time between vaginal penetration and ejaculation.

However, there is not an agreement on how long this time should be. Therefore, to Waldinger et al. (2), the patient with PE ejaculates in less than a minute; to Strassberg et al. (3) in less than two minutes; to Althof et al. (4), in less than four minutes and to Schover et al. (5) in less than seven minutes.

Nowadays, the definition almost universally accepted is the “DSM IV”, Mental Disorders Diagnostic and Statistical Manual – 4th Edition, from the Psychiatric American Association, published in 1994: “Premature Ejaculation is an ejaculation, persistent or recurrent, with minimal sexual stimulation, before or thereupon ejaculation, sooner than desired”. Occasional problems, not persistent and non-recurrent, or not accompanied by great suffering or personal relationship difficulty, do not characterize the diagnosis.

Many authors (6-11) have considered anxiety the most important etiologic factor in the PE.

The non-drug treatment for PE has been traditionally performed with behavioral therapies, using training, associated or not to psychotherapy. This therapeutic modality demands very well-selected patients and the results are generally not long lasting.

As from the sixties, it has been observed that antidepressant, such as monoamine oxidase inhibitors (MAOIs), produce side effects delaying or inhibiting ejaculation and orgasm (12).

As from the seventies, the use of serotonin reuptake inhibitors (clomipramine, fluoxetine, paroxetine and setraline) on a large scale to treat depression, showed that they also affect ejaculation significantly.

Clomipramine has been the most used one; however, the side effects make its usage difficult in an expressive number of cases (4,12,13).

The fluoxetin hydrochloride is an antidepressant with strong action as selective serotonin re-uptake inhibitor, with few or no effect on monoamines re-uptake. Therefore, it has a lower incidence of side effects when compared to tricyclic antidepressants.

The objective of this study was to evaluate, through a prospective, randomized, double-blind, cross-over, placebo-controlled study, the efficacy of this drug in the treatment of PE and its side effects. We also tried to evaluate the results in relation to anxiety and depression, when present.

MATERIALS AND METHODS

One hundred and eighty-three men were interviewed, without distinction of color or race, with

PE complaint for at least six months. Data were collected from June 5th, 1998 and January 7th, 2000.

One hundred and twenty-eight patients were excluded: 48 had erectile dysfunction, 3 were using antidepressants, and 24 did not have a fixed partner or had irregular sexual intercourse. A total of 53 patients did not return after the first interview. At the end, 55 patients attended all inclusion criteria, but 5 abandoned the study as soon as it started because of personal problems not-related to the medication.

In the first appointment, after explaining the study and giving the written consent, the patient was asked to return after 4 weeks. During this period, the patient was asked to have at least one intercourse per week, and to evaluate the time between penetration and ejaculation. Time evaluation should be made by the partner with a clock marking seconds.

Initial time was obtained through the arithmetic mean of the four times measured. Besides the latency time obtained, a subjective evaluation of the satisfaction level in relation to the sexual intercourse was requested. Satisfaction level could vary from bad, fair or good.

In the first appointment, the patient was asked to answer 2 questionnaires: the Hamilton Anxiety Scale, to evaluate the anxiety level, and Beck et al. Depression Scale, to evaluate the depression state.

Biographic data of all patients are summarized in Table-1. All of them reported good affective relationship with their partner and considered their sexual performance bad.

Patients were randomized in 2 groups: one using 20 mg of fluoxetin a day, and the other using placebo, one tablet a day, at 10 o'clock. The medication, identified by the letters A or B, were provided by the pharmacological laboratory in identical tablets. Boxes contained 56 tablets and the code (the letter corresponding to the fluoxetin or the letter corresponding to the placebo), which was kept in sealed envelope until the completion of data collection from all patients. Both the researcher and the patients did not know who was taking the active drug and who was taking the placebo (double-blind).

Patients started with the medication A or B and returned 8 weeks later, when the first phase was over, bringing the time of 8 sexual intercourse recorded.

Table 1 - Characteristics of 50 patients.

	Range	Mean	Median	SD
Age (years)	19 - 65	37.4	36.5	10.7
Marital Status	Married - 88%	Single - 12%		

SD = standart deviation.

