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# The role of selective serotonin re-uptake inhibitors in the management of premature ejaculation

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## Abstract

A prospective, randomized, placebo-controlled study was designed to investigate the efficacy and side effects of the selective serotonin re-uptake inhibitor, fluoxetine hydrochloride, on postponing ejaculation in patients with premature ejaculation (PE). A total of 55 men with PE were scheduled to begin this study, but 5 of them have been dropped out for unknown reason, so the study was completed with a total number of 50 patients. The ages of these patients (who experienced primary premature ejaculation (lifelong rapid ejaculation)) ranging between 19 to 65 years. The patients were asked to determine the time in seconds between vaginal penetration and ejaculation (latency time), by using a clock for four weeks before starting the treatment,and a baseline mean ejaculatory latency time was measured. Then the patients were given either flouxetine hydrochloride or placebo for aditiomal 8 weeks. All patients were interviewed before and 8 weeks after beginning the treatment.Baseline mean ejaculatory latency time was 60.6 s; 20 mg/day of fluoxetine increased it to 199.3 s, while in patient using placebo it was 68.15 s ($p < 0.001$). This resulted in significantly greater sexual satisfaction for men: 73% ($p < 0.001$). Generally, fluoxetine was well tolerated and there were no major side effects. None of the patients discontinued therapy due to adverse effects. Fluoxetinae hydrochloride may be regarded as a safe and effective option in the treatment of premature ejaculation.

# دور مثبط الأسترجاع الانتقائي للسيروتونين في علاج تأخير القذف المنوي

## ياسر عباس الجنابي

## المستخلص

صممت الدراسة الاستطلاعية ذات العينة العشوائية لبحث الفعالية والتأثيرات الجانبية لعلاج الفلوكستين كلوريد الهيدروجين (مثبط الاسترجاع الانتقائي للسيروتونين) لغرض تأخير القذف المنوي لدى المرضى الذين يعانون من حالة القذف المبكر.شملت الدراسة ٥٥ مريض يعانون من مرض القذف المبكر الأولي ولكن خمسة من بينهم سقطوا من الدراسة لأسباب مجهولة,تراوحت أعمارهم بين ١٩-٦٥ سنه. طلب من المرضى تسجيل الوقت المستغرق بين ولوج القضيب و حدوث القذف باستخدام ساعة توقيت وتم قياس معدل الوقت المستغرق لهولاء المرضى.تم تقسيم المرضى إلى مجموعتين أعطيت الأولى (٣٠ مريض) علاج الفلوكستين والمجموعة الثانية (٢٠ مريض) أعطيت علاجا وهميا لمدة ٨ أسابيع وتمت مقابله المرضى قبل وبعد ٨ أسابيع من العلاج المنتظم.كان معدل الوقت المستغرق للقذف قبل العلاج ٦٠,٦ ثانيه و باستخدام الفلوكستين ٢٠ ملغم يوميا زاد المعدل الى ١٩٩,٣ ثانية, و قد أكد ٧٣% من المرضى زيادة الرضا والإشباع الجنسي. ولم تظهر أعراضا جانبيه جدية تؤدي إلى ترك العلاج من قبل أي مريض. و بناءا على هذه النتائج فأن علاج الفلوكستين يعتبر علاجا أمين وفعال لعلاج حالات القذف المبكر لدى الذكور.

## Introduction

From a biological point of view, the whole purpose of sex is procreation. In most animals, intercourse is brief, and ejaculation occurs shortly after penetration. In humans, though, sex involves a broad array of psychological and interpersonal factors. As a result, premature ejaculation is defined not by the clock but by the desire and satisfaction of both partners. Premature Ejaculation (PE) is the most common sexual dysfunction, which, according to some authors 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 consensu[1].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., the patient with PE ejaculates in less than a minute[2]; to Strassberg et al. in less than two minutes[3]; to Althof et al. in less than four minutes[4] and to Schover et al. in less than seven minutes[5]. Nowadays, the definition almost universally accepted is the "DSM IV", 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[6-7]. ***Aetiology of PE***: The cause of premature ejaculation is considered psychological, although no one really knows. Idiopathic primary premature ejaculators may have lower penile sensory thresholds[6] and/or greater cortical penile representation[7] than their normal counterparts. Other workers contend that men with PE become sexually aroused more rapidly than normals[8].Both anxiety and depression have been associated with PE[9] although this may be a consequence of the condition rather than a cause. Others have failed to find such an association .A number of psychodynamic theories have been proposed to explain PE, as well as psychosocial and relationship factors (e.g. family problems or a recent new baby)[10]. There are a number of anecdotal reports of PE being associated with neurological disease, diabetes, pelvic injury, vascular disease, prostatic hypertrophy, chronic prostatitis and hypogonadotrophic hypogonadism [9].***Premature ejaculation*** may be treated by behavioral techniques, medication, or a combination of the two. ***The objective of this study*** was to evaluate, through a prospective, randomized, placebo-controlled study, the efficacy of fluoxetin hydrochloride in the treatment of PE and its side effects.

