Dapoxetine for the management of premature ejaculation

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Summary

Premature ejaculation is the most prevalent male sexual disorder and is more common in South Asia. Bangladesh is no exception. Premature ejaculation causes dissatisfaction in the relationship, frustration for the patient and partner as well as reason of marital failure. Since 1970s sex therapy was the mode of treatment for premature ejaculation. Now treatment with drugs also seems effective. Now a days dapoxetine is used in Bangladesh for the treatment of premature ejaculation. The aim of the study was to determine the efficacy and tolerability of dapoxetine in patients with premature ejaculation. It was a prospective study conducted in private chamber of Dhaka city during the period of March 2016 to February 2017. A total of 60 patients within 21 to 75 years were enrolled in the study according to criteria of International Society for Sexual Medicine (ISSM). We determined the efficacy of dapoxetine 30 mg/day for 12 weeks. The primary endpoint was intra vaginal ejaculatory latency time (IELT) measured by stopwatch. Safety and tolerability were assessed. All analysis was done on an intention-to-treat basis. The results showed that, dapoxetine significantly prolonged IELT ($p<0.001$) after 12 weeks. After treatment of 1st, 4th ,8th week mean IELT were 1.71 (SD±0.50) minutes, 2.36 (±0.46) minutes and 2.98 (±0.66) minutes respectively. At the end of 12th week 3.89 (±0.87) minutes was evaluated. Common adverse effects were observed as nausea (11.0%), diarrhoea (3.5%), headache (5.6%), dizziness (5.8%), insomnia (2.1%) and backache (1.8%). So from this study it could be said that, dapoxetine was an effective and generally well tolerated treatment for men with premature ejaculation.

Introduction

Premature ejaculation (PE) is a common male sexual disorder prevalent in all parts of the world. Some men who complain of PE may have begun their sex life as an in-experienced and immature, with difficulty in holding back ejaculation until the phase of ejaculatory inevitability. The problem with PE is that, they do have orgasm but the timing is short. This early ejaculation may results partner's dissatisfaction, annoyance, lack of intimacy, distress and may lead up to separation.[1] According to International Society of Sexual Medicine (ISSM), PE is a male sexual dysfunction characterized by ejaculation which always occurs prior to or within about one minute of vaginal penetration from the first sexual experiences (lifelong), or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE) and the inability to delay ejaculation on all or nearly all vaginal penetrations and negative personal consequences, such as distress, bother, frustration and / or the avoidance of sexual intimacy".[2, 3]

Diagnostic and Statistical Manual for Mental Disorder on their fifth edition (DSM 5) adopted ISSM definition of PE. However, they didn't subtype PE into lifelong and acquired rather they made a uniform definition of PE. According to the criteria of DSM-5, there should be persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately one minute following vaginal penetration and before the individual wishes it. Total duration should be six months and must be experienced all or all (almost approximately 75-100%) occasions of sexual activities. There should be significant distress due to symptoms and the symptom is not due to non-sexual mental disorder or due to consequence of severe relationship distress or effect of substance use.[4]

With a general prevalence rate of between 20% to 40%, PE is the most common sexual dysfunction in men.[5-7] As the role of PE on the individual and the sexual relationship is very significant, it is important to treat patients with PE in order to improve quality of life.[8] The intra vaginal ejaculatory latency time (IELT) is defined as the time from vaginal intromission to intra vaginal ejaculation.[7] In practice the IELT is often used as a method of quantifying the response to treatment and as a standardized method of comparing treatments within clinical trials.[8]

Until recently PE was treated by behavioral techniques such as the squeeze technique and stop–start method.[8-11] There were no approved pharmacological therapies for PE prior to the use of Dapoxetine. So treatment involved the off-label use of selective serotonin reuptake inhibitors (SSRIs) and topical agents, aloneand in combination with other drugs.[12-15] Dapoxetine is a novel SSRI, which acts by potent inhibition of 5-HT transport. Dapoxetine has a short half life and a good medicine for premature ejaculation. As a short acting SSRI, Dapoxetine is probably better suited to use as daily (reference, it is basically on demand) or an on-demand treatmentfor PE.[16-18] In Bangladesh sexuality is not talked publicly. Even physicians are uncomfortable to address the issue.[19] We failed to identify study of outcome of treatment with SSRI or Dapoxetine in Bangladesh. So the objective of the study was to find out the efficacy and tolerability of Dapoxetine in patients with premature ejaculation.

