Research Article

On demand dapoxetine treatment in premature ejaculation: effectiveness and safety profile. A single-blind placebo controlled study from Iraq

Ali Badan Mohsen,[1] Mohammed Bassil Ismail,[2] Hasanain Farhan Hasan,[3]

[1] MBChB, Urology Department, Medical City Complex, Baghdad, Iraq.
[2] Urosurgeon, CABMS (urology) Urology Department, Medical City Complex, Baghdad, Iraq.
[3] Urosurgeon, FICMS (urology), Urology Department, Medical City Complex, Baghdad, Iraq.

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Abstract

Background: Premature ejaculation is a worldwide problem, characterised as the most common male sexual complaint. Selective serotonin reuptake inhibitors are widely used "off label" as pharmacotherapeutic agents in the treatment of premature ejaculation. Many pharmacological agents have been used for treatment with diverse results regarding effectiveness and safety.

Objectives: To test the effectiveness and safety of on-demand usage of Dapoxetine in the treatment of premature ejaculation.

Methods: Single-blind, placebo-controlled, stopwatch monitored study was conducted on 100 patients with lifelong premature ejaculation visited the outpatient clinic of urology at Ghazy Al-Hariri Teaching Hospital/Medical City Complex/Baghdad. The study covered the period from October 2010 to December 2012.Premature ejaculation was defined as intravaginal ejaculation latency time of <60 seconds in 80% or more of intercourse episodes. A total of 60 mg of dapoxetine hydrochloride was given to one group (50 patients) and placebo was supplied for the other group (50 patients). Drug or placebo was used 1-2 hours before the sexual act. Patients in both groups were followed up for 8 weeks. Our primary output was to measure the change in the intravaginal ejaculation latency time and sexual satisfaction.

Results: Ninety-one (91%) completed the whole treatment schedule. The mean intravaginal ejaculation latency time after Dapoxetine and placebo increased from 57.6 and 54.2 seconds to approximately 322.5 and 92.1 seconds, respectively ($P < 0.001$).

Sexual satisfaction was the second variable in this study and used to assess the cut-off values in definition of minimal and best clinical response to either treatment. Patients in dapoxetine group have more adverse events; however, none of these adverse events in both groups were severe enough to necessitate withdrawal from the study.

Conclusion: Dapoxetine seems to provide significantly better results in terms of intravaginal ejaculation latency time and intercourse satisfaction versus placebo. Further studies are required to draw final conclusions on the efficacy of this drug in premature ejaculation.

Key words: Premature ejaculation, dapoxetine, intravaginal ejaculation latency time.

INTRODUCTION

Over the past 20–30 years, premature ejaculation (PE) treatment paradigm, which was previously limited to behavioural psychotherapy, has expanded to include drug treatment.[1-3] Animal and human sexual psychopharmacological studies have demonstrated that serotonin,5-hydroxy-tryptamine (5-HT), and 5-HT receptors are involved in ejaculation and have confirmed a role for selective serotonin re-uptake inhibitors (SSRIs) in the treatment of PE.[4-6]

Data from The Global Study of Sexual Attitudes and Behaviors (GSSAB), an international survey investigating the attitudes, behaviours, beliefs, and sexual satisfaction of 27,500 men and women aged 40–80 years, reported the global prevalence of PE (based on subject self-reporting) to be approximately 30% across all age groups.[7,8]

In 2009, the International Society of Sexual Medicine (ISSM) produced its guidelines of the diagnosis and management of PE. It postulated an evidence-based definition of PE and defined PE as a male sexual dysfunction characterized by:

1. Ejaculation which always or nearly always occurs prior to or within about 1 minute of vaginal penetration.
2. Inability to delay ejaculation on all or nearly all vaginal penetrations.
3. Negative personal consequences, such as distress,

Corresponding Author: Mohammed Bassil Ismail, Urology Department, Medical City Complex, Baghdad, Iraq.
E mail: mohammed_albassil@yahoo.com.

bother, frustration and/or the avoidance of sexual encounters.

This definition is regarded as the most robust to date owing to its evidence-based nature and has largely replaced the previous definitions as the standard definition of PE.[9]

Dapoxetine was created by Eli Lilly and it is in phase I clinical trial as an antidepressant. However, It never worked out well as a medication for the treatment of depression and was shelved for a while before subsequently developed to treat PE.[10]

The mechanism through which dapoxetine affects premature ejaculation is still unclear. However, it is presumed that dapoxetine works by inhibiting serotonin transporter and subsequently increasing serotonin's action at pre and postsynaptic receptors.[11] Dapoxetine undergoes rapid absorption and elimination resulting in minimal accumulation and has dose-proportional pharmacokinetics, which are unaffected by multiple dosing and do not vary between ethnic groups. The pharmacokinetic profile of dapoxetine suggests that it is a good candidate for on-demand treatment of PE. [12-14]

