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Comparison of the treatment efficacies of paroxetine, fluoxetine and dapoxetine in low socioeconomic status patients with lifelong premature ejaculation

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Introduction To assess the treatment efficacies of paroxetine, fluoxetine and dapoxetine in patients with lifelong premature ejaculation (PE).

Material and methods One hundred and seventy male patients with lifelong PE were included in our study. Premature ejaculation profile (PEP) and Intravaginal ejaculation latency times (IELT) were recorded. Paroxetine 20 mg/d was given in Group 1 (n = 64), fluoxetine 20 mg/d was given in Group 2 (n = 47) and dapoxetine 30 mg on demand (at least two times/week) was given in Group 3 (n = 59) patients. After 1 month of treatment, the patients' IELT, PEP and patient reported clinical global impression of change (CGIC) were completed.

Results The mean age was 36 ±9.2 years. There was no difference between the groups' age, PEP and IELT before treatment ($p > 0.05$). PEP and IELT improved in all three groups ($p < 0.001$). The changes in the 1st and 3rd questions of PEP was significantly higher in group 1 than in the other groups (pPEP-1 = 0.042, pPEP-3 = 0.001). The changes in the 2nd and 4th questions of PEP were similar between groups (pPEP-2 = 0.444, pPEP-4 = 0.442). In group 1 and 3 IELT changes were better than group 2 (pIIEL1-3 = 0.297, pIIEL1-2 = 0.017, pIIEL2-3 = 0.100). There was no difference between CGIC scores ($p = 0.087$). The treatment was terminated by 8 patients in Group 1 and 9 patients in Group 2 because of side effects.

Conclusions While paroxetine treatment seemed to be better than the other medications, dapoxetine 30 mg treatment has less side effects than the two others and its' on demand usage makes it more prominent than the others.

Key Words: fluoxetine ‹› premature ejaculation ‹› paroxetine ‹› dapoxetine

INTRODUCTION

Premature ejaculation (PE) is the most common male sexual dysfunction. The prevalence of PE ranges between 20% and 40% [1, 2]. Patients with PE complain about decreased sexual self-confidence and overall quality of life. Thus, it seriously impairs couples' sexual relationships and satisfaction with sexual intercourse [3, 4]. Pharmacotherapy for PE includes selective serotonin reuptake inhibitors (SSRIs), phosphodiesterase type 5 inhibitors, tricyclic antidepressants, tramadol and topical anesthetic creams or sprays [5]. As of yet, none of these agents have been approved by the US Food and Drug Administration (FDA) for PE treatment. This has resulted in an increased 'off-label' prescription of SSRIs for the management of the sexual disorder because of the unique side effect profile observed

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with these agents. The newer SSRI, dapoxetine, has been approved for the 'on-demand' treatment of PE in more than 60 countries in Europe, Latin America and Asia [6]. The aim of the present study was to compare the safety and efficacy of Paroxetine 20 mg/day, Fluoxetine 20 mg/day and on-demand dapoxetine 30 mg, in PE patients.

MATERIAL AND METHODS

A total of 170 consecutive patients seeking PE treatment during the period of October 2013 and October 2015 were retrospectively analyzed. Written informed consent was obtained by all patients prior to study inclusion. Sexually active, heterosexual patients who had a sexual partner for at least six months and sexual intercourse at least twice a week were included in this study. A sexual and medical history was collected from all subjects followed by complete a physical examination including genital examination. Patients with erectile dysfunction or other sexual dysfunctions and chronic psychiatric or systemic diseases were excluded from the study. PE was assessed by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) [7]. Patients were divided into three treatment groups. Patients in Group 1 (n = 64) received paroxetine 20 mg/day, Group 2 (n = 47) received fluoxetine 20 mg/day and Group 3 (n = 59) received dapoxetine 30 mg on demand (at least two times/week).

Patient reported outcomes (PROs) have clinical utility in the assessment of treatment response [8]. Premature Ejaculation Profile (PEP) is an instrument for the assessment of PE that deals with all domains of the condition as defined by the DSM-IV-TR: perceived control over ejaculation, personal distress related to ejaculation and interpersonal difficulty related to ejaculation, as well as satisfaction with sexual intercourse. The measures of control over ejaculation and satisfaction with sexual intercourse includes five response options ranging from 'very poor' (0) to 'very good' (4), with higher scores reflecting a more favorable response. The measures of personal distress related to ejaculation and interpersonal difficulty related to ejaculation includes five response options ranging from 'not at all' (0) to 'extremely' (4), with lower scores reflecting a more favorable response [9].

The Clinical global impression of change (CGIC) obtains a rating of the patient's impression of the change from the onset of treatment with a question: "Compared to the start of the study, would you describe your premature ejaculation problem as: much worse, worse, slightly worse, no change, slightly better, better, or much better". A seven point scale is used ranging from 'much worse' (-3) to 'much better' (3) to score the response [8]. PROs measures are summarized in Table 1.

Primarily, our patients were of a low socioeconomic status (87.6% low and 12.4% middle); socioeconomic status was based on the ADIMARK index which is used by the Chilean government to classify socioeconomic level of individuals. This index is comprised of education level, income of the household's head and possession of goods (among other variables), resulting into three levels or categories: high (more than 15 years of schooling and more than U$ 44,000/ year); middle (up to 15 years schooling and U$ 17,000/ year); and low status (less than 10 years schooling and less than U$ 7,200/year) [10].

Patients completed International Index of Erectile Function 5 (IIEF-5) and PEP assessments before

Table 1. *Premature ejaculation profile*

		Question	Scores and response options
Premature Ejaculation profile	Perceived control over ejaculation	Over the past month, was your control over ejaculation during sexual intercourse:	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
	Satisfaction with sexual intercourse	Over the past month, was your satisfaction with sexual intercourse:	
	Personal distress related to ejaculation	Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse?	0: Not at all 1: A little bit 2: Moderately 3: Quite a bit 4: Extremely
	Interpersonal difficulty related to ejaculation	Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner?	
Global impression of change in premature ejaculation		Compared to the start of the study, would you describe your premature ejaculation problem as:	-3: Much worse -2: Worse -1: Slightly worse 0: No change 1: Slightly better 2: Better 3: Much better

the start of treatment. Intravaginal ejaculation latency times (IELT) were recorded. IELT was measured with self-estimation of IELT (Patient reported estimated ejaculation time) ISSM recommends the use self-estimation by the man or his partner as the accepted method of determining IELT in clinical practice [11]. At the end of the four weeks treatment period all patients' IELT, IIEF-5, PEP and patient reported CGIC were completed. In addition to CGIC, pre-treatment and post-treatment IELT, IIEF-5 and PEP measures were compared among the groups.

Statistical analysis

Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) 13.0 for Windows (SPSS Inc.,Chicago, IL, USA). Results were given as mean ±standard deviation. A value of $p < 0.05$ was considered as statistically significant.

RESULTS

The mean age of the subjects was 36 ±9.2 years. The age, pre-treatment PEP score, IIEF-5 score and IELT values were not statistically different among the groups ($p > 0.05$). IIEF-5 score, PEP score and IELT values showed an improvement in all three groups when compared to pretreatment values ($p < 0.001$).

IELT

The increase in IELT from baseline to post-treatment was 336% in Group 1 ($p < 0.01$), 181% in Group 2 ($p < 0.01$), and 240% in Group 3 ($p < 0.01$). The improvement of baseline IELT was similar for Group 1 and Group 3 ($p = 0.297$), whereas the improvement of IELT in Group 1 ($p = 0.017$) was better than Group 2 (Table 2).

IIEF-5

The alteration in IIEF-5 score was significantly higher in Group 1 than in Group 2 and 3. Also, change for IIEF-5 score in Group 3 was higher than in Group 2 (pIIEF1-2 <0.001), pIIEF1-3 = 0.001, pIIEF2-3 = 0.03) (Table 2).

Patients Reported Outcomes (PRO) Measures

Control Over Ejaculation: Less than 1.0% of subjects across groups reported 'good' or 'very good' control over ejaculation at baseline; by week 4, this measure improved to 39%, 19.1% and 37.2% in Group 1, Group 2 and Group 3, respectively. The mean changes were significantly higher in Group 1 than in the other groups (Table 2).
Satisfaction with Sexual Intercourse: At baseline, 22.5% of subjects across the groups reported 'good' or 'very good' satisfaction with sexual intercourse; by week 4, this increased to 51.6%, 32% and 59% in Group 1, Group 2 and Group 3, respectively. The mean changes were not statistically different among the groups (Table 2).
Personal distress related to ejaculation: While 76.8% of subjects across groups reported 'quite a bit' or 'extremely' for their level of ejaculation-related personal distress at baseline, by week 4 this decreased to 20.3%, 25.5% and 25.4% in Group 1, Group 2 and Group 3, respectively. The mean changes were significantly higher in Group 1 than in the other groups (Table 2).
Interpersonal Difficulty Related to Ejaculation: Approximately one-fourth of subjects reported 'quite a bit' or 'extremely' for their level of ejaculation-related interpersonal difficulty at baseline; by week 4 this decreased to 7.8%, 19% and 16.9% in Group 1, Group 2 and Group 3, respectively. The mean changes were similar among the groups (Table 2).

Table 2. *Results*

	Group 1	Group 2	Group 3	p
Over the past month, was your control over ejaculation during sexual intercourse: (1st question of PEP) (mean change)	1.7	1.2	1.1	0.042
Over the past month, was your satisfaction with sexual intercourse: (2nd question of PEP) (mean change)	0.9	0.6	0.8	0.444
How distressed are you by how fast you ejaculate (come) during sexual (vaginal) intercourse? (3rd question of PEP) (mean change)	-1.7	-1.0	-0.9	0.001
To what extent does how fast you ejaculate (come) during sexual (vaginal) intercourse cause difficulty in your relationship with your partner? (4th question of PEP) (mean change)	-0.9	-0.6	-0.9	0.442
IIEF-5 (mean change)	3.4	1.2	1.9	<0.001
IELT (mean change/s)	149.8	82	123.5	0.051
Patient reported global impression of change	1.73	1.28	1.26	0.087

Clinical Global Impression of Change: Subjects in the paroxetine 20 mg/day, fluoxetine 20 mg/day and on demand dapoxetine 30 mg groups described their PE problem as at least 'better' and 'slightly better' 56.2% and 12.5%, 25.5% and 17%, 40.6% and 22% respectively, when compared to the beginning of the treatment. The mean changes were not statistically different among the groups (Table 2).

Safety

Adverse events occurred in 15 (23.4%), 15 (32%), and 8 (13%) subjects with paroxetine 20 mg/day, fluoxetine 20 mg/day and on demand dapoxetine 30 mg, respectively. Sexual dysfunction occurred in 4 (6.3%) patients in the paroxetine group, in 4 (8.5%) patients in the fluoxetine group and 1 (1.7%) patient in the dapoxetine 30 mg group. The treatment was terminated by 8 patients in the paroxetine and 9 patients in the fluoxetine groups due to the side effects of the treatment, while in the dapoxetine 30 mg group there was no treatment discontinuation due to side effects.

DISCUSSION

The use of antidepressant SSRIs has become the cornerstone of PE treatment. SSRIs increase the extracellular level of the neurotransmitter serotonin by inhibiting its reuptake into the presynaptic cell, increasing the level of serotonin stimulation of postsynaptic 5-HT2C receptors and ejaculatory delay [12]. Studies have shown that the IELT increases between 2 to 8-fold with the use of SSRIs and the effect of delayed ejaculation can be seen days after the start of treatment with a plateauing of the effect within four weeks.

Paroxetine and fluoxetine provide significant efficacy in patients with PE [13]. In 1994 Forster first described the use of fluoxetine as treatment for PE [14] and Waldinger et al. [15] enrolled the first randomized trial assessing paroxetine in PE treatment. Paroxetine treatment results in a 5 to 8-fold increase in IELT. Current guidelines recommend the off-label use of SSRIs for the treatment of PE.

Dapoxetine hydrochloride with a short half-life and rapid acting pharmacokinetic profile supports its role as an on-demand treatment for PE. In several countries, on-demand dapoxetine was approved for the treatment of patients with PE [16]. Receiving on demand dapoxetine 30 mg or 60 mg 1–2 hours before intercourse results in a 2.5 to 3.0-fold increase in IELT from the first dose and is more effective than a placebo in terms of decreased distress, increased ejaculatory control and satisfaction [17, 18].

An increase in IELT is the main goal of PE treatment. In this study the mean average IELT at baseline was 47.3 seconds, with 87% of subjects having an IELT of 1 minute or less. At baseline, overall, 81.1% of subjects reported 'poor' or 'very poor' control over ejaculation, and 76.8% of subjects reported high levels of personal distress related to ejaculation. In addition, 42% of subjects reported low levels of satisfaction with sexual intercourse. After treatment, the mean IELT value was 172.6 seconds and this study provided that paroxetine, fluoxetine and dapoxetine 30 mg could prolong IELT significantly. However, comparison of the groups according to post-treatment IELT showed that paroxetine 20 mg/day led to significantly longer IELT values than the fluoxetine 20 mg/day treatment. Although the post-treatment IELT value was greater in Group 1 than Group 2, the difference was not statistically significant.