## Materials and Methods

Fifty five men with PE complaint for at least six months were interviewed. Data were collected from June 2005 to July 2007. Five patients were excluded from the study: 2 had erectile dysfunction, 3 patients did not return after the first interview. At the end, 50 patients attended all inclusion criteria. 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. Biographic data of all patients are summarized in Table-1. All of them reported good affective relationship with their wives and considered their sexual performance bad.Then the patients were randomized in 2 groups: the first group(30 patients) given 20 mg of Fluoxetine a day, and the other group(20 patients) using placebo, one tablet a day, at night for 8 weeks.The patients started with the medication (either Fluoxetine 20 mg or placebo treatment) and asked to return 8 weeks later, bringing the time of at least 8 sexual intercourse recorded. At the end of this period, 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. The results were compared to the ones initially obtained.The chosen fluoxetin 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 numerical data obtained were described in mean, standard deviation and median. The chi-square test, and Z test were used for the statistical analysis of my data. 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.In relation to the satisfaction level with sexual intercourse, the results showed that 18 patients (60%) reported good improvement with fluoxetin, 4 (13.5%) reported fair improvement and 8 (26.5%) didn't report any alteration, that is, they still had bad quality sexual intercourse. While in the group of placebo management, only 2 patients (10%) reported fair improvement and 18 (90%) did not report improvement (Table-2). The difference was statistically significant ($p < 0.001$).The results of latency time are shown in table (3). Patients using fluoxetin 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 fluoxetin and placebo use, are demonstrated in Table-4. There was a statistically significant difference, with higher incidence in the fluoxetin group, of drowsiness ($p = 0.002$) and headache ($p = 0.03$).

**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 = standard deviation** | | | | |

**Table( 2): Degree of satisfaction with sexual activity following intake of 20 mg fluoxetin or placebo management for eight weeks.**

| Satisfaction | Fluoxetine No. | % | Placebo No. | % |
|---|---|---|---|---|
| Good | 18 | 60 | 0 | 0 |
| Fair | 4 | 13.5 | 2 | 10 |
| Poor | 8 | 26.5 | 18 | 90 |
| *□2 = 32.96 (grade of freedon =1).* | | | | |

**Table( 3): Variation of latency time, in seconds, before and after the use of fluoxetine 20 mg and placebo management for eight weeks.**

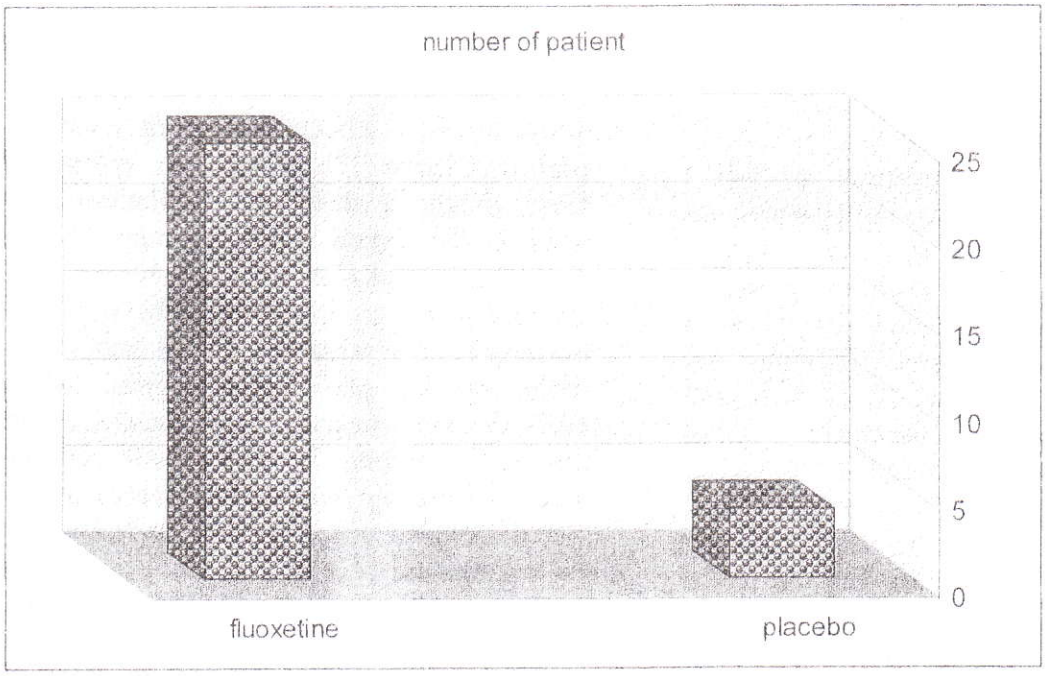
| | Fluoxetine | placebo |
|---|---|---|
| Initial | Mean = 60.6<br>Median = 43.5<br>Standard Deviation = 51.83 | Mean = 62.7<br>Mediana = 42.5<br>Standard Deviation = 64.12 |
| Final | Mean = 199.3<br>Median = 160<br>Standard Deviation = 178.98 | Mean = 68.1<br>Median = 45.5<br>Standard Deviation = 64.30 |