At the end of this period, patients did not use the medication for 4 weeks (wash-out), and returned bringing the time of 4 sexual intercourse recorded. After that, they started to take the second medication (B or A), for more 8 weeks and returned again with the duration of 8 sexual intercourse recorded.

The arithmetic mean of the latency time measured, the satisfaction level with the sexual intercourse and the eventual side effects were written in the protocol every time the patient returned.

In the last day, patients filled out once again the Hamilton and the Beck et al. Scales to evaluate their anxiety level and depression state. The results were compared to the ones initially obtained.

The chosen fluoxetine dose was 20 mg once a day, since this is the most common dose used in the treatment of anxiety and depression, which causes ejaculation delay in many patients without PE. This effect can be initiated in the first days of use. The four-week period for wash out chosen was based on the fluoxetine half-life. The numerical data obtained were described in mean, standard deviation and median.

The chi-square test, Fisher exact test, Mann-Whitney test and Z test were used for the statistical analysis. We adopted a significance level of 5% for all tests.

RESULTS

By the end of the data collection period, the analysis of the 50 patients' data provided results about many characteristics of patients with PE.

Using the data obtained from the Hamilton Anxiety Scale and the Beck et al. Depression Scale, it was observed that, in the beginning of the research, 11 patients had major anxiety, 26 minor anxiety and 13 no anxiety (Table-2). Three patients had moderate depression, 9 light depression and 38 no depression (Table-3).

The questionnaires answered at the end of the study reveled that no patient changed his anxiety level or depression.

In relation to the satisfaction level with sexual intercourse, the results showed that 27 patients (54%) reported good improvement with fluoxetine, 7 (14%) reported fair improvement and 16 (32%) didn't report any alteration, that is, they still had bad quality sexual intercourse. During the placebo period, only 5 patients (10%) reported fair improvement and 40 (90%) did not report improvement (Table-4). The difference was statistically significant (p < 0.001).

It was observed that the improvement occurred independently from the initial anxiety level (Figure-1) and depression (Figure-2).

The results of latency time are shown in table 5. Patients using fluoxetine achieved mean final latency time of 199.3 seconds, while patients using placebo achieved 68.1 seconds. The comparison between theses times reveled a statistically significant difference (p < 0.001).

The side effects observed, with fluoxetine and placebo use, are demonstrated in Table-6. There was a statistically significant difference, with higher incidence in the fluoxetine group, of drowsiness (p = 0.002) and headache (p = 0.03).

DISCUSSION

Serotonine (5-hydroxytryptamine, or 5-HT) is an amine formed from tryptophan, an essential

Table 2 - Anxiety before treatment (Hamilton Anxiety Scale).

	No. of Patients	%
No anxiety	11	22
Minor anxiety	26	52
Major anxiety	13	26

Table 3 - Depression before treatment (Beck et al. Scale).

	No. of Patients	%
None	38	76
Mild	9	18
Moderate	3	6
Severe	0	0

aminoacid. It acts as a neurotransmitter, almost exclusively in the mesencephalon, pons and bulb. Its action in the central nervous system involves the regulation of the cerebral blood flow and sleep, tolerance to persistent stress, behavioral and impulsiveness inhibition. Its liberation is stimulated by aversive events, leading to the regulation of defensive behavior and/or anxiety. Besides, it is the neurotransmitter of the pain inhibitor descendent ducts to the spinal cord (14).

The way serotonin interferes in ejaculation is still not well-known. Svensson & Hanson (15) demonstrated that this amine causes, experimentally in rats, ejaculation inhibition through central and spinal ducts.

Ejaculation is a phenomenon periferically mediated by alpha-1 noradrenergic stimulation, probably with colinergic influence. The selective serotonin reuptake inhibitors do not have sympathicolitic effects not even over the parasympathetic. Therefore, the effects of these drugs in delaying ejaculation must occur in the central nervous system (16,17).

Table 4 - Degree of satisfaction with sexual activity following intake of 20 mg fluoxetine or one placebo tablet a day for eight weeks.

Satisfaction	Fluoxetine		Placebo	
	No.	%	No.	%
Good	27	54	0	0
Fair	7	14	5	10
Poor	16	32	45	90

$\chi^2 = 32.96$ (grade of freedom =1).