Waldinger et al. assessed 4 SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) for PE treatment. The authors reported that paroxetine 20 mg/day treatment led to the longest ejaculatory delay [12]. Simsek et al. evaluated the efficacy of dapoxetine and paroxetine for the treatment of PE in a study involving 150 patients. The authors reported the IELT increased from baseline to post-treatment by 117% in both the paroxetine 20 mg/day and on demand dapoxetine 30 mg groups [19]. A current meta-analysis showed that treatment with SSRIs (both on demand and daily) had a significantly greater effect than placebo on IELT. Conversely, according to analyses, paroxetine treatment did not significantly differ from placebo in improving IELT ($p = 0.08$) while fluoxetine seemed to be efficacious compared to placebo ($p < 0.05$). This contrast was explained by the authors with differences in patient selection, baseline IELT, and drug dosages among the studies evaluated. The authors concluded that data for PE treatment were characterized by an unclear or high risk of bias and comprise quite heterogeneous outcomes and dapoxetine was currently the only drug available for which efficacy could be confirmed in a meta-analysis [20].

Several studies have reported an association between PE and negative psychological consequences in patients and their female partners. The psychosocial or interpersonal distress that results from PE may affect the men's partner relationships and quality of life, their self-esteem, and self-confidence, and new partner relationships [21]. PROs are a useful adjunct to diagnose and assess the treatment benefits in men with PE [22].

Our results showed that paroxetine 20 mg/day treatment significantly improved two PRO measures (control over ejaculation and personal distress related

to ejaculation) compared with fluoxetine 20 mg/day and on demand dapoxetine 30 mg treatments. The differences in 'satisfaction with sexual intercourse' and 'difficulty in relationship with partner' were not statistically significant. (Table 2) In CGIC, 'better' and 'much better' response rate was 52.1%. In addition, all treatments improved IIEF-5 score.

In a study by Pryor, placebo (n = 872), dapoxetine 30 mg (n = 876) and dapoxetine 60 mg (n = 870) were compared in PE treatment. In the dapoxetine 30 mg group 58% of the patients gave a response as 'Slightly better', 'better', or 'much better' for CGIC measurement. Dapoxetine 30 mg treatment improved perception of control over ejaculation (0.44 to 1.65) and satisfaction with sexual intercourse (1.65 to 2.21) [23]. A 2008 Multicenter, observational study showed that IELT had an effect on control over ejaculation, no direct effect on satisfaction with sexual intercourse, and a small direct effect on ejaculation related personal distress [3].

Adverse-effects are one of the major concerns of chronic use of SSRIs; a lot of patients have prompted discontinuation from therapy. The side effects include drowsiness, nausea, dry mouth, insomnia, diarrhea, nervousness, agitation or restlessness, dizziness, sexual problems, such as reduced sexual desire and erectile dysfunction, headache and blurred vision [24]. In our study sexual dysfunction occurred in 6.3% of the paroxetine group, in 8.5% of the fluoxetine group and 1.7% of the dapoxetine 30 mg group. Other adverse events (nausea, diarrhoea, headache, dizziness etc.) were also less frequent in the dapoxetine 30 mg group as compared to the paroxetine and fluoxetine groups (13% vs. 23.4% vs. 32%). Eight patients (12.5%) in the paroxetine group and 9 patients (19.1%) in the fluoxetine group discontinued treatment due to side effects. No patients in the dapoxetine group suspended treatment. Nausea is one of the most common adverse events ranging from 0.3–37.1% in all three treatments [23, 25]. In the literature variable treatment discontinuation rates have been reported. Verze et al. [26] reported treatment discontinuation due to adverse events as 1% for dapoxetine while it was 4% in another study [23].

To the best of our knowledge, our study is the first to compare the efficacy of paroxetine, fluoxetine and dapoxetine 30 mg on PRO and IELT in low socioeconomic status PE patients. Limited patient population, non-randomization and lack of long-term follow-up can be considered as limitations in our study.

CONCLUSIONS

In conclusion, this study demonstrated that paroxetine 20 mg/day, fluoxetine 20 mg/day and on demand dapoxetine 30 mg provided significant treatment efficacy, including prolonged IELT, improved PRO measures and CGIC in low socioeconomic status PE patients. While the paroxetine 20 mg/day treatment seemed to be better than the other medications, the on demand dapoxetine 30 mg treatment had a lesser side effect profile than the other two medications and its' on demand usage could make it more prominent than the others.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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