The most common effects when taking dapoxetine are nausea, dizziness, dry mouth, headache, diarrhea, and insomnia.[15] Unlike other SSRIs used to treat depression, which have been associated with high incidences of sexual dysfunction,[16] dapoxetine is associated with low rates of sexual dysfunction. Taken as needed, dapoxetine has very mild adverse effects on loss of libido (<1%) and ED (<4%).[17]

Chronic SSRI treatment for psychiatric conditions is known to predispose patients to withdrawal symptoms if medication is suspended abruptly. The SSRI withdrawal syndrome is characterized by dizziness, headache, nausea, vomiting and diarrhoea and occasionally agitation, impaired concentration, vivid dreams, depersonalization, irritability and suicidal ideation.[18-20] In the International Study, the incidence of discontinuation syndrome was 3.0%, 1.1% and 1.3% for those continuing to take dapoxetine 30 mg, 60 mg as needed and placebo respectively, and 3.3% for those who switched from dapoxetine 60 mg as needed to placebo.[21]

This study was desigened to measure the effectivness and safety of on demand usage of dapoxetine in the treatment of PE.

METHODS

A single blind, placebo controlled clinical trial is conducted at outpatient urology clinic, Ghazi AL-Hariri Teaching Hospital/ Medical City in Baghdad over the period from October 2010 to December 2012.

Inclusion Criteria: Potent married man, who has active sexual life presenting to outpatient urology clinic at Ghazy Al-Hariri Teaching Hospital complaining of PE and proved to fulfill the definition of PE was enrolled in this study. PE was defined according to the (ISSM) as ejaculation that always or nearly always occurs before or within about 1 minute of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences such as distress, bother, frustration.[9] IVELT was calculated as the time between the start of vaginal insertion and the start of intravaginal ejaculation as being measured by a stopwatch given to the patient. Patient potential to have PE was interviewed to have his written consent to participate in the study and to explain how to measure IVELT. Each patient was instructed to fill in a diary reporting number of sexual intercourse acts and IVELT for each one over a period of 4 weeks. All patients have been instructed to withhold any drugs treating PE at least 4 weeks before starting the study. Through reading the diary, patient who reported IVELT < 60 second in ≥ 80 % of sexual intercourse attempts in 4 weeks and had at least one sexual intercourse act per a week had been considered to fulfill the criteria for being included in this study.

Exclusion criteria: They included patients with erectile dysfunction according to the International Index of Erectile Function (IIEF), an organic cause of PE, genital infections, neurological disorders, low libido, chronic depression, psychiatric or physical illness; alcohol, drugs, or substance abuse; organic illness causing limitation in use of SSRIs; use of psychotropic and antidepressant medication; and serious relationship problems with his wife at the last 6 months before the study.

Exclusion criteria were investigated through careful medical history including detailed socio-sexual history and comprehensive physical examination with essential laboratory investigations including: fasting blood glucose level, urine analysis, complete blood count, sex hormones, and prolactin levels.

Randomization to groups: Patients who fulfilled the inclusion criteria were randomized into two equal sized groups; dapoxetine group and placebo group. Patients in former group were given 60 mg dapoxetine hydrochloride while those in the later one were given placebo. Patients in both groups were unaware about the type of treatment they have been given, and they were instructed to have their drugs 1-2 hours before the sexual act.

The primary outcome: 1) Intravaginal ejaculation latency time improvement, defined as the difference between IVELT at the end of treatment period and baseline. 2) Sexual satisfaction as measured by the Premature Ejaculation Profile (PEP).[22]

Procedure: All patients underwent preliminary assessment, including IVELT and IIEF at the first visit. A stopwatch and instructions on how to measure the IVELT were also provided. Stopwatch was used to measure intravaginal ejaculation latency time in order to avoid the high variability in the clinical outcome seen by using other methods like subjective estimation, question and questionnaire for the same purpose.

Couples were also instructed not to pause during intercourse, or to have interrupted intromission and also not consume alcoholic drinks within 6 hours of sexual activity, not to use condoms or topical anesthetic cream. Furthermore, they were requested not to increase their intercourse frequency, and if intercourse took place more than once in a single session, only the first intercourse was measured. Pretreatment frequency of sexual intercourse was the mean number of attempts per week during the previous 2 months.

All patients were followed for 8 weeks, 3 visits were scheduled at the end of the first week, 4th weeks, 8th weeks. At each visit the patients have been asked to provide the diary recording of the frequency of sexual intercourse acts, and the IVELT recorded by stopwatch by the patient or his wife in each one of the acts. During these visits patient's blood pressure and heart rate were recorded, also we recorded the development of some side effects of the drugs like nausea, diarrhea, headache, dizziness and others.

Sexual satisfaction was assessed using the Premature Ejaculation Profile (PEP),[22] a validated self-administered

four-item tool that includes measures of perceived control over ejaculation, satisfaction with sexual intercourse, ejaculation-related personal distress, ejaculation-related interpersonal difficulty, each assessed on five-point response scales. Patients were also asked about their tolerance to the drug and if there were any side-effects.

Statistics: SPSS (statistical package for social science) software for windows, version 16,3. US was used to tabulate and analyse the data. T test was used to compare the difference in groups. Statistical significance was determined if P value ≤ 0.05.

RESULTS

Hundred patients were included in this study, 50 in each group. Ninety-one patients have continued the study. We have lost 9 patients: 5 from control group (10%) and 4 from Dapoxetine group (4%). **Table 1** shows some demographic features of both groups.

Both groups showed increase in IVELT after 1, 4 and 8 weeks of follow up; however the magnitude of this increase was very different. The mean IVELT at 1, 4 and 8 weeks of Dapoxetine treatment was 197.6, 301.6, 322.4 second respectively which were significantly higher than the placebo group. These changes were highly significant and amounted to 3.8, 5.8, 6.2 folds of increment compared to pretreatment IVELT at 1, 4, 8 weeks of Dapoxetine treatment respectively **table 2 and 3**.

All patients before treatment were sexually unsatisfied (100%), however after 8 weeks of treatment there was significant improvement in sexual satisfaction of Dapoxetine group in comparison with placebo group, as shown in **table 3-4**.

Table 1 : The difference in mean of selected variables between the 2 intervention groups.

		Treatment (N=46)	Placebo(N=45)	P
Age in years	Mean	32. 8 ± 8.9	31. 3 ± 7.3	0. 72 NS
	Range	18 - 55	22 - 53	
IVELT at baseline (sec)	Mean	52.3 ± 8.19	42.1 ± 12.4	0. 14 NS
	Range	35 - 56	23 - 52	
Duration of marriage in years	Mean	4	5	0. 81 NS
	Range	1 to 23	1 - 21	

Table 2: The mean change in IVELT (sec) after 1, 4 and 8 weeks of follow up period in the test treatment group compared to placebo group.

		Dapoxetine Group		Placebo group	
		Mean	Range	Mean	Range
Baseline		52 ± 8.4	35-56	42.1±12.4	23-52
After one week	Actual duration	197.6±19.1*	39-330	46.3± 21.6	25-64
	The change	145.6±26.1 †	(-13)-278	4.2±3.1	(-17)-22
After 4 weeks	Actual duration	301.6±23.5*	105-444	54.7±17.8	18-80
	The change	249.6±43.1 †	53-393	12.6±6.7	(-24)-38
After 8 week	Actual duration	322.4±26.2*	118-542	58.9±18.3	29-95
	The change	270.4±39.7 †	218-490	16.8±7.9	(-13)-53

* P (Independent samples t-test) for difference in mean change between Dapoxetine and placebo groups
† P (Paired t-test) for significance of mean change

Table (3) Increment in folds of IVELT after treatment

Group	After 1 weeks	After 4 weeks	After 8 weeks
Dapoxetine	3.8	5.8	6.2
Placebo	1.1	1.3	1.4
P (chi square)	<0.001	<0.001	<0.001

Table (4): The difference in magnitude of sexual satisfaction between Dapoxetine and placebo group.

Sexual satisfaction	Placebo		Dapoxetine	
	N	%	N	%
Unsatisfied	31	68.8	4	8.6
Average satisfaction	9	20	10	21.7
High satisfaction	5	11.2	32	69.7
Total	45	100.0	46	100.0

Table (5): Showing the numbers and percentages of side effects as reported by subjects treated with dapoxetine

Side effects (n=46)	N	%
Nausea	8	17.3
Diarrhea	3	6.5
Headache	4	8.6
Dizziness	2	4.3
Dry mouth	4	8.6
Insomnia	1	2.1

DISCUSSION

SSRIs may need days to weeks to reach a maximum steady-state concentration in order to exhibit efficacy;therefore, SSRIs are commonly used in a daily dosing schedule for the treatment of PE. In addition to the potentially desirable side-effect of delaying ejaculation, this dosing regimen for long-acting SSRIs is associated with a number of undesirable side-effects, such as decreased libido and ED.[23] An ideal compound for the treatment of PE should exhibit pharmacokinetic profiles having rapid absorption, adequate availability to establish therapeutic exposure at the target site, and rapid elimination to reduce total drug exposure and minimize the incidence of side-effects.[14]

PE is a sort of disease in which the patients should not have to chronically take potent psychoactive drugs, with long-lasting actions and debilitating side effects. Dapoxetine is a selective serotonin transport inhibitor with unique pharmacokinetic and pharmocodynamic properties that account for its clinical effects, suggesting that it is a good candidate for on-demand treatment of PE.

The current study demonstrates that dapoxetine, administered on need, will prolong the ejaculation interval. This effect was significantly superior to placebo. On-demand regimen has clearly significant clinical effect because of better compliance and less cumulative side effects.

In a study by Pryor et al (2006), the efficacy and tolerability of dapoxetine in the treatment of PE were evaluated. Men with PE (n = 2614) as defined by DSM-IV-TR criteria had an IVELT of less than or equal to 2 minutes in 75% or more intercourse episodes, were enrolled in 2 randomized, double-blind, placebo-controlled, multi-center, phase III clinical trials of identical design, preliminary results of this study demonstrated that there were significant differences between placebo and each active treatment group in mean IVELT, control over ejaculation, and satisfaction with sexual intercourse. Changes from baseline to study end point for mean IVELT were 0.90–1.75 min (placebo), 0.92–2.78 minutes (30 mg dapoxetine), and 0.91–3.32 minutes (60 mg dapoxetine). Both dapoxetine 30 mg and 60 were found to be more effective than placebo in increasing IVELT on first dose.[15]

The present study provided another significant quantitative placebo controlled evidence for the effectiveness of Dapoxetine on demand treatment in PE.

In comparison with clomipramine, In three double-blind, placebo-controlled, crossover studies, on-demand use of clomipramine (25 mg, 12 to 24 hours before intercourse) increased IVELT fourfold in PE patients,[24,25] while it is six folds for dapoxetine in our study.

Waldinger and colleagues (2004) investigated the ejaculation delay induced by on-demand treatment of paroxetine and clomipramine in a randomized, double-blind, fixed-dose study of 30 PE patients. It was found that on-demand treatment of 20 mg of paroxetine did not cause clinically relevant delay in ejaculation, but with the daily use of the same SSRI for 6 weeks, the IVELT increased significantly.[26]

In comparison with tramadol, In a double-blind, placebo-controlled study, on-demand use study, tramadol 50 mg, taken 2 hours before sexual intercourse, was associated with clinically discernible ejaculation delay with 28% of patients reporting adverse effects (including drowsiness, dependence and ED),[27,28] while tolerability of dapoxetine in our study is significant with no effect on libido.

For 5 phosphodiestrase (PDE-5) inhibitor, in a prospective randomized double-blind crossover study of 31 potent men with lifelong PE, Abdel-Hamid and associates (2001) compared the efficacy and safety of "on-demand" clomipramine, sertraline, paroxetine, sildenafil, and the pause/squeeze technique. Sildenafil was associated with a significantly higher IVELT and sexual satisfaction score than all other treatments.[29] But till now PDE-5 inhibitor mono-therapy for PE treatment has no solid foundation.[30]

In comparison with topical local applicants, the largest double-blind clinical trial of lidocaine-prilocaine cream included 42 cases and demonstrated a 5.5 fold increase in IVELT in the treatment arm. However, only 29 of 42 participants completed the study. Sixteen percent of patients reported adverse effects including penile numbness, retarded ejaculation, penile irritation, and decreased vaginal sensitivity,[31] while in our study only 4 patients did not complete the study.

PE is not a life-threatening condition, and therefore, safety should be a primary consideration in pharmacotherapy. Various doses and dosing regimens of the SSRIs and tricyclic antidepressants have been evaluated in efficacy and safety studies of PE.[32-34] At the dosages used in the management of PE, these treatments have been shown to have safety profiles that are generally appropriate to support their use.

Safety data for dapoxetine have been described by (Pryor JL, A,etl,2006).[15] The most frequent adverse events with dapoxetine 30 and 60 mg were nausea (9-20%), diarrhea (4-7%),headache (6-7%),and dizziness (3-6%). Dapoxetine is associated with low rates of sexual dysfunction. Taken as needed, dapoxetine has very mild adverse effects on loss of libido (<1%) and ED (<4%).[17] In our study side effects for dapoxetine is as follow nausea 17%,diarrhea 6%,headache 8%,dizziness 4%,dry mouth 8%,and insomnia 2%.

In our study the rates of adverse effects are fluctuated over these reported in published articles. This can be attributed to small sample size of our study.

CONCLUSION

The present study showed that, on demand treatment with 60 mg dapoxetine led to a clinically relevant ejaculation delay and sexual satisfaction. Dapoxetine seems to be a useful and well-tolerated oral treatment of PE on as-needed basis. Dapoxetine at the dosage used in the study has safety profiles in a short term period.

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