ORIGINAL RESEARCH

The Combination of Dapoxetine and Behavioral Treatment Provides Better Results than Dapoxetine Alone in the Management of Patients with Lifelong Premature Ejaculation

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ABSTRACT

Introduction. It is not known whether the efficacy of dapoxetine, the only drug approved for the on-demand treatment of premature ejaculation (PE), can be increased by the addition of sexual behavioral treatment (SBTx).
Aim. To test the hypothesis that combined dapoxetine and SBTx provide better result than dapoxetine alone in the management of patient with lifelong PE.
Methods. After a 4-week run-in period, 50 patients with lifelong PE entered a 24-week, open-label, prospective study with a 1:1 assignment. Twenty-five patients (group A) received on-demand dapoxetine 30 mg alone, and the remaining 25 patients (group B) combined on-demand dapoxetine 30 mg and SBTx. The CONSORT 2010 statement was adhered to where possible.
Main Outcome Measures. The intravaginal ejaculatory latency time (IELT), the premature ejaculation diagnostic tool (PEDT) score, and the treatment-emergent adverse events (TEAEs) were analyzed.
Results. Mean age was 34.16 years in group A and 34.44y in group B. From baseline to 4-, 12- and 24-week evaluation, both groups experienced a significant ($P < 0.0001$) increase in mean IELT and decrease in mean PEDT score, but patients in group A showed a significantly lower increase in mean IELT (85.0; 84.8; 130.7; 160.0 vs. 92.0; 137.9; 232.7; 370.7 seconds, respectively; $P < 0.0001$) and a significantly lower decrease in mean PEDT score (20.4; 18.16; 15.88; 14.68 vs. 19.56; 16.0; 11.96; 7.92, respectively; $P < 0.0001$) than those in group B. At 24-week evaluation, no patient in group A reached a PEDT score ≤8 (absence of PE) as opposed to 80% of patients in group B. There was no difference between groups in TEAEs rate (16% vs. 16%; $P = 1.00$). Limitations included the absence of a group receiving SBTx alone or group crossover.
Conclusions. Combined dapoxetine and SBTx proved to be more effective than dapoxetine alone in treating patients with lifelong PE, up to restoring a normal ejaculatory function in most of them. **Cormio L, Massenio P, La Rocca R, Verze P, Mirone V, and Carrieri G. The combination of dapoxetine and behavioral treatment provides better results than dapoxetine alone in the management of patients with lifelong premature ejaculation. J Sex Med 2015;12:1609–1615.**

Key Words. Dapoxetine; Behavioral Therapy; Premature Ejaculation; Sexual Dysfunction

Introduction

Premature ejaculation (PE) is one of the most common male sexual disorders, affecting up to 30% of all men [1]. It involves both physiologic disturbances and psychological concerns over ejaculatory latency, control over ejaculation, and ensuing distress [2,3]. Recently, the International Society for Sexual Medicine (ISSM) has proposed the first evidence-based definition of PE [4].

According to this new definition, PE (lifelong and acquired) is a male sexual dysfunction characterized by the following:

1. Ejaculation that always or nearly always occurs prior to or within circa 1 minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE).
2. The inability to delay ejaculation in all or nearly all vaginal penetrations.
3. Negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy. Various treatment options are commonly used in clinical practice, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), tramadol, phospfodiesterase 5 inhibitors (PDE5-Is), alpha 1-adrenoceptor antagonists, topical anaesthetics, and sex behavioral therapy [5].

Among pharmacological agents, the rapidly acting SSRI dapoxetine hydrochloride is the only currently approved drug for the on-demand treatment of PE [6]. In the pooled dataset of more than 6,000 subjects [7], on-demand administration of 30 or 60 mg dapoxetine resulted in a 2.5- and 3.0-fold (respectively) increase in the intravaginal ejaculatory latency time (IELT) and in significantly better scores than placebo in the four items of the Premature Ejaculation Profile questionnaire. Dapoxetine hydrochloride also provided benefits for female partner-reported outcomes [7] and had similar efficacy in primary (lifelong) and acquired PE, and across different geographic areas as well [8].

Sex behavioral and sex counseling therapies have been widely used around the world since early reports by Masters and Johnson [9] and Semans [10], respectively. According to the ISSM guidelines for PE [11–14], there is a 2b level of evidence regarding the efficacy of such PE treatments; however, the only two studies using contemporary assessment methods (IELT) showed that sex behavioral therapy was more effective than no treatment (wait-list control group) but less effective than pharmacological treatment with either paroxetine or lidocaine-based spray [12,13].

The possibility of combining pharmacological and behavioral treatment, though recommended in the ISSM guidelines for PE with a 2a level of evidence [11], has received little attention. The ISSM guidelines recommendation is based on three Chinese studies [14–16] comparing pharmacological treatment alone: sildenafil, clomipramine, citalopram with combined pharmacological and behavioral treatment. In all three studies, combination therapy was superior to pharmacotherapy alone on both the Chinese Index for Premature Ejaculation and/or the IELT [11]. These finding provide grounds for assuming that sex behavioral treatment might improve the results of pharmacotherapy by improving the psychological and physical control of ejaculation. In spite of such evidence and with dapoxetine being the only approved pharmacological treatment for PE, no study has been published that determines whether the addition of sex behavioral therapy improves the efficacy of dapoxetine or not.

Aims

The present study was designed to test the hypothesis of combined dapoxetine and sex behavioral treatment providing better results than dapoxetine alone in the management of patients with lifelong PE.

Patients and Methods

Men between the ages of 18 and 70 years with a history of lifelong PE who met the ISSM definition criteria were considered eligible for the study [4]. The Consolidated Standards of Reporting Trials (CONSORT) 2010 statement was adhered to where possible. Study inclusion criteria was the following: (i) a stable, heterosexual relationship with a single sexually active female partner for at least 6 months and with at least four intercourses per month; (ii) Premature Ejaculation Diagnostic Tool (PEDT) score ≥11 [17]; and (iii) no previous or concurrent treatments for PE. Exclusion criteria were: (i) a history of medical or psychiatric illness; (ii) use of SSRIs, TCAs, and PDE5-Is or other medications potentially interfering with dapoxetine; (iii) erectile dysfunction (ED) as determined by an International Index of Erectile Function five items (IIEF-5) score <22; and (iv) any form of sexual dysfunction in the female partner as assessed by interview.

After the preliminary evaluation for eligibility including medical and sexual history, physical examination, and self-administration of IIEF-5 and PEDT questionnaires, enrolled patients underwent a 4-week baseline period during which couples were encouraged to experience sexual intercourse at least four times and record the IELT for each event using the stopwatch technique. At

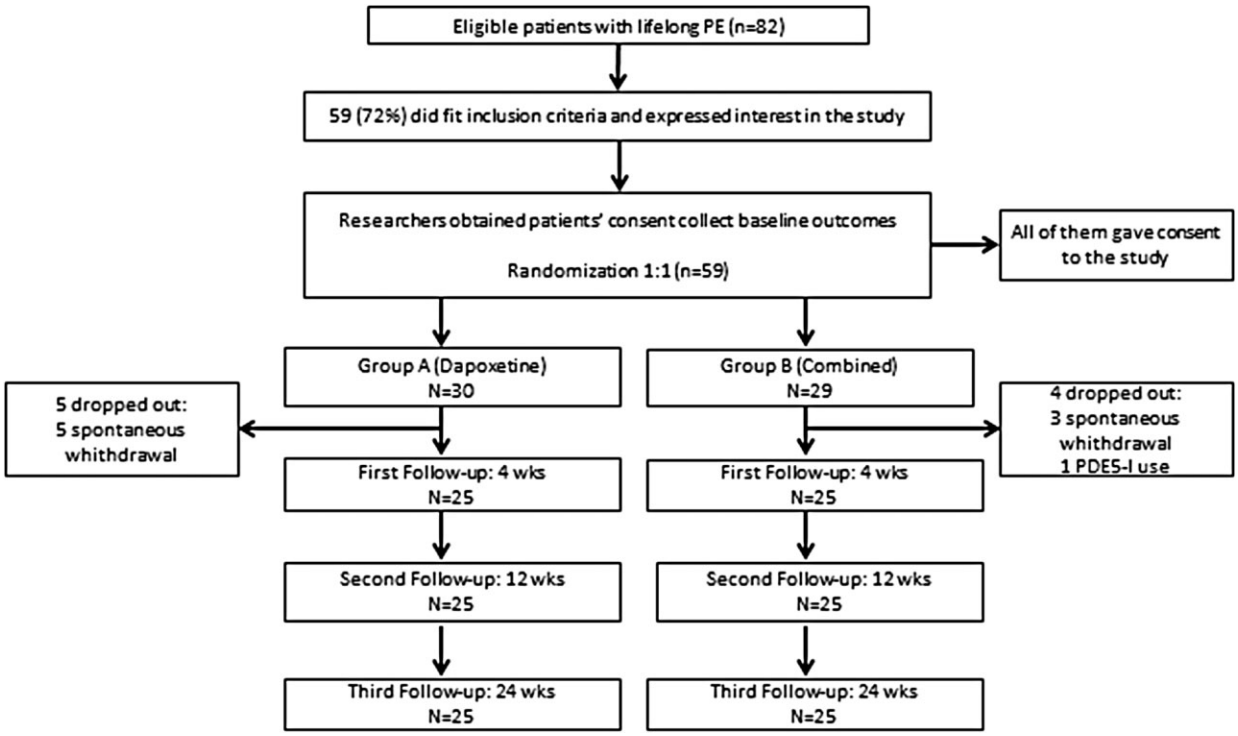

Figure 1 Shows a CONSORT flow chart of participants in the study

the end of the baseline period, patients were assigned 1:1 (Figure 1) using the sealed envelope system to receive on-demand dapoxetine 30 mg alone (group A) or combined on-demand dapoxetine 30 mg and sex behavioral treatment (group B). Patients assigned to group B were received by one of our staff urologists (P.M.) trained in the field of sexual medicine and comprehensive sex behavior instructions including the stop and start technique, the squeeze technique, the identification of the point of no return, and couples counseling. In particular, patients were carefully explained the concept of the start and stop technique and its goal, namely the identification of the pre-ejaculatory response and the way to prevent it as well as the concept of the squeeze technique and its purpose, namely to prolong the physiological ejaculatory response. The couples were instructed to carry out such techniques only during masturbation for the first week and thereafter, also during sexual encounters, and that these had to be carried out at least three times a week, independently of masturbation or sexual encounters. It was explained to the couples that the exercises could be repeated several times during intercourse providing partner consent and that the end goal of such exercises was the identification of the "point of no return." They were also told that once the point of no return was achieved and recognized, efforts had to be made to try to handle it, stop it, and then resume the exercises to extend the sexual encounter. Finally, great efforts were made to identify potential sources of couples' conflicts and try to address them. This sexual behavior counseling session was conducted face to face with the couple and lasted a mean of 90 min at first consultation. At the end, a short leaflet illustrating what had been discussed in the session was given to each couple.

In both groups, dapoxetine had to be taken 2–3 hours before engaging in sexual intercourse, according to the Summary of Product characteristics, and the couple had to record the IELT and the treatment-emergent adverse events (TEAEs) at each intercourse session. Follow-up visits were scheduled at 4, 12, and 24 weeks. All visits were carried out by one of the research team (P.M.) who, at each visit, recorded the mean IELT, the TEAEs, and the PEDT scores. In addition, at each follow-up visit, the outcome of sexual behavior treatment was discussed with those couples receiving it, and further instructions and explanations were provided if requested.

Table 1 Patients' baseline demographic and clinical characteristics

Variables	Group A (n = 25)	Group B (n = 25)	*P* value
Age (years)	34.16 ± 11.43	34.44 ± 13.22	0.932
Blood pressure (mm Hg):			
Systolic	122.40 ± 9.37	121.28 ± 9.19	0.718
Diastolic	77.40 ± 5.23	76.60 ± 6.31	0.915
Heart rate (bpm)	74.44 ± 8.17	72.64 ± 10.60	0.532
PEDT (score)	20.40 ± 2.77	19.56 ± 1.80	0.231
IIEF-5 (score)	24.28 ± 0.68	24.20 ± 0.71	0.703
Mean IELT (sec)	85.0 ± 34.5	92.0 ± 33.6	0.451

All variable data are expressed as mean ± standard deviation (SD)

The study was approved by the Ethical Committee of both participating Institutions, and all patients were made to sign and give their informed written consent to be enrolled.

Statistical Analysis

Based upon previous findings [15], sample size was calculated to test the hypothesis of combined treatment providing a 68-second increase in mean IELT over dapoxetine alone. To detect such differences with a 90% study power and a 5% significance level, a total of six patients per arm were required. Eventually, 25 patients per arm were enrolled.

Continuous data are reported as mean ± standard deviations (SDs) and were analyzed by the Student's *t*-test for paired data. Differences in rates were assessed by the Fisher's exact test. Statistical analysis was carried out using commercially available software (MedCalc version 11.1.0.0; MedCalc Software bvba, Ostend, Belgium). Significance was set at $P < 0.05$.

Results

Baseline demographic and clinical characteristics were similar across the two groups (Table 1). Overall, the dropout rate was 16.6% for group A (100% spontaneous withdrawal) and 13.79% for the group B (25% due to concomitant PDE5-I use, 75% spontaneous withdrawal).

Table 2 summarizes intra and intergroup changes over the study period in the main study end points, namely PEDT score and mean IELT. Both groups experienced a statistically significant reduction in mean PEDT score over time (group A, baseline 20.40 ± 2.77 vs. 24 weeks 14.68 ± 2.78, $P < 0.0001$; group B baseline 19.56 ± 1.80 vs. 24 weeks 7.92 ± 1.50, $P < 0.0001$). Patients in group B however experienced a significantly ($P < 0.0001$) greater reduction in mean PEDT score than those in group A, already reaching a statistical significance at 4-week evaluation (group A 18.16 ± 2.51 vs. group B 16.0 ± 1.96, *P* 0.0024). Interestingly, although all patients in group A experienced a significant reduction in their PEDT score, none reached a PEDT score ≤8 (absence of PE) at 24-week evaluation. Conversely, as much as 80% (20/25) of the patients in group B reached a PEDT score ≤8 at 24-week evaluation.

Both groups experienced an increase in mean IELT over the study period (group A, baseline 85.0 ± 34.5 vs. 24 weeks 160.0 ± 36.6, $P < 0.0001$; group B, baseline 92.0 ± 33.6 vs. 24 weeks 370.7 ± 130.5, $P < 0.0001$). It is worth highlighting that in group A, after the first follow-up visit (4 weeks), no statistically significant difference was detected (baseline 85.0 ± 34.5 vs. 4 weeks 84.8 ± 14.2, *P* 0.979). Furthermore, patients in group B experienced a significantly greater increase in mean IELT ($P < 0.0001$) than those in group A, and this difference was already evident at the 4-week evaluation.

Table 3 lists TEAEs occurring during study period. Nausea was the most frequently reported AE (group A 8%, group B 12%), followed by headache (both groups 4%). No significant difference

Table 2 Changes in PEDT score and mean IELT over the study period

PEDT score	Baseline	4 weeks	12 weeks	24 weeks	*P* value
Group A	20.40 ± 2.77	18.16 ± 2.51	15.88 ± 1.97	14.68 ± 2.78	<0.0001
Group B	19.56 ± 1.80	16.0 ± 1.96	11.96 ± 2.21	7.92 ± 1.50	<0.0001
	0.231	0.0024	<0.0001	<0.0001	
Mean IELT	**Baseline**	**4 weeks**	**12 weeks**	**24 weeks**	***P* value**
Group A	85.0 ± 34.5	84.8 ± 14.2	130.7 ± 24.2	160.0 ± 36.6	<0.0001*
Group B	92.0 ± 33.6	137.9 ± 48.4	232.7 ± 81.3	370.7 ± 130.5	<0.0001
	0.451	<0.0001	<0.0001	<0.0001	

All variable data are expressed as mean ± standard deviation (SD)
*Group A, baseline vs. 4 weeks: *P* = 0.979

Table 3 Treatment-emergent adverse events occurring during study period

Event	Group A (n = 25)	Group B (n = 25)
Nausea, n (%)	2 (8%)	3 (12%)
Headache, n (%)	1 (4%)	1 (4%)
Palpitation, n (%)	1 (4%)	0
Overall, n (%)	**4 (16%)**	**4 (16%)**

Bold values represent the total number of patients reporting a side effect.

between groups in the overall incidence of TEAEs nor in the incidence of each adverse event was noted.

Discussion

To our knowledge, this is the very first study addressing the efficacy of combined dapoxetine and sex behavioral treatment in lifelong PE patients. The efficacy and safety of dapoxetine in treating PE are well established [6,11,18,19]. In the present study, the outcome of patients who received dapoxetine alone was in line with that reported in literature as it involved a mean 45- and 75-second (statistically significant) increase in baseline IELT at 12- and 24-week evaluation, respectively, with a 16% rate of TEAEs resolving spontaneously within 24 hours. The addition of sex behavioral treatment to dapoxetine resulted into a further mean 102- and 210-second (statistically significant) increase in baseline IELT over dapoxetine alone at 12- and 24-week evaluation, respectively, with the same rate (16%) of TEAEs resolving spontaneously within 24 hours.

This first interesting observation arising from our study, namely that combined dapoxetine and sex behavioral treatment are more effective than dapoxetine alone, is in line with previous studies that compared combined pharmacological and sex behavioral treatment with pharmacological treatment alone [14–16]. One study [16] showed that combined citalopram and sex behavioral treatment significantly improved IELT (RR [risk ratio] 0.52, 95% CI 0.34–0.78) over citalopram or sex behavioral treatment alone. Tang et al. [14] demonstrated that combined sildenafil and sex behavioral treatment provided a mean IELT increase of 61 seconds over sildenafil treatment alone. Similarly, Li et al. [15] demonstrated that combined clomipramine and 6-week sex behavioral treatment provided a mean IELT increase of 68 seconds over clomipramine treatment alone. Accordingly, our study showed that combined dapoxetine and sex behavioral treatment provided a mean IELT increase of 102 seconds over dapoxetine alone at 12 weeks and that such increase rose to 210 seconds at 24 weeks. Therefore, our study provides further evidence that the combination of sexual behavioral techniques with pharmacotherapy is superior to pharmacotherapy alone in treating PE patients [5].

Novel information coming from our study was that including sex behavioral therapy with dapoxetine provided better results than dapoxetine alone in patients with lifelong PE, a circumstance whereby sexual behavioral therapy is usually considered not effective [5]. Such assumption is mainly grounded on the Steggall et al.'s study [13] whereby patients with PE were randomized to receive paroxetine or lidocaine spray for 2 months, followed by a 9-week sex behavioral program. In the overall population, the IELT increased by 807% after the pharmacological phase and by 170% after the behavioral phase. However, in men with lifelong PE, the IELT increased by 825% after the pharmacological phase and decreased by 6% after the behavioral phase, whereas in men with acquired PE, the IELT increased by 806% after the pharmacological phase and by 348% after the behavioral phase. Based on our findings, we can confidently assume that providing dapoxetine can act positively on the dominant organic/neurobiological etiology of lifelong PE [5], and sex behavioral treatment can impact the physical and psychological control of sexual performance, thus providing better results than dapoxetine alone.

In the present study, both treatments provided a significant decrease in mean PEDT scores which correlated well with the mean increase in IELTs. Interestingly, in spite of a significant decrease in mean PEDT scores, no patients in group A reached a normal ejaculatory function (PEDT score ≤8). Conversely, this goal was obtained in as many as 80% of patients in group B. These findings provide further evidence for the synergistic effects of the two treatments in patients with lifelong PE thereby leading to a better control over ejaculation. Unfortunately, the present study was not designed to address the question of whether restoration of normal ejaculatory function can allow weaning the patient from dapoxetine. Nevertheless, at the last follow-up visit, several patients in group B reported not using dapoxetine during intercourse at all. Whether prolonged behavioral treatment could result in weaning or even discontinuing dapoxetine deserves further investigation.

Safety profile was in line with that reported in literature [20] and confirms that dapoxetine is safe when used in routine clinical practice. No serious TEAEs were reported, and all events resolved spontaneously within 24 hours after taking the study medication.

There are a several limitations to the present study that must be acknowledged however. Firstly, the study design was not blinded, and the study sample was limited in size. Furthermore, a group receiving sex behavioral treatment alone, which would probably have provided more information on the role of such treatment in men with lifelong PE, is lacking. Another limitation is the absence of group crossover which would have probably led to a better understanding of the role of each treatment, both pharmacological and behavioral, in the setting of a combined treatment.

Conclusions

In patients with lifelong PE, the combination of on-demand dapoxetine 30 mg and sex behavioral treatment proved to be more effective than on-demand dapoxetine 30 mg alone in increasing IELT and decreasing PEDT scores. Restoration of normal ejaculatory function in those patients treated with combined therapy alone confirms the synergistic effects of the two treatments in patients with lifelong PE leading to better overall control over ejaculation.

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