A randomized study examining the effect of 3 SSRI on premature ejaculation using a validated questionnaire

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Aim: This study reports the results of a large prospective single-blinded clinical trial of 3 SSRI (paroxetine, fluoxetine and escitalopram) in PE using a validated questionnaire.

Methods: A total of 100 normally potent men suffering from PE were enrolled in a randomized single-blinded comparative study of fluoxetine, paroxetine and escitalopram Patients were randomized into 3 treatment groups. Group 1 comprised 33 men who received fluoxetine 20 mg daily, group 2 comprised 37 men who received escitalopram 10 mg and group 3 comprised 30 men who received paroxetine 20 mg daily. All drug regimens were given in early morning dose and continued for 4 weeks.

Results: All 100 (100%) patients experienced a significant increase in their AIPE total score after drug treatment. There was no significant difference regarding any of the 7 items of the AIPE between the 3 treatment groups. All 3 drugs were generally well tolerated.

Conclusions: Our relatively large study, using a validated questionnaire confirmed similar useful effect of paroxetine, fluoxetine and escitalopram on ejaculation time. Further large cohort studies with long-term follow up are needed to evaluate the sustained effects of these drugs on ejaculation latency.

Introduction

One of the most commonly reported sexual difficulties is premature ejaculation, occurring in 66% of men with sexual dysfunction complaint. More conservative estimates indicate that 35– 40% of men treated for sexual dysfunction experience this condition, and it is more prevalent than erectile dysfunction (Kaplan And Saddock 1998; Aschka et al 2001). Premature ejaculation describes a condition in which a male climaxes before he desires to do so. Diagnostic criteria for premature ejaculation in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision, include "persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it," the disturbance "causes marked distress or interpersonal difficulty," and the disturbance "is not due to effects of a substance." (Diagnostic and statistical manual of mental disorders). Ejaculatory latency of less than 1–1.5 and perhaps 2 minutes may qualify a man for the diagnosis (Waldinger et al 2005). According to DSM-IV-TR and the AUA the diagnosis can only be made when there is marked distress (Lue et al 2004). We recently reported a new diagnostic tool for PE using a validate questionnaire, The Arabic Index of Premature Ejaculation (AIPE) (Arafa and Shamloul 2005) (Appendix I).

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The etiology of this disorder may be physiologic, psychogenic, or behaviorally conditioned. Previous methods of treatment include behavioral therapy and exercises known as the "squeeze technique" or the "start and stop technique," modalities that often require partner participation. Pharmacologically, tricyclic antidepressants (TCAs) such as clomipramine have been used, but undesirable adverse effects frequently accompanied treatment (Kaplan and Saddock 1998).

It is generally assumed that selective serotonin reuptake inhibitor (SSRI)-induced sexual side effects are related to increased central serotonin (5-HT) neurotransmission and activation of postsynaptic 5-HT receptors (Olivier et al 1998). SSRIs may, in particular, cause delayed ejaculation or anorgasmia (Leonard 1996). SSRIs are selective for inhibition of 5-HT uptake, with selectivity over noradrenaline uptake ranging from 54 nm (fluoxetine) to 3,400 nm (citalopram), whereas selectivity over dopamine uptake or direct influence on various 5-HT receptors is even higher. Ranking SSRIs regarding their selectivity reveals citalopram, sertraline, paroxetine, fluvoxamine, and fluoxetine, in decreasing order (Waldinger et al 2001). Potency (ie, dose to generate, eg, antidepressant effects) does not reflect this selectivity, indicating that at the average daily therapeutic doses for each SSRI, the 5- HT transporter is adequately blocked and that at these doses the influence on other systems is not part of the therapeutic effects (Waldinger et al 2001). This study reports the results of a large prospective single-blinded clinical trial of 3 SSRI (paroxetine, floxetine and escitalopram) in PE using a validated questionnaire (AIPE). The ejaculation latency will be chosen as the primary criterion of efficacy, while the other questions of the AIPE will be used only as secondary criteria of evaluation.

Methods

A total of 100 normally potent men suffering from PE were enrolled in a randomized single-blinded comparative study of fluoxetine, paroxetine and escitalopram. All men were heterosexual, had no other sexual disorders, and were married and sexually active (at least 2 sexual intercourses/week). Premature ejaculation was defined as ejaculation that occurred within 2 minutes of vaginal intromission. All patients were asked to complete the AIPE before inclusion in the study. Patients scoring 31 or more were diagnosed as not having PE and were excluded, while patients scoring 30 or less were considered as having PE and were included in further therapeutic trial. Patients with erectile dysfunction, reduced sexual desire, inhibited male orgasm, chronic psychiatric or physical illness, alcohol or substance abuse and use of medication, including psychotropic medication, were excluded from the trial. Written informed consent was obtained from all patients prior to study inclusion. The study was approved by our institution's relevant review board.