Materials and methods

It was a prospective non randomized clinical trial conducted in private chamber of Dhaka city of Bangladesh during the period of March 2016 to February 2017. A total of 60 patients within 21 to 75 years of age were consecutively selected according to criteria of ISSM. But ten patients (20%) dropped out during the period of 12 weeks of our study (two were dropped out due to expectation failure with the prescribed medication, five for cost of drug and three for side effects like nausea and headache). Ultimately we enrolled 50 patients for the study. The patients with erectile dysfunction, low libido, other psychiatric disorders, alcohol, drugs or substances abuse, organic diseases (hypothyroidism or hyperthyroidism, asthma, cardiac arrhythmias, diabetes mellitus) were excluded from the study. We determined the efficacy of dapoxetine 30 mg/day for 12 weeks. The primary endpoint was intra vaginal ejaculatory latency time (IELT) measured by stopwatch. Safety and tolerability were assessed. All analysis was done on an intention-to-treat basis. All patients were married potent men in a stable relationship for at least 6 months and had an uncontrolled ejaculation within 1 min of vaginal intromission with no obvious organic cause for PE. A detailed history, including a medicaland sexual history, was recorded and a complete physical examination performed. Female partner satisfaction was not assessed during or after the study. Patients completed the International Index of Erectile Function questionnaire and IELT recorded before and after drug administration. IELT was determined by stopwatch method for every intercourse attempt. Patients received 30 mg dapoxetine once a day one hour before planned intercourse. All respondents followed up at 1st, 4th, 8th and 12th weeks' interval after initiation of treatment to observe the efficacy and side effects. Responses on the categories of socio demographic characteristics were presented as a percentage except age groups are shown as mean ± standard deviation. Descriptive results of IELT of different time periods were reported as mean and SD values. Analysis of variance (ANOVA) was used to compare the effect of

Dapoxetine on IELT on different time interval. $P < 0.05$ was accepted as a statistically significant value. The analysis was performed with the use of SPSS version 16.

Results

In the present study the average age of all the patients was 43.38 (SD±15.09) years. In occupation status, 34% were service holders and maximum income group (46%) were within range of 125-250 dollars (Table 1). Anthropometric status of the studied subjects in percentage based on their BMI found that, maximum (76%) had normal body mass index (BMI) (Figure 1). Mean Intra vaginal ejaculatory latency time (IELT) before treatment based on age group found 0.52 (±0.19) minute and it was found highest in 30 to 40 yearage group (Table 2). There was statistically significant difference among the four points of time on ejaculatory latency time. The mean ejaculatory latency time was significantly ($P < 0.001$) increased at the twelfth week from the base line and other point of time after treatment with Dapoxetine (Table 3). The time of ejaculatory latency also increased at fourth and eight week of treatment. Mean ejaculatory latency time increased from the baseline at the twelfth week of intervention with the ages (Figure 2). The mean ejaculatory latency time increased from base line to twelfth week of treatment based on age group. The drug Dapoxetine did not significantly increase the ejaculatory latency time of participants of 61-75 years age group. The mean ejaculatory latency time increased (1.59 min) from the base line was lowest in the 61-75 years age group. The latency time increased higher for 51-60 years age group (2.78 min) compare to other groups (Table 4). The common adverse effects were nausea (11%), dizziness (5.8%) and headache (5.6%) where as the lowest adverse effect was backache (1.8%) (Table 5).

Table 1: Socio-demographic characteristics of the studied sample (n=50)

| Demographic variables	Frequency	Percentage (%)
Age group		
21-30 years	11	22
31-40 years	14	28
41-50 years	9	18
51-60 years	7	14
61-75 years	9	18
Mean ± SD 43.38±15.09		
Occupation		
Farmer	7	14
Service	17	34
Business	9	18
Retired	4	8
Student	5	10
Others	8	16
Income group		
$125- $250	23	46
$251-$375	17	34
$376-$625	10	20
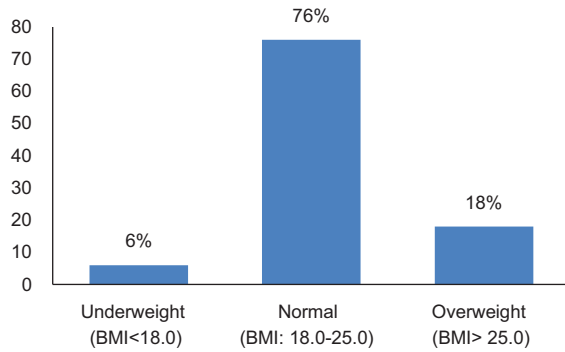
Figure 1: Anthropometric status of the studied subjects in percentage based on their BMI (n=50)

Table 2: Mean Intra vaginal ejaculatory latency time (IELT) before treatment based on age group (n=50)

Age group (years)	Mean (minutes)	Standard deviation
21-30	0.48	0.17
31-40	0.60	0.21
41-50	0.50	0.24
51-60	0.57	0.11
60-75	0.44	0.17

Table 3: Mean ejaculatory latency time of the respondents on different time interval after the treatment with dapoxetine (n=50)

Follow up time	Mean (minutes)	IELT Standard deviation	p value
First week	1.713	0.508	<0.001
Fourth week	2.364	0.464	
Eight week	2.988	0.665	
Twelfth week	3.892	0.876	
Total	2.739	1.031	
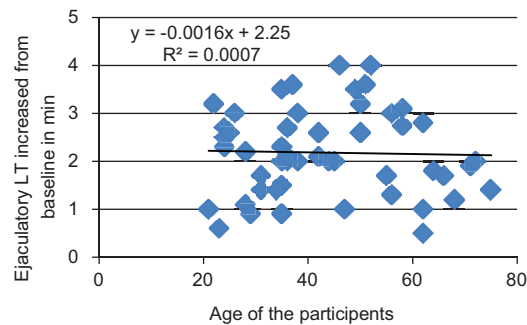
Figure 2: Scatter plot of age and ejaculatory latency time increased from baseline including all the participants (n=50)

Table 4: Mean intra vaginal ejaculatory latency time (IELT) increased from the base line up to the twelfth week of treatment based on age groups (n=50)

Age group	Number	Mean IELT increased (minute)	Standard deviation	95% CI
21-30 years	11	2.01	0.93	1.38-2.63
31-40 years	14	2.15	0.80	1.69-2.61
41-50 years	9	2.56	0.91	1.86-3.26
51-60 years	7	2.78	0.97	1.88-3.68
61-75 years	9	1.59	0.66	1.08-2.09
Total	50	2.18	0.90	1.92-2.44

CI= Confidence interval

Table 5: Adverse effects of dapoxetine among all the participants (n=50)

Adverse effect	Percentage (%)
Nausea	11
Dizziness	5.8
Headache	5.6
Diarrhoea	3.5
Insomnia	2.1
Backache	1.8

(Adverse effects were not developed in all respondents)

Discussion

Before the past decade, the major approach to treating PE was behavioral and psychotherapy, relying on such techniques as the 'start and stop' and 'squeeze' methods.[11, 20] In Bangladesh many clinicians were uncomfortable asking about sexuality.[19] Lack of skilled psychotherapists also left the clients suffer in misery. However, the application of the principles of evidence-based medicine showed that, there was little evidence to support the psychological approach and behavioral treatment. Dapoxetine gave chronically improved latencies over baseline.