Adler-Graschinsky et al. (18) believe that serotonin has an inhibitory role over the noradrenergic mechanism of the orgasm, by inhibiting the presynaptic neuron, which facilitates the simpathetic neurotransmission, that is, it inhibits the sympathetic nervous system, delaying ejaculation.

Ertekin et al. (19) concluded that there are evidences that the premature ejaculators are unable to maintain the regional depression of the adrenergic activity during erection. Thus, the lack of serotonin would impede the regional depression of the adrenergic activity, allowing the ejaculation. The replacement of serotonin obtained with the fluoxetin use would revert this situation.

This would justify the results obtained in the present study, where the level of satisfaction with sexual intercourse with the use of fluoxetin hydrochloride was significantly different from the use of placebo (Figure-3).

When we evaluate the latency time, this fact is even more evident. A statistically significant differ-

Table 5 - Variation of latency time, in seconds, before and after the use of fluoxetine 20 mg and one placebo tablet a day for eight weeks.

	Fluoxetine	Placebo
Initial	Mean = 60.6	Mean = 62.7
	Median = 43.5	Mediana = 42.5
	Standard Deviation = 51.83	Standard Deviation = 64.12
Final	Mean = 199.3	Mean = 68.1
	Median = 160	Median = 45.5
	Standard Deviation = 178.98	Standard Deviation = 64.30

Mann Whitney test (z value = -4.093): significant for placebo final time x fluoxetine final time (p < 0.001).

SEROTONIN INHIBITOR IN PREMATURE EJACULATION

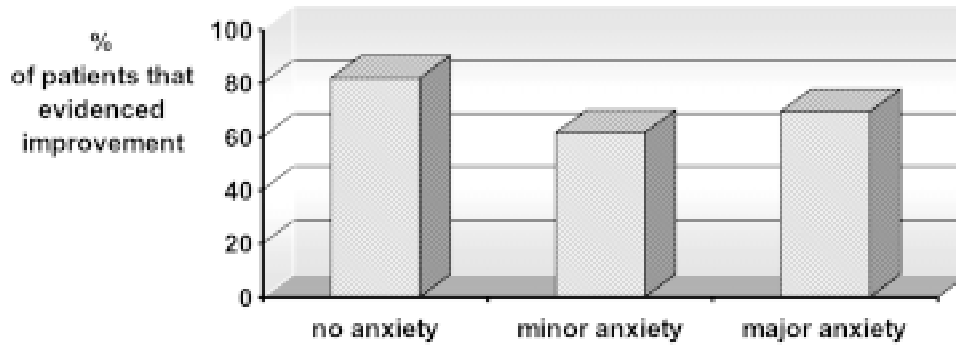


Figure 1 - Percentage of patients that reported improvement in the degree of satisfaction (good and regular) of their sexual activity, considering the degree of anxiety after treatment with fluoxetine for eight weeks. No statistically significant difference was found among 3 groups. Fisher's exact test ($p = 0.232$).

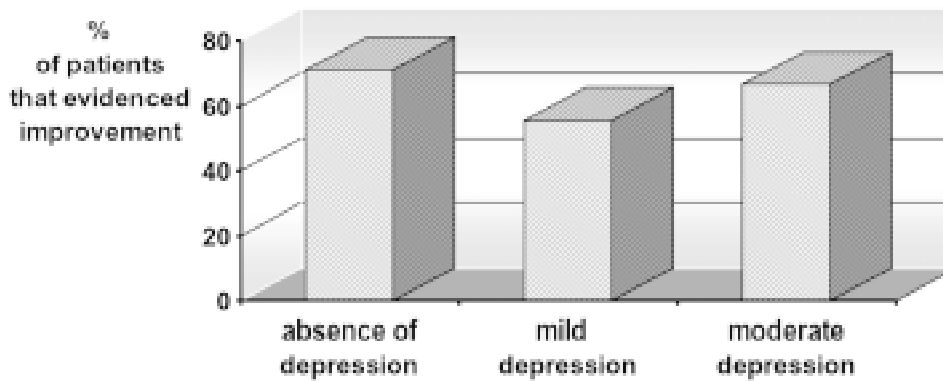


Figure 2 - Percentage of patients that reported improvement in the degree of satisfaction (good and regular) with regard to their sexual activity, considering the degree of depression after 8 weeks of treatment with fluoxetine. No statistically significant difference was observed among 3 groups. Fisher's exact test ($p = 0.880$).