Patients were randomized into 3 treatment groups. Group 1 comprised 33 men who received fluoxetine 20 mg daily, group 2 comprised 37 men who received escitalopram 10 mg and group 3 comprised 30 men who received paroxetine 20 mg daily. All drug regimens were given in early morning dose and continued for 4 weeks. None of the patients received any formal psychosexual counseling. All patients were blinded regarding the type of treatment received. Partners were asked to measure and record ejaculatory latency time, during a 4-week baseline period and throughout the study, using a stopwatch. Patients were asked not to used condoms, or topical penile anesthetic creams or sprays. At the end of the treatment period all patients were asked to re-fill the AIPE for a second time. The ANOVA test was used to compare means between the 3 groups.

Results

The mean (SD) age of patients in group 1, 2 and 3 was 37.6 ± 11.2y, 38.2 ± 10.1y and 36.7 ± 10.2y, respectively. The baseline mean IELT (range 20–80 seconds) showed no significant difference between the 3 groups ($p > 0.05$). All 100 men complained of secondary premature ejaculation reporting previous satisfactory ejaculatory control with no report of extra-vaginal ejaculation. Mean frequency of coitus was not statistically different among the 3 groups during the one month treatment period.

All 100 (100%) patients experienced a significant increase in their AIPE total score after drug treatment. In groups 1,2 and 3 the total AIPE scores increased from a pretreatment mean of 20.3 ± 2.3, 20.3 ± 2.8, 19.7 ± 3.2 to 24 ± 2.3, 24.2 ± 2.3, 23.6 ± 2.3 after 4 weeks of treatment, respectively (Table 1). There was no significant difference regarding any of the 7 items of the AIPE between the 3 treatment groups. Table 2 illustrates the mean IELT of all groups. The mean IELT increased significantly from baseline levels after drug treatment.

All 3 drugs were generally well tolerated. Most side effects were minor and none prompted withdrawal from the study. Drowsiness, anorexia and insomnia occurred in 3 patients on fluoxetine and 3 patients on escitalopram. Five patients complained on paroxetine complained of somnolence. Erectile dysfunction, reduced libido or reduced orgasmic intensity were not noted.

Table 1 Mean (SD) of AIPE scores of all patients (n = 100)

		Baseline	Active drug
Group 1	Q1	3.9 ± 0.3	4 ± 0.3
n = 33	Q2	4.4 ± 0.4	4.4 ± 0.1
	Q3	2.7 ± 0.2	3.6 ± 0.4*
	Q4	1.5 ± 0.2	2.2 ± 0.3*
	Q5	2.6 ± 0.6	3.4 ± 0.5*
	Q6	2 ± 0.5	2.4 ± 0.3
	Q7	3 ± 0.7	3.7 ± 0.2*
	Total score	20.3 ± 2.3	24 ± 2.3*
Group 2			
	Q1	4.3 ± 0.3	4.2 ± 0.2
n = 37	Q2	4.4 ± 0.1	4.5 ± 0.1
	Q3	2.5 ± 0.3	3.7 ± 0.5*
	Q4	1.3 ± 0.4	2.2 ± 0.2*
	Q5	2.4 ± 0.3	3.1 ± 0.7*
	Q6	2 ± 0.6	2.3 ± 0.3
	Q7	3.3 ± 0.3	4 ± 0.4*
	Total score	20.3 ± 3.3	24.2 ± 2.3*
Group 3			
n = 33	Q1	4.2 ± 0.3	4.3 ± 0.7
	Q2	4.2 ± 0.5	4.2 ± 0.5
	Q3	2.2 ± 0.3	3.2 ± 0.6*
	Q4	1.4 ± 0.6	2.2 ± 0.2*
	Q5	2.7 ± 0.3	3.1 ± 0.7*
	Q6	2.3 ± 0.2	2.6 ± 0.6
	Q7	2.9 ± 0.5	3.8 ± 0.6*
	Total score	19.7 ± 3.1	23.6 ± 2.3*

Note: *p < 0.05 vs baseline.

Discussion

The SSRIs block 5-HT reuptake, and these results in an increased 5-HT neurotransmission and activation of postsynaptic 5-HT receptors. SSRI-induced delayed ejaculation and anorgasmia is probably related to an increased central 5-HT neurotransmission and activation of postsynaptic 5-HT receptors (Olivier et al 1998). Waldinger suggested that activation of 5-HT_{2C} receptors delays ejaculation, whereas activation of 5-HT_{1A} receptors accelerates ejaculation latency (Waldinger 2005). Consequently, the ejaculation-delaying effect of some SSRIs may be used therapeutically to treat premature ejaculation (Waldinger tal 1994; Mendels et al 1995; Kara et al 1996).