Prolongation of the ejaculatory interval within few days of treatment suggested that, this acute effect was due to direct blocking of central serotonergic reuptake by dapoxetine. Ejaculation was a reflex comprising different sensory pathways, motor centers, and nerve pathways. This ejaculatory reflex had been shown to be controlled primarily by both serotonin and dopamine.[21] Among the different subtypes of 5-HT receptors, the most important ones on ejaculation were 5-HT1A, 5-HT1B, and 5-HT2C receptors.[22] The mechanism of action of dapoxetine was the inhibition of neuronal reuptake of serotonin. It was also shown to bind and inhibit the reuptake transporters of dopamine and norepinephrine.[23-24] Elimination was biphasic, with an initial half-life of approximately 1.4 hours and a terminal half-life of approximately 20 hours. The pharmacokinetics of dapoxetine metabolites, desmethyldapoxetine and dapoxetine-N-oxide were unaffected by multiple dosing.[18]

In our study, 20% of patients dropped out within 12 weeks of treatment period where as Mondaini et al. reported that, 26% dropped out after 1 month dapoxetine treatment.[23] The study showed that, the drug dapoxetine did not significantly increase the ejaculatory latency time of participants of 61-75 years age group. The mean ejaculatory latency time increased 1.59 minutes from the base line was lowest in the 61-75 years age group. Mean ejaculatory latency time increased from the baseline at the twelfth week of intervention with the ages. The latency time increased higher for 51-60 years age group (2.78 minutes) compare to other groups. Mean IELT at the baseline was 0.90 (SD±0.47) min, 0.92 (SD±0.50) min, and 0.91 (SD±0.48) min and at study end point (week 12 or final visit) was 1.75 (SD±2.21) minutes for placebo, 2.78 (SD±3.48) min for 30 mg dapoxetine and 3.32 (SD±3.68) min for 60 mg dapoxetine.[25]

Of the SSRIs, paroxetine, sertraline, fluoxetine, citalopram, and tricyclic antidepressants (clomipramine) had all been shown to be effective in the treatment of PE reported on a study comparing the relative effects of placebo and the SSRI antidepressants: fluoxetine, fluvoxamine, paroxetine and sertraline on PE.[26] Latencies were increased from a baseline of 18-29 seconds on placebo and for the fluoxetine, fluvoxamine, paroxetine and sertraline, 211, 55, 476 and 117 seconds respectively.[25] In a study the efficacy and safety of dapoxetine, paroxetine, and placebo were compared for the oral pharmacotherapy of PE.[27]

The current study showed adverse effects such as nausea, dizziness and headache were 11.0%, 5.8% and 5.6% respectively. The lowest adverse effect was backache (1.8%).In other studies side effects are dose specific. In one study by Waldinger et al, nausea was the most common adverse effect. Nausea was reported by 20.1% of patients in the 60 mg group and 8.7% of patients in the 30 mg group.[27] The adverse effects of dapoxetine were dose dependent. The other most common

adverse effects associated with dapoxetine were diarrhoea, dizziness, and headache. IELT distribution behaved positively skewed among the male healthy population and in the individual man.[26] In the above-mentioned studies, the authors did not measure geometric mean IELT. They did not provide confidence intervals of their fold-increase outcomes, which was necessary for a good impression of the potency of the drug.[28]

Conclusion

Dapoxetine is the only drug specifically formulated and licensed for PE in adult males. The unique pharmacology of dapoxetine has made it ideal for on-demand dosing, allowing great convenience and flexibility for the patient. In many studies dapoxetine 60 mg on demand was used but in present study we didn't use 60 mg dose for any of our patients. The clinical evidence indicates that dapoxetine 30 mg once daily was an efficacious and tolerable treatment for PE, leading to significant improvement of IELT. Dapoxetine is clearly a promising treatment option for PE and its use can result in great quality of life for the patient and their sexual partner. So it can be recommended that, dapoxetine is safe and clearly promising drug for premature ejaculation.

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