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REVIEW ARTICLE

Effect of Dapoxetine on intravaginal ejaculatory latency time (IELT) in premature ejaculation: a systematic review

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ABSTRACT

Introduction: The safety and efficacy of Dapoxetine for the treatment of premature ejaculation (PE) is still controversial. Thus, we decided to conduct a systemic review to determine the sufficiency of conclusions.

Objective: To evaluate the efficacy and safety of Dapoxetine in the treatment of patients with premature ejaculation and assess the reliability of the findings.

Materials & Methods: Four original articles were identified by a systematic search of MEDLINE Database. Those articles were included in the review with clear mention of PE and Dapoxetine in titles and abstracts.

Results: The mean IELT score recorded at baseline of each study is much lower than recorded after treatment with Dapoxetine. The difference between baseline IELT and post treatment IELT is significant in all studies.

Conclusion: The evidence suggests that Dapoxetine may be a safe and effective drug for patients with PE.

Keywords: Premature Ejaculation; Systematic Review; Serotonin; Dopamine.

The authors declared no conflict of interest. All authors contributed substantially to the planning of research, data collection, data analysis, and write-up of the article, and agreed to be accountable for all aspects of the work.

INTRODUCTION

Premature ejaculation is "a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, or, a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE); and, 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". The prevalence of Premature Ejaculation is much high and due to the nature of the condition; the exact prevalence is more likely to be under reported.[1,2] Since there was no evidence-based definition previously, so the reported prevalence has also been variable. Previously, psychological element had been considered as the sole cause of PE, so psychotherapy was the accepted mode of treatment. Ever since the biological component has been proposed and understood, pharmacotherapy has become the center of focus.

The two widely known classes of PE are lifelong or primary and acquired or secondary. Lifelong PE is experienced from the very first intercourse and almost every attempt of intercourse is affected throughout the life. The etiology of lifelong PE is accepted to be neurobiological. Acquired ED follows a period of perceived normal ejaculatory control. The proposed etiology of acquired PE carries both neurobiological and psychological components. The triggers of acquired PE may be stress or adverse drug reactions.[3,4] Natural variable PE and premature-like ejaculatory dysfunction are two other classes of PE in addition to these well recognized types of PE.[5] Natural variable PE is the condition in which men report occasional early ejaculation in the course of normal events, on the other hand premature like ejaculatory dysfunction is reporting of PE by man having prolonged or normal IELT.[6,7]

Irrespective of the type of premature ejaculation, it is characterized by incompetence to control ejaculation, ejaculation shortly after vaginal penetration or prior to penetration, embarrassment,

low confidence, personal distress, interpersonal difficulty and relationship problems due to sexual dissatisfaction of both partners.[8,9] The International Society for Sexual Medicine has also defined PE as "ejaculation which always or nearly always occurs prior to or within about 1 minute of vaginal penetration", i.e., an IELT of 1 minute or less.

Other listed criteria are "… 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".[10] Earlier, researchers recruiting patients for clinical studies of PE had a tendency to use the DSM-IV-TR criteria, which resembles criteria of the International Society for Sexual Medicine but lacks an IELT threshold.[8]

Psychological, environmental, endocrine, and neurobiological factors contribute to the etiology of PE. Ejaculatory control is under neuronal control from the supraspinal level using multiple neurotransmitters, serotonin (5-hydroxytryptamineor 5-HT) is the mostly widely investigated so far. Serotonin (5-HT) plays a complex role in the pathophysiology of PE and at least three subtypes of receptors (5-HT1a, 5-HT1b, 5-HT2c) are believed to be involved in it.[11] Recently, genetic links for PE have been explored by researchers.[12] Polymorphism of the serotonin transporter gene (5-HTT) is postulated to influence the response to treatment with Selective Serotonin Reuptake Inhibitors (SSRIs).[13]

The adverse effect of SSRIs i.e., delayed ejaculation or anorgasmia led to the possibility of SSRIs as pharmacotherapy for PE.[10,14] Further research on the 5-HT led to the confirmation of serotonergic pathways involvement at central and presynaptic level in process of ejaculation thus confirming the mechanism of action of SSRIs in PE.[11]

Multiple SSRIs including paroxetine, fluoxetine, fluvoxamine, sertraline, and citalopram are currently used off label for treating PE[15]. According to a study, paroxetine 20–40 mg per day over a 6-week period was found to increase median IELT by 9.5 minutes, while placebo provided no change in IELT ($p=0.002$).[16,17] This improvement in IELT by using SSRIs is associated with adverse effects like erectile dysfunction, loss of libido, mood changes, and discontinuation syndrome.[18] Koyunchu et al reported that the use of escitalopram by patients of PE adversely affected their spermiogram and could have negative impact on their fertility.[19]

Dapoxetine was the first SSRI developed and approved specifically for treating PE. Pharmacokinetic profile of Dapoxetine makes it unique from other SSRIs used off label to treat PE.[20,21] In contrast to other SSRIs Dapoxetine achieves steady-state concentrations quickly due to its rapid absorption[22]. By taking a dose of 30mg or 60mg of Dapoxetine the peak plasma levels are reached in approximately 1 hour.[20,21] Dapoxetine has a rapid elimination and a short half-life.[22] The pharmacokinetics of Dapoxetine remain unchanged despite multiple dosing, and it does not appear to accumulate considerably.[20]

The probability of unwanted side effects is much lower in Dapoxetine due to the novel pharmacokinetic characteristics.[20,23] Earlier Phase II studies recommended the optimal dose to be 30 mg initially which can be increased to 60 mg if needed. Pharmacodynamic studies identified the optimal dose administration time to be 1–3 hours before sexual intercourse.[24]

The outstanding pharmacokinetic and pharmacodynamics properties make it an ideal drug for treatment of PE. The purpose of this systemic review is to evaluate the efficacy and safety of Dapoxetine in the treatment of patients with PE and assess the reliability of the findings.

MATERIALS & METHODS

Systematic review was conducted to determine the efficacy and safety of Dapoxetine in the treatment of patients with PE and assess the reliability of the findings.

Data sources and search strategy

We searched the MEDLINE database from 2001 onwards on PubMed. We used free text words and specific key terms (MeSH in MEDLINE). The MeSH words included "Premature ejaculation" and "Dapoxetine". The Boolean operator 'and' was used. Prisma flow chart for the systematic review is shown in Figure 1.

Eligibility Criteria:

Studies were **included** if they meet the following criteria:

1. Studies published after 2001
2. Randomized Control Trials
3. Studies conducted on humans
4. Free full text articles.

Studies were **excluded** if:

1. Were basically regarding diseases other than PE
2. Were performed on animals
3. Effects of air pollution was observed,
4. Studies which did not include efficacy of Dapoxetine,
5. Narrative reviews and editorials and
6. Studies not in English language.

Data extraction

The data was then extracted from the eligible studies by a structured data extraction form. The excel sheet was then used containing the following parameters:

Preliminaries

First author, region of study, year of study, aim of study

Methods

Study population type (adults or children), study design, sampling technique, study duration, sample size.

Outcomes

IELT

Dose of Dapoxetine used

Dose of Dapoxetine administered.

Limitations

Strength, limitation.

Conclusion

Key conclusion.

Data Synthesis

Data were analyzed by SPSS version. 20. Results were presented in the form of tables and figures.

