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Evaluation of Efficacy and Safety of Dapoxetine in Premature Ejaculation: A Placebo Controlled Study

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Introduction

Premature Ejaculation (PE) is a common male sex problem and incidence wise it is much commoner than erectile dysfunction with incidence in some studies being greater than 30% [1, 2]. In spite of this it does not attain enough attention of research workers. Ejaculation time (ET) may vary, but patient usually seeks medical help when it consistently becomes short at every coitus and causes distress to the couple. American Urological Association (AUA) defines PE when it "occurs sooner than desire" and causes "distress to one or both partners" [3]. For clinical assessment quantification is essential and in this case is possible by measuring Intravaginal Ejaculation Latency Time (IELT).this calculated by time period between vaginal penetration of phallus and intravaginal ejaculation. A more categorical and working definition comes from the International Society for Sexual Medicine (ISSM) which states that PE is "ejaculation that occurs prior to or within 1 minute of vaginal penetration" [4]. In our study we have taken IELT of less than 1 minute as PE. Serotonin has been found to have an inhibitory action on seminal emission/ejaculation via action on brain, brainstem, raphe nuclei and reticular formation. These observation leads to several studies which show that selective serotonin reuptake inhibitor (SSRI) achieve significant increase in IELT [5].

Dapoxetine is one of SSRI, which was conventionally used for psychiatric disorders, mainly depression. It is unique molecule because it reaches rapid plasma levels after oral intake within 1 hour. It is excreted rapidly in the urine, with plasma concentration of drug being only 4%, 24 hours after administration [6]. This unique property of the molecule has made it obvious choice for "on-demand therapy". Therefore, we directed our patients to take it on "on-demand" basis. As our protocol, patients were asked to use the drug twice weekly on an "on-demand" basis 1 hour before intercourse. Recently Dapoxetine has been tried in different European and American countries with variable success.

We have conducted a single blind placebo controlled trial evaluating the effectiveness of "on-demand" 30mg Dapoxitine in the management of Premature Ejaculation. To best of our knowledge no study has been conducted on the role of Dapoxetine in PE in Indian Urological practice.

Materials and Methods

Study Area:

The study was conducted in the Department of Urology from July 2013 to July 2015.Approval of Ethical Committee of the institute was taken and informed consent of the patients was taken before enrollment into the study.

Study Population:

The study included 20 male patients between 20-50 years of age with a satisfactory erectile function with no addiction of any form and no need of Phosphodiesterase – 5 inhibitors.

Patients with psychiatric disorders, marital disharmony, diabetes mellitus, hypertension, hepatic and renal impairment, multiple sexual partners and significant LUTS were excluded from the study.

Study Protocol:

All the patients were explained the procedure and programme. Baseline IELT score of patients were calculated in seconds over a period of 3 weeks with the help of stop -watch.

Half of the patients were given tablet Dapoxetine 30 mg twice weekly 1 hour before sexual intercourse for a period of 3 weeks and IELT score was noted. Afterwards patients were given a drug free period of 2 weeks and then again started on

placebo treatment (vitamin tablets) with a similar protocol as dapoxitine. Again IELT score was noted after 3 weeks of placebo.

Other half patients were initially started on a 3 weeks of placebo, followed by a 2 weeks interval and then a 3 weeks period of active treatment with Dapoxetine in the dose of 30mg twice weekly. Patients were blinded throughout the duration study.

Mean IELT score were calculated from the initial baseline, post Dapoxetine and post placebo administration. Repeated measure ANOVA test was used for statistical analysis. P-value of less than 0.05 was considered significant and confidence interval was set at 95%. Adverse events, if any, were noted.

Results

Baseline parameters:

After screening 40 cases for PE, finally 20 cases were included in the study after applying the inclusion and exclusion criteria. Mean age of patients was 40±15 years. All the patients were married and the mean IELT score was 34.8±15.3 seconds.

Outcome in Dapoxitine and Placebo Group:

After 3 weeks of therapy, mean IELT score of the Dapoxitine and Placebo group was 273±58 seconds and 129±57 seconds, respectively [table 1].

Table 1: Mean IELT score (in seconds) at baseline and after 3 weeks of dapoxitine and placebo therapy

Case No.	Baseline	Dapoxitine Group	Placebo Group
1	50	254	105
2	55	326	220
3	30	248	66
4	50	359	190
5	20	288	69
6	55	359	184
7	40	385	98
8	10	268	84
9	10	216	107
10	50	339	220
11	15	297	184
12	25	244	195
13	30	231	150
14	40	225	90
15	35	242	125
16	15	190	70
17	28	198	105
18	38	205	92
19	52	310	122
20	48	280	118

Repeated Measure ANOVA test revealed significant difference in IELT score at baseline and between Dapoxitine and placebo group at 3 weeks [F (2, 38) =224.3, p=<0.05].

Adverse Effects:

11 patients (55%) on dapoxitine and 4 patients (20%) on placebo experienced adverse-effects which were mild in nature and patients could easily tolerate it with little necessary medications e.g. analgesics, anti-histaminic [table 2]. None of the patients discontinued dapoxitine therapy due to side-effects.

Table 2: Frequency of adverse events in Dapoxitine and Placebo group.

Adverse Effects	Dapoxitine Group	Placebo Group
Headache	4	2
Allergic Rash	1	0
Nausea	1	1
Vomiting	1	0
Lethargy and Dizziness	2	1

Discussion

Over the past 20–30 years, the premature ejaculation (PE) treatment paradigm, previously limited to behavioural psychotherapy, has expanded to include drug treatment [7]. Animal and human sexual psychopharmacological studies have demonstrated that serotonin (5-hydroxy-tryptamine, 5-HT) and 5-HT receptors are involved in ejaculation and confirm a role SSRIs in the treatment of PE [8]. More recently, there has been increased attention paid to the psychosocial consequences of PE, its epidemiology, its etiology and its pathophysiology by clinicians and the pharmaceutical industry. The development of consensus statements by the International Consultation on Sexual Dysfunction and treatment guidelines by the ISSM has done much to standardize the management of PE [9].

Based on patient self-reporting, PE is routinely characterized as the most common male sexual complaint and has been estimated to occur in 4–39% of men in the general community. Schapiro classified PE into types A and B. patients with type B PE suffered from a very rapid ejaculation (or short latency), whereas in type A PE, the rapid ejaculation develops later in life and is often associated with erectile dysfunction (ED). Later, these types were respectively referred to as lifelong (primary) and acquired (secondary) PE [10].

The off-label use of antidepressant SSRIs has revolutionized the approach to and treatment of PE. These drugs block axonal reuptake of serotonin from the synapse by 5-HT transporters, resulting in enhanced 5-HT neurotransmission, stimulation of postsynaptic membrane 5-HT2C receptors and ejaculatory delay. Several studies have shown the efficacy of dapoxitine in improving the IELT in phase II and phase III clinical studies. Men with PE who were treated with Dapoxetine reported significant improvements in perceived control over ejaculation and satisfaction with sexual intercourse compared with placebo at study endpoint. Study conducted by Kaufman et al, showed that apart from IELT Dapoxetine improved perceived control over ejaculation, satisfaction with sexual intercourse, personal distress related to ejaculation,

interpersonal difficulty related to ejaculation parameters also. More than 96% of patients reported an improvement in their PE status from baseline to endpoint in this study [11]. In a phase III randomized controlled double blind study from 22 countries, Dapoxitine increased mean average IELT from 0.9 min at baseline (all groups) to 1.9min, 3.2 min, and 3.5 min with placebo, Dapoxetine 30 mg and Dapoxetine 60 mg, respectively [12]. In our study all the participants responded to dapoxitine 30mg with change of mean IELT from 34.8 seconds to 273 seconds after 3 weeks of therapy.

The incidence of side-effects in our study is 20% after placebo and 50% after 30mg of Dapoxitine. This is quite comparable to the data offered by the Asia-Pacific Study where they found incidence of adverse-effects in 18% on placebo, 33% on 30mg dapoxitine and 50% in those on 60mg of dapoxitine [13]. Similar to various studies the common side-effects included headache, nausea, vomiting, dizziness and lethargy. Diarrhea which was a common side-effect in different trials was not seen in our study. Syncope has been associated with the use of Dapoxitine, usually at the initial few doses and has been characterized to be vasovagal in nature [14, 11]. Dapoxitine does not interfere with the cardiac electrophysiology [14, 12]. The adverse effect profile of Dapoxetine once daily was similar to that of Dapoxetine "on-demand" therapy in various studies.

Chronic SSRI treatment for psychiatric conditions is known to predispose patients to withdrawal symptoms if medication is suspended abruptly. The lack of chronic serotonergic stimulation with on-demand Dapoxetine precludes serotonin receptor desensitization and the down regulation of postsynaptic serotonin receptors that typically occurs with chronic SSRI use, so that on-demand dosing for PE may minimize the risk of withdrawal symptoms [15]. Dapoxitine is not associated with withdrawal syndrome following abrupt discontinuation [16].

Conclusion

Dapoxetine is an effective, safe and well tolerated on-demand treatment for PE. There was significant improvement in the IELT with dapoxitine over placebo and baseline. On demand dosing makes the drug more acceptable to the patients and increase the compliance. Side effects associated with the drug are usually mild and well tolerated by the patients.

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