Several studies demonstrated the useful effect of SSRI on PE. However, not all these studies used evidence-based medicine methodological approaches to precisely examine the effects of sertraline on ejaculation (Waldinger et al 2004). Waldinger and colleagues reported in a recent review that in the current literature only eight (18.5%) studies on antidepressant treatment fulfilled all criteria used in evidence-based medicine, for example, randomized and with prospective real time (stopwatch) assessment of the IELT at each intercourse (Waldinger et al 2004).

In this study we attempted to investigate the effects of 2 well-known SSRI used in the treatment of PE (fluoxetine and paroxetine) and another new drug, escitalopram, using a validated index (AIPE) that incorporates several parameters including mean intravaginal ejaculation time as its determinants. We have recently reported a successful assessment of sertraline, another SSRI, on PE using the same index (Arafa and Shamloul 2006). AIPE's determinants include, sexual desire, erectile function, IELT, ejaculation control, patient satisfaction, partner satisfaction and anxiety-depression status. These different factors can accurately differentiate patients with PE and those without PE (Arafa and Shamloul 2005). During AIPE development and validation, each of the 7 items was scored on a five-point ordinal scale where lower values represent poorer sexual function. Thus, a response of 1 for a question was considered the least functional, whereas a response of 5 was considered the most functional. Possible scores for the AIPE range from 7 to 35. The corresponding sensitivity was found to be 0.98 while the specificity was 0.88. The estimated kappa coefficient of 0.85 indicated substantial agreement, above and beyond chance, between clinical diagnosis and predicted diagnosis (Arafa and Shamloul 2005).

In this study, 100 patients with PE treated with either a 4-week regimen of paroxetine, fluoxetine or escitalpram experienced a significant increase in 4 out of the 7 modules of the AIPE compared to their baseline values. These results clearly demonstrate the high efficacy of these 3 drugs in treatment of PE over a short period of time. Paroxetine has been shown to have the greatest effect of all SSRI on PE, with fluoxteine slightly weaker (Waldinger et al 2001). Also, it was previously reported that citalopram, the parent drug of escitalopram, exhibited only mild ejaculatory delay in patients with PE (Waldinger et al 2001). Contrary to these reports our results show no significant difference between the 3 SSRI in any of the AIPE parameters including the IELT.

Table 2 Mean (SD) IELT (min) of all patients (n = 100).

	Baseline	Active drug*
Fluoxetine	0.6 ± 0.2	2.4 ± 0.4
Escitalopram	0.5 ± 0.3	2.5 ± 0.3
Paroxetine	0.7 ± 0.3	2.7 ± 0.2

(*p < 0.05 vs baseline)

Waldinger and colleagues reported that that neither potency nor 5-HT reuptake selectivity has a major role in the differences between SSRIs in delaying ejaculation (Waldinger et al 2001). However, contrary to that there exists no adequate explanation on why do different SSRI exhibit differential effect on ejaculation. All SSRIs are active in the same diseases, including depression, anxiety disorders, obsessive-compulsive disorder, and various others, but it still remains unclear on why would these drugs differ in their inhibitory action on ejaculation. Findings from our study agree with the current dogma that that different SSRI can show similar efficacy in inhibiting ejaculation if given at effective dosages, through a SSRI-increased 5-HT levels in the brain.

Unlike other antidepressants that can cause ED and low sexual desire, SSRI treatment did not result in any alteration of erectile function or libido. Also, only mild adverse effects were reported with all 3 drugs indicating a good tolerability of SSRI by the patients.

Conclusion

Our relatively large study, using a validated questionnaire (AIPE) confirmed similar useful effect of paroxetine, fluoxetine and escitalopram on ejaculation time. Further large cohort studies with long-term follow up are needed to evaluate the sustained effects of these drugs on ejaculation latency.

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Appendix I

Arabic Index of Premature Ejaculation

Patient's name: Patient's number:

Please respond to each question by circling ONLY ONE statement that best describes your condition.

Q1. How do you rate your sexual desire?

a) Very low
b) Low
c) Average
d) High
e) Very high

Q2. How often do you have hard erections, with sexual stimulation, sufficient to complete sexual intercourse?

a) almost never
b) rarely
c) sometimes
d) often
e) most of the time

Q3. How much time does it take from intromission to ejaculation (using a stop-watch)?

a) <30 seconds
b) Around 1 minute
c) 1–2 minutes
d) 2–3 minutes
e) >3 minutes

Q4. How difficult is it for you to prolong your ejaculation time?

a) most of the time
b) often
c) sometimes
d) rarely
e) almost never

Q5. How often was sexual intercourse satisfactory for you?

a) almost never
b) rarely
c) sometimes
d) often
e) most of the time

Q6. How often was sexual intercourse satisfactory for your partner?

a) almost never
b) rarely
c) sometimes
d) often
e) most of the time

Q7. During sexual intercourse, do you feel anxious, depressed or stressed?

a) most of the time
b) often
c) sometimes
d) rarely
e) almost never

Date of assessment: Doctor's initials: