ORIGINAL ARTICLE

Randomized Clinical Trial Between Fluoxetine and Dapoxetine for Premature Ejaculation and Its Effect on Marital Relationship.

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ABSTRACT

INTRODUCTION: Premature ejaculation(PE) decreases sexual pleasure and quality of life, and both Fluoxetine and Dapoxetine were used in PE therapy. Dapoxetine is the first SSRI with a short half-life and fewer side effects, primarily designed for PE therapy. The aim is to evaluate and compare the effects of Fluoxetine and Dapoxetine on PE symptoms and marital satisfaction. **MATERIALS AND METHODS:** 44 participants aged between 18 and 64 with a PEDT score of ≥9 from Hospital USM's Primary-Care-Clinic, Kelantan Malaysia were selected and randomized into two groups: Fluoxetine(FG) and Dapoxetine Group(DG), and administered for 8 weeks with either regular Fluoxetine(20mg) or Dapoxetine (30mg) on-demand at least once a week. Premature Ejaculation Diagnostics Tool(PEDT) score was used to assess PE symptoms and Dyadic Satisfaction-Dyadic Adjustment Scale (DS-DAS) used to evaluate marital satisfaction at baseline and the 8th week. **RESULT:** 22 and 21 participants in FG and DG completed the study. For both groups, PEDT scores decreased substantially [from 11.41 to 5.45(P<0.001) among FG, from 13.43 to 3.10(P<0.001) among DG]. After adjustment of the baseline PEDT score, PEDT scores in DG(6.03 vs 2.49, P<0.001) were lower at the 8th week. All groups showed significantly improved DS-DAS scores [from 34.50 to 40.68(P<0.001) in FG, from 36.57 to 44.33(P<0.001) in DG]. No marked difference in DS-DAS was scored after adjustment of the baseline DS-DAS score(41.13 vs 43.86, P=0.055) at the end of the assessment. **CONCLUSION:** Treatment of PE with either Fluoxetine or Dapoxetine decreases PE symptoms and increases marital satisfaction.

KEYWORDS: Premature ejaculation, Dapoxetine, Fluoxetine

INTRODUCTION

Premature ejaculation (PE) is the most common male sexual dysfunction, resulting in reduced sexual satisfaction and quality of life for men and partners.[1,2] Strong association between PE and impaired quality of life warrants recognition of PE as a significant public health issue.[3]

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Prevalence of PE among men between the age of 18 to 70 years old was reported to be 22.7% [4] while the prevalence of PE was 31% [5] and 20.3%[6] in the Asia-Pacific region and Malaysia respectively. Despite these figures, PE is still considered to be under-detected and under-treated as only 9% of men with PE seek consultation.[7,8]

Current evidence postulates that PE is a neurobiological phenomenon.[9] The process of ejaculation is centrally regulated by inter-connected cerebral sensory areas and motor centres involving a range of neurotransmitters including serotonin, dopamine, and oxytocin.[10] Serotonin and specific serotonin receptor subtypes have been identified to play a key role in ejaculation that involves the process of delaying ejaculation.[11]

It has been suggested that PE may be related to the presence of low synaptic levels of serotonin in regions of the central nervous system that modulate ejaculation, possibly because of variations in serotonin receptor sensitivity.[12]

For many years, selective serotonin reuptake inhibitors (SSRIs) have been proven to be an effective treatment for PE.[10] SSRIs such as Paroxetine, Sertraline, and Fluoxetine were originally developed to treat depression and other psychiatric disorders. These drugs are currently used widely as off- label treatment for PE.[13] Daily long-acting SSRI Fluoxetine is regarded as an effective treatment for PE [14] and is widely used as an off-label treatment of PE. However, Fluoxetine increases the risk of adverse effects such as neurological issues, dermatological reactions, anticholinergic side effects, bodyweight changes, drugs reaction, and sexual side effects such as erectile dysfunction (ED) and loss of libido.[15]

Recently, with the new era of short-acting SSRIs, Dapoxetine was specially developed for the treatment of PE with on-demand dosing to minimize the incidence of side effects with regular dosing of daily long-acting SSRIs.[16] Several trials have shown its effectiveness and it is well tolerated by patients.[16] This study aimed to determine and compare the effect of both medications in the treatment of PE in terms of changes in PE symptoms and marital satisfaction. We hypothesize that both types of medications will result in an improvement of PE symptoms and marital satisfaction equally.

MATERIALS AND METHODS

Participants

This open-labelled, randomized controlled trial was conducted from July 2013 until June 2015 involving patients from the Primary Care Clinic of Hospital USM, Kelantan, Malaysia. The clinic is a tertiary referral centre for the treatment of PE and receives patients from the East Coast of Peninsular Malaysia. Men with PE who attended the clinic during the recruitment period were included in this study. Inclusion criteria were those aged between 18 and 64 years old, married for at least 6 months, frequency of intercourse of at least once per week, and who had a PEDT score of at least 9 and above. Patients who were on SSRIs or had contraindication for SSRIs [17] were excluded.

Randomization and Blinding

Eligible participants were randomly allocated to either the Fluoxetine group(FG) or the Dapoxetine group(DG) after completing an informed consent. Block randomization sequences were generated using Statistical Package for Social Science software (SPSS) Version 22. Concealment and allocation were done using sealed envelopes. Randomization sequences were executed as generated with no modification or adaptation. No blinding procedure was applied in this study.

Sample Size

The largest sample size was obtained using a sample size calculation for comparison of PEDT between FG and DG (two independent means). With a type, I error of 5%, a type II error of 80%, a standard deviation of PEDT score of 4.4[18], and a clinically important difference of 4, the minimum sample size was 20 participants per group. After considering a 10% non-response rate, the calculated sample size was 22 participants per group.

Investigational Products

Both types of drugs were registered and licensed under the Ministry of Health (MOH) Malaysia (Tablet Fluoxetine HCL 20mg (FDA- 1977): MAL 08010743AC, Tablet Dapoxetine HCL 30mg (FDA- 2004): MAL 20102027AR, Tablet Dapoxetine HCL 60mg (FDA- 2004): MAL 20102028AR).

Fluoxetine Group (FG) Intervention

During recruitment, participants in FG have given the Dyadic Satisfaction-Dyadic Adjustment Scale(DS-DAS) questionnaire for the assessment of marital satisfaction score following obtaining informed consent. The participants have been prescribed a tablet of Fluoxetine (20mg) daily regularly for up to 8 weeks. At the 4th week, compliance with medication and side effects were assessed. Also, at the end of the 8th week, PEDT and DS-DAS scores were measured again. Any participants taking less than 80% of their prescribed medication during the period were considered non-compliant.

Dapoxetine Group (DG) Intervention

During recruitment, participants in DG were given the DS-DAS questionnaire for the assessment of marital satisfaction scores. They were prescribed with on-demand one tablet of Dapoxetine (30mg) that need to be taken at least once a week up to 8 weeks. Dapoxetine needs to be taken between one to three hours before performing sexual intercourse with a full glass of water.[17] At the 4th and 8th weeks, compliance with the medication and side effects were assessed. At the end of the

8th week, PEDT and DS-DAS scores were re-measured. Any participants taking less than 80% of their prescribed medication during the period were considered non-compliant.

Main Outcome Measures

The primary outcome was determined by changes in the PEDT score assessed by the PEDT questionnaire and the DS -DAS score assessed by the DS-DAS questionnaire. Within-group changes of PEDT and DS-DAS scores were determined within each group from baseline at enrolment to completion, 8 weeks after initiation of the intervention. Between groups differences of PEDT and DS-DAS scores were compared at 8 weeks.

PEDT is a brief, multi-dimensional validated instrument devised for the diagnosis of PE.[20] The 5- item question measures the salient issues regarding control, frequency, minimal sexual stimulation, distress, and interpersonal difficulty that capture the essence of the DSM-5-TR definition of PE.[20] A scoring system for diagnosing PE was developed: no-PE (≤8), 'possible PE'[11, 21], and PE (≥11). Responses to each of the 5–items are based on a rating scale from zero to four; they are summed to yield a total PEDT score that can range from 0 to 25.

The development and validation of this PEDT have resulted in a new, friendly, and brief questionnaire for implementing in clinical trials to facilitate the diagnosis of PE.[20] The questionnaire has been shown to have an Internal Consistency Cronbach Alpha of 0.88[20] which demonstrates that it has good reliability. The questionnaire was translated to the Malay language by a research team from Universiti Sains Malaysia with a satisfactory construct validity and internal consistency reliability (Cronbach alpha) of 0.86.[22]

DS-DAS is a 10-item questionnaire that specifically covers marital satisfaction. It is regarded as a simple, brief, and user-friendly questionnaire. A higher score indicates higher marital satisfaction The translation to Malay language and its validation was published in 2009 with internal consistency reliability (Cronbach alpha) of 0.7.[23]

Ethical Consideration

The patients were informed regarding the indication of medication, dosages, and common adverse events related to Fluoxetine and Dapoxetine medication before obtaining informed consent. Patients were also given a comprehensive explanation regarding the proposed treatment involved and the nature of the therapy. A summary of this information was presented in a written form. They were given adequate time to consider before giving their decision to participate in the study. Ethical permission was obtained from the Human Research Ethics Committee of the Universiti Sains Malaysia [Ref: USMKK/PPP/JEPeM [264.3(15)].

Statistical Analysis

Data entry and statistical analysis were done using SPSS software version 22.0 (SPSS inc. Chicago). Numerical variables were expressed as means and standard deviation (SD) or median and interquartile range (IQR), whereas categorical variables were presented as frequencies and percentages. Baseline characteristics were compared using an independent t-test or the Mann Whitney test for numerical variables; the Chi-square test or Fisher's exact test were used for categorical variables.

Changes of PEDT and DS-DAS scores within FG and DG from baseline to 8-weeks were made using a paired t-test. Comparison of post-intervention PEDT and DS-DAS scores were made using a one-way analysis of covariance (One way ANCOVA)[24], adjusting the baseline of PEDT and DS-DAS score.

In this study, the participants were analysed based on their assigned group; the study included only participants who completed the treatment originally allocated (per-protocol analysis). List-wise deletion of missing data was applied. The level of statistical significance was set at 0.05.

RESULTS

The total number of patients screened between mid of July 2014 until the end of April 2015 was 168. Only 52 fulfilled the study criteria, and 44 patients consented to participate in this study. All 44 participants were randomized and allocated into either the FG or the DG group. Figure 1 illustrates the flow of study participants from recruitment to the end of this study.

All 22 participants within FG and 21 out of 22 participants within DG completed this study. One of the participants from DG was excluded from the study after visit 1 because of non-compliance (retention rate was 97.7%). There were no serious adverse events reported by study participants. All the physical examinations and vital signs were within normal limits.

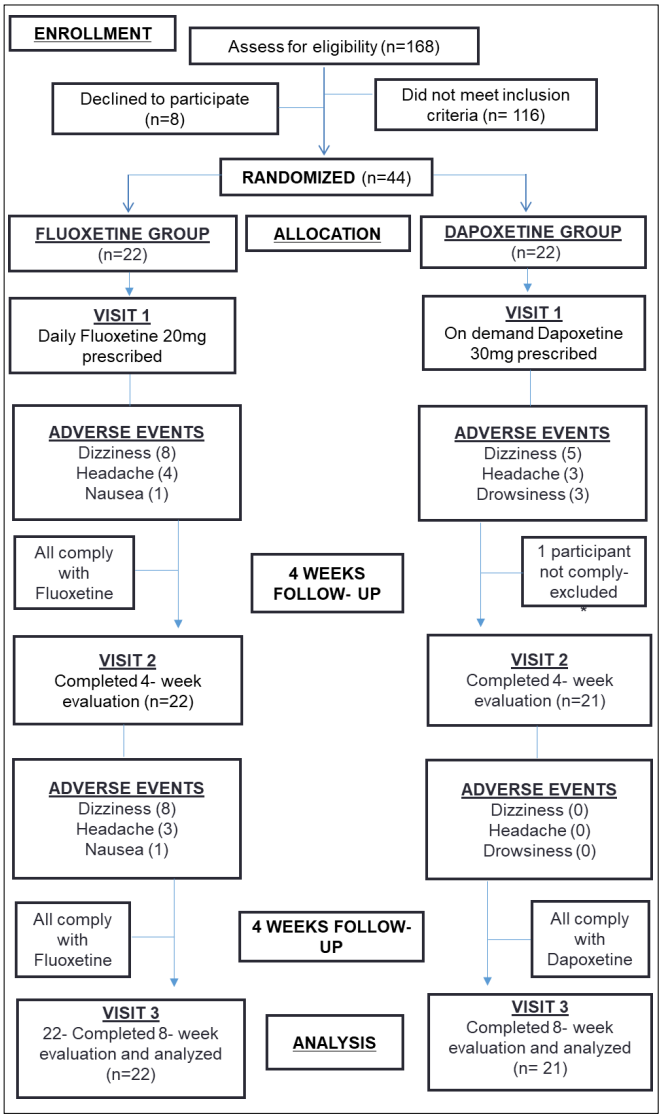

Figure 1: Study Participant Flow Chart (Consort Flow Chart)

The common minor adverse event experienced by 13 participants in FG was based on the frequency of dizziness, headache, and nausea. However, the participants were still keen to continue the medication. The symptoms were experienced during the first two weeks, and they reduced subsequently in severity by subsequent doses but persisted until the end of the study for the majority of study participants. For the DG, 11 participants experienced minor adverse events including dizziness, headache, and drowsiness mostly after the first dose. The symptoms reduced and almost disappeared after taking subsequent dosages of Dapoxetine. At the end of the study, none of the participants had any side effects.

DISCUSSIONS

PE is related to lower levels of serotonin concentration, and men with PE may have decreased levels of serotonin.[25,26] Serotonergic pathways are involved in central inhibitory control of ejaculation,[27] and the reduction of serotonin levels correlate well with a shorter ejaculatory response.[13] Serotonin is considered to be the key inhibitory neurotransmitter involved in the control of ejaculation. The synaptic cleft serotonin is regulated by a transporter re-uptake system and several auto-receptors. Generally, the SSRI's inhibit the serotonin transporter system, increasing levels of serotonin in the synaptic cleft.[26]

In recent years, the long-acting SSRI Fluoxetine has been used as the first-line treatment in Malaysia for the treatment of PE as an off-label medication with proven efficacy. Fluoxetine can be effective as a treatment of PE with a minimal dose of 20 mg daily.[28] A double-blind placebo-controlled study revealed that Fluoxetine demonstrated a 7-fold increment of ejaculatory interval 1 week after initiation.[14]

Table 1: Sociodemographic characteristics of study participants

Characteristics	Group		p-value
	Fluoxetine (n=22)	Dapoxetine (n=21)	
Age (years)	46.0 (9.13)	39.8 (8.88)	0.031[a]
Race			
Malay	21 (50.0)	21 (50.0)	>0.95[b]
Non- Malay	1 (100.0)	0 (0.0)	
Duration-marriage (years)	19.5 (18.00)	10.0 (19.0)	0.063[d]
Education Level			
SPM	14 (53.8)	12 (46.2)	0.663[c]
University/ college	8 (47.1)	9 (52.9)	
Occupational status			
Self- employed	20 (51.3)	19 (48.7)	>0.95[b]
Pensioner	2 (50.0)	2 (50.0)	
Smoker			
Yes	4 (40.0)	6 (60.0)	0.488[b]
No	18 (54.5)	15 (45.5)	
Diabetes Mellitus			
Yes	8 (80.0)	2 (20.0)	0.069[b]
No	14 (42.4)	19 (57.6)	
Number of sexual intercourse (per week)			
>10 times	2 (28.6)	5 (71.4)	0.205[b]
6-10 times	8 (42.1)	11 (57.9)	
2-5 times	10 (71.4)	4 (28.6)	
once	2 (66.7)	1 (33.3)	

Data were described as mean (SD) for age and median (IQR) for the duration of the marriage. Categorical variables were described as frequency and %.
[a]Independent sample t-test
[b]Fisher Exact test
[c]c square test
[d]Mann-Whitney test

Table 2: Changes in PEDT Score within Fluoxetine and Dapoxetine group

	Measurement, mean (SD)		p-value*
	Baseline	**Post Intervention**	
Fluoxetine, n=22	11.41 (2.72)	5.45 (4.11)	<0.001
Dapoxetine, n=21	13.43 (3.34`)	3.10 (2.66)	<0.001

Changes in DS-DAS Score within Fluoxetine and Dapoxetine group

Group	Measurement, mean (SD)		p-value*
	Baseline	**Post Intervention**	
Fluoxetine, n=22	34.50 (6.12)	40.68 (4.83)	<0.001
Dapoxetine, n=21	36.57 (5.74)	44.33 (5.41)	<0.001

*Paired t-test

In this study, we observed a high retention rate (97.7%) mainly because all of these study participants participated voluntarily and lived near the trial centre. Participants in FG were observed to have an older age. We did not treat age as one of the potential confounders in the statistical analysis since a previous study reported no significant association between age and PE.[6]

In this study, we observed significant improvement related to premature ejaculation status and marital satisfaction with Fluoxetine. The beneficial effect of Fluoxetine on PE can be explained by an enhanced serotonin neurotransmitter resulting from several adaptive processes.[29] This finding is consistent with the study of McMahon *et.al* in 2007 who reported that Fluoxetine is an effective treatment of PE with doses as low as 20 mg daily.[28] Another study by Hatzimouratidis *et.al* in 2010 also demonstrated that daily administration of the long-acting SSRI Fluoxetine was linked with superior fold increases in intravaginal ejaculatory latency time (IELT) compared to on-demand SSRIs.[13]

Table 3: Comparison of PEDT Score post-intervention

Group	n	PEDT Score Post-Intervention		F-stats (df)	p-value
		Adj.mean (95% CI)[a]	**Adj.mean diff (95% CI)[b]**		
Fluoxetine	22	6.03 (4.69, 7.36)	3.54 (1.57, 5.52)	13.18 (1,40)	0.001
Dapoxetine	21	2.49 (1.11, 3.86)			

[a]Adjusted mean using ANCOVA for baseline PEDT Score
[b]Bonferroni Method of adjustment for 95% CI of mean diference

A double-blind placebo-controlled study of Fluoxetine showed a 7-fold increment of the ejaculatory interval 1 week after treatment, and it was concluded that Fluoxetine is a safe and effective treatment for PE.[14] Fluoxetine was also found to be better than Tricyclic antidepressant Clomipramine in terms of tolerability of adverse effects.[30] Unlike other antidepressants that can

Table 4: Comparison of DS-DAS Score post-intervention

Group	n	DS-DAS Score Post Intervention		F-stats (df)	p-value
		Adj. mean (95% CI)[a]	**Adj. mean diff (95%**		
Fluoxetine	22	41.13 (39.20, 43.06)	-2.73 (-5.51, 0.056)	3.92 (1,40)	0.055
Dapoxetine	21	43.86 (41.88, 45.84)			

[a]Adjusted mean using ANCOVA for baseline DS-DAS Score
[b]Bonferroni Method of adjustment for 95% CI of mean difference

Similarly, we also observed a significant improvement in both premature ejaculation status and marital satisfaction score with Dapoxetine. Dapoxetine is the only SSRI with a short half-life specifically formulated for the treatment of PE.[16] The beneficial effect of Dapoxetine on PE can be explained by the demonstration of rapid absorption and higher elimination of serotonin neuro- transmitter with minimal accumulation at pre-synaptic cleft with extensively metabolized by multiple enzymes. It is well absorbed and highly eliminated faster than other types of long-acting SSRI's.[32]

Our finding is consistent with the findings by Hellstrom in 2009 who reported that Dapoxetine has demonstrated efficacy and safety in five large, randomized, placebo-controlled phase III clinical trials by significantly prolonging IELT. Participants receiving Dapoxetine have been reported to show improvements in all other measures of PE including perceived control over ejaculation, satisfaction with sexual intercourse, personal distress related to PE, interpersonal difficulty related to PE, and overall impression of change in PE severity. The study also revealed that Dapoxetine is generally well-tolerated, and the discontinuation rate was low (around 1.7 to 5.3%).[25] A more recent study done in 2016 by Verze *et al* also demonstrated

Dapoxetine has significantly better safety profiles in mood and related adverse events, neurocognitive related effects, urogenital system, and sexual function compared to the alternate oral therapy group in the study population.[33] Our findings are also consistent with the study conducted by McMahon *et al* in 2011. This study revealed that average IELT increased from baseline to a significantly greater extent with Dapoxetine 30 and 60 mg versus placebo post 12 weeks of intervention; therefore they concluded that Dapoxetine significantly prolonged IELT with improvement in all PE parameters and was generally tolerated well.[34]

A post-marketing observational study by Mirone *et.al* in 2014 revealed that Dapoxetine for treatment of PE has a good safety profile and low prevalence of treatment-emergent adverse events compared to Clomipramine, Paroxetine, Fluoxetine, Sertraline, topical drugs, condoms, and behavioural counselling.[35] Severe adverse events like syncope and major cardiovascular adverse events were not reported from this study. Another study by Sangkum *et.al* in 2013 revealed Dapoxetine is a short-acting SSRI specifically designed for on-demand use and demonstrated clinical efficacy and a favourable side effect profile, and currently, it is the only oral drug of choice for on-demand treatment of PE.[36]

This study suggests that both Fluoxetine and Dapoxetine significantly improved PE parameter status after 8-weeks with greater magnitudes of changes in DG for improving PE parameters. From this current study, however, we did not observe any significant differences in DS-DAS score between the two groups at the end of our study. This study demonstrated that both Fluoxetine and Dapoxetine improved marital satisfaction with comparable outcomes in both groups. Our findings are comparable with one recent randomized controlled trial study done in 2014 involving 150 participants that compared short-acting SSRI Dapoxetine and a long-acting SRRI (i.e. Paroxetine). The study reported that both medications are effective agents in the treatment of PE.[37] They concluded that an on-demand low dose of 30 mg Dapoxetine is no more effective than a daily low dose Paroxetine (20 mg). The study also demonstrated that on-demand Dapoxetine (60 mg) taken 1 to 3 hours before sexual intercourse is a very effective agent that produces a greater increase in IELT for men with PE compared to Dapoxetine (30 mg) and daily Paroxetine (20 mg). For this present study, we only compared the low dose of Fluoxetine and the low dose of Dapoxetine without incrementing for both drugs. In clinical practice, the incrementing dosage will depend on each patient's response.

Several limitations were identified in this study. The study involved men with PE who attended our tertiary referral clinic and volunteered to participate. The majority of patients were Malays, and therefore the study participants do not represent the entire Malaysian population, which consists of a multi-racial community. The treatment of Fluoxetine ideally is titrated up to 40 mg/day as the maximum dose; for Dapoxetine, the maximum dosage is 60 mg on-demand if participants do not respond with a lower dose of 30 mg of baseline drug. However, in this study, we only used a continuous low dose of Fluoxetine and Dapoxetine.

More randomized controlled trials comparing the treatment of PE are required to investigate the effects of different types of SSRI approaches for PE patients. Long-term studies are needed to measure the lasting effects of the intervention for PE's patients and to determine which groups of patients benefit most from the treatment programme. This study was conducted in a tertiary centre in which all patients were managed by medical officers and respective physicians. In the future, further studies should be conducted at government health clinics to obtain a proportion that represents the overall population with PE. Future research should be conducted regarding cost analysis to identify the most cost-effective health care for PE treatment.

CONCLUSIONS

Our study has provided additional data supporting the remarkable benefits of treatment of PE by both Fluoxetine and Dapoxetine treatments. Eight weeks of intervention resulted in significant improvement in PEDT and DS-DAS scores for the men with PE for both groups. Better improvement in PE symptoms was observed with Dapoxetine treatment with no difference in marital satisfaction score between the two groups at the end of this study. We concluded that both Fluoxetine and Dapoxetine can be used in the treatment

of PE with proven effectiveness to improved PE parameters and marital satisfaction among men with PE.

CONFLICT OF INTEREST

None.

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