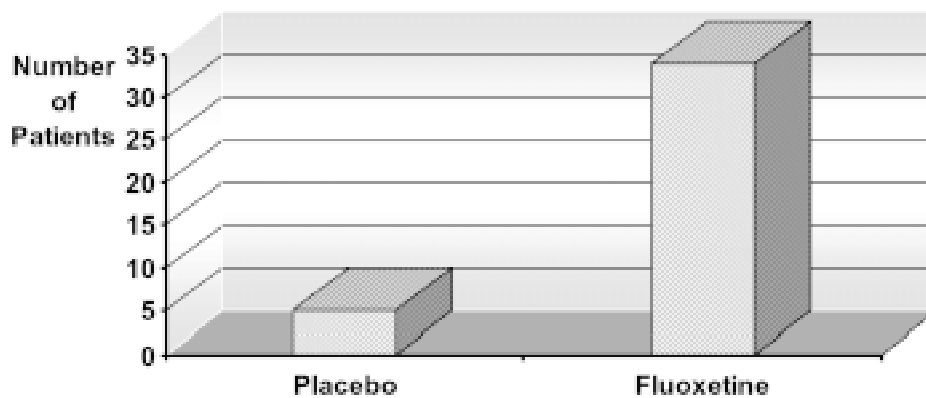


Figure 3 - Number of patients that reported improvement in the degree of satisfaction regarding their sexual activity, after an 8-week treatment with placebo or fluoxetine. $\chi^2 = 32.96$ (degree of freedom = 1), $p < 0.001$.

SEROTONIN INHIBITOR IN PREMATURE EJACULATION

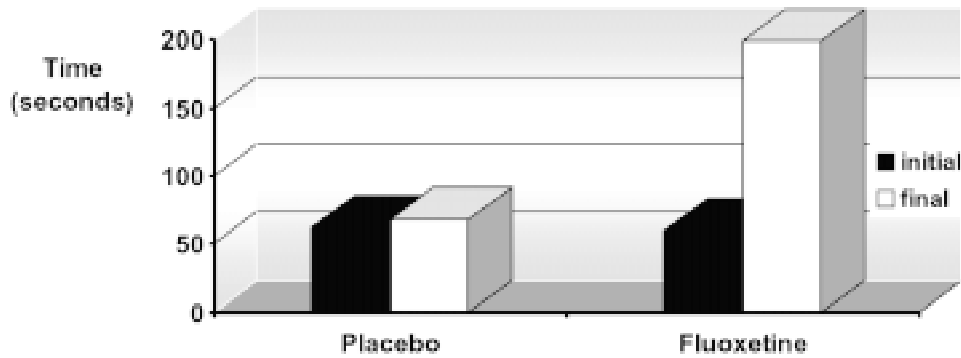


Figure 4 - Variation of mean time latency following treatment with placebo or fluoxetine. Mann Whitney test – placebo final time x fluoxetine final time ($p < 0.001$).

Table 6 - Side effects with the use of fluoxetine and placebo.

Side Effects	Fluoxetine		Placebo	
	No.	%	No.	%
Drowsiness	15	30	3	6
Dizziness	1	2	3	6
Insomnia	3	6	2	4
Decreased libido	2	4	1	2
Headache	7	14	1	2
Dry Mouth	1	2	0	0

Fisher's exact test: significant for drowsiness ($p = 0.002$) and headache ($p = 0.03$).

ence between the results obtained by patients using fluoxetin and placebo was observed (Figure-4).

Like Metz et al. (20), we believe that “the pharmacological agents can offer hope to some men particularly those who have a physiologic predisposition to PE”.

CONCLUSIONS

Fluoxetin hydrochloride is effective in the treatment of primary PE, increasing ejaculatory latency

time with minor and temporary side effects. The improvement occurs independently from patients anxiety level or depression and independently from an improvement in those aspects.