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

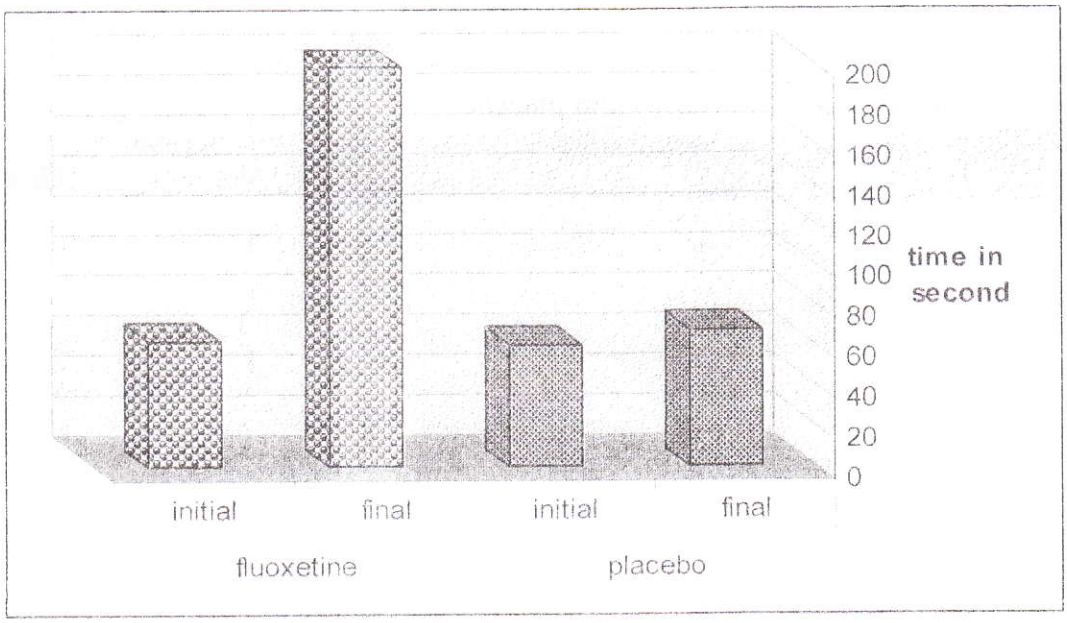
Table (4): Side effects with the use of fluoxetine and placebo.

| Side Effects | Fluoxetine | | Placebo | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Drowsiness | 10 | 33 | 3 | 6 |
| Dizziness | 1 | 3 | 3 | 6 |
| Insomnia | 2 | 6 | 2 | 4 |
| Decreased libido | 1 | 3 | 1 | 2 |
| Headache | 6 | 20 | 1 | 2 |
| Dry Mouth | 1 | 3 | 0 | 0 |

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




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




**Figure( 2): Variation of mean time latency following treatment with placebo or fluoxetine. Mann Whitney test – placebo final time x fluoxetine final time ($p < 0.001$**

## Discussion

Serotonine (5-hydroxytryptamine, or 5-HT) is an amine formed from tryptophan, an essential 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). 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-1). When we evaluate the latency time, this fact is even more evident. A statistically significant difference between the results obtained by patients using fluoxetin and placebo was observed (Figure-2).

**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.

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

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