FARMASA laboratory has provided the fluoxetin and the placebo used in this study

REFERENCES

1. Spector IP, Carey MP: Incidence and prevalence of the sexual dysfunctions: a critical review of the empirical literature. *Arch Sex Behav*, 19: 389-408, 1990.
2. Waldinger MD, Hengeveld MW, Zwinderman AH: Ejaculation-retarding properties of paroxetine in patients with primary premature ejaculation: a double-blind, randomized, dose-response study. *Br J Urol*, 78: 592-595, 1997.
3. Strassberg DS, Mahoney JM, Schaugaard M, Halev E: The role of anxiety in premature ejaculation: A psychophysiological model. *Arch Sex Behav*, 19: 251-259, 1990.
4. Althof SE, Levine SB, Corty EW: A double-blind crossover trial of clomipramine for rapid ejaculation in 15 couples. *J Clin Psychiatry*, 56: 402-407, 1995.
5. Schover LR, Friedman JM, Weiler SJ, Heiman JR, Lopiccolo J: Multiaxial problem-oriented system for sexual dysfunction. *Arch Gen Psychiat*, 39: 614-619, 1982.
6. Cooper A, Cernovsky ZZ, Colussi K: Some clinical and psychometric characteristics of primary and secondary premature ejaculators. *J Sex Marital Ther*, 19: 276-288, 1993.
7. Costa M: Ejaculação precoce: os minutos que valem ouro. *Urol Contemp*, 3: 81-86, 1997.
8. Kaplan HS: *A Nova Terapia do Sexo*. Rio de Janeiro, Nova Fronteira, p. 75, 1974.
9. Masters WH, Johnson VE: *A Incompetência Sexual*. Rio de Janeiro, Civilização Brasileira, pp. 93-95, 1979.
10. McMahon CG: Treatment of premature ejaculation with sertraline hydrochlorider: a single-blind placebo controlled crossover study. *J Urol*, 159: 1935-1938, 1998.
11. Schapiro B: Premature ejaculation: a review of 1130 cases. *J Urol*, 50: 374-379, 1943.
12. Bennett D: Letter to editor on use of MAOIs for premature ejaculation. *Lancet*, 2: 1309, 1961.
13. Haensel SM, Klem TM, Hop WC, Slob AK: Fluoxetine and premature ejaculation: a double-blind, crossover, placebo controlled study. *J Clin Psychopharmacol*, 18: 72-77, 1998.
14. Graeff FG, Brandão ML: *Neurobiologia das Doenças Mentais*. São Paulo, Lemos Editorial e Gráfica Ltda, pp. 45-46, 1993.
15. Svensson L, Hanson S: Spinal monoadrenergic modulation of masculine copulatory behaviour in the rat. *Brain Research*, 302: 302-315, 1984.
16. Segraves RT: Effects of psychotropic drugs on human erection and ejaculation. *Arch Gen Psychiat*, 46: 275-284, 1989.
17. Waldinger MD, Berendsen HHG, Blok BFM, Olivier B, Holstege G: Premature ejaculation and serotonergic antidepressant-induced delayed ejaculation: the involvement of serotonergic system. *Behav Brain Res*, 92: 111-118, 1998.
18. Adler-Graschinsky E, Butta NV, Elgoyhen AB: Serotonin uptake inhibitors and the prejunctional effects of serotonin on peripheral sympathetic nerves. *Life Sci*, 39: 61-68, 1986.
19. Ertekin C, Çolakaglu Z, Altay B: Hand and genital sympathetic skin potentials in flaccid and erectile penile states in normal potent men and patients with premature ejaculation. *J Urol*, 153: 76-79, 1995.
20. Metz ME, Pryor JL, Nesvacil LJ, Abuzzahab F, Kosnar J: Premature ejaculation: a psychophysiological review. *J Sex Marital Ther*, 23: 3-23, 1997.

Received: October 11, 2001

Accepted after revision: March 1, 2002

Correspondence address:

Dr. José Pedro Trevisan Novaretti
 Rua Carlos Botelho, 520
 Marília, SP, 17516-190, Brazil
 Fax: ++ (55) (14) 422-3600
 E-mail: novaretti@terra.com.br