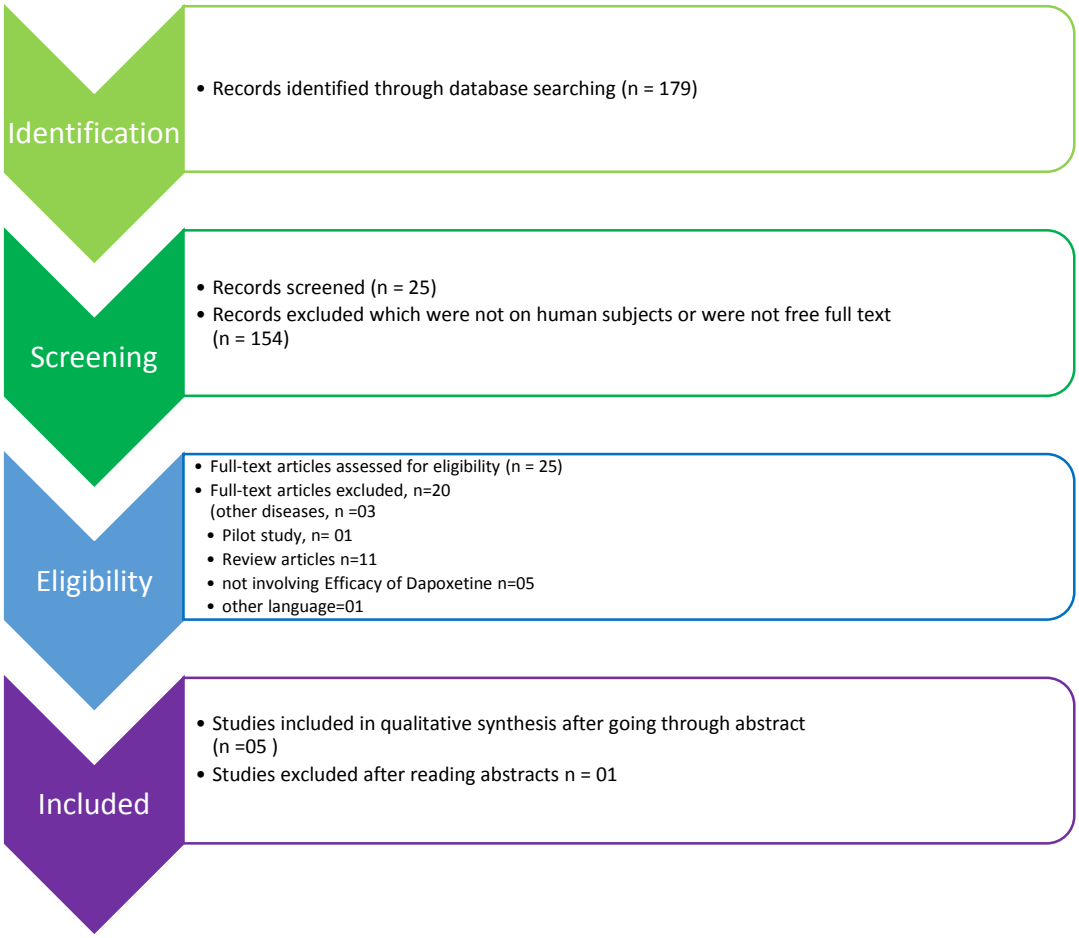

Figure 1: PRISMA flow chart showing the selection process.

RESULTS

The data search yielded 04 eligible studies as shown in Table 1. Most of the research on efficacy of Dapoxetine in premature ejaculation has been conducted in the last decade. Studies included in this systematic review were conducted in various countries as shown in Figure 2.

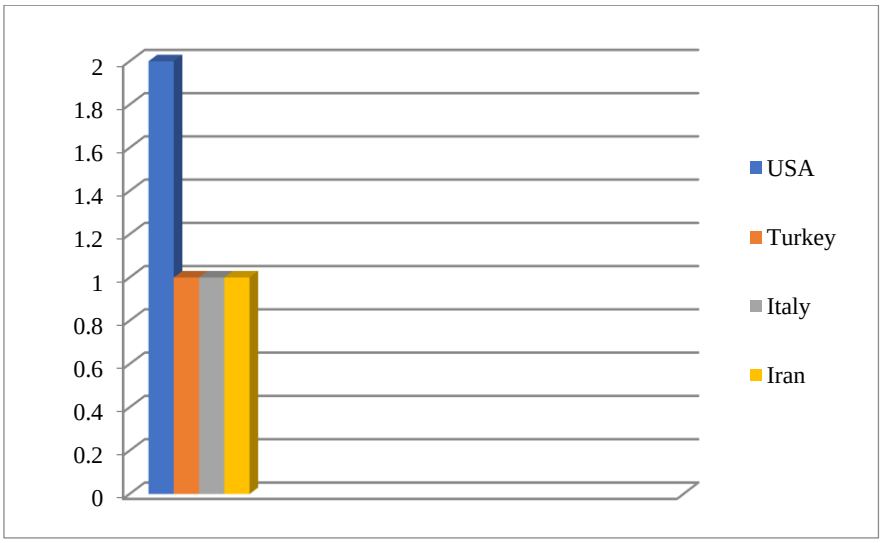

Figure 2: Region wise distribution of studies.

All of the studies included adult sexually active males. Two of the four studies included in systemic review were randomized control trials while the other two were of experimental type (Table 1). The outcome tool was IELT in all studies.

Table 1: Assessment of methodological quality of included studies.

First author	Study design	Study technique	Study duration	Sample size	Inclusion criteria	Exclusion criteria	Conclusion
Pavone C. Premature ejaculation: Pharmacotherapy vs group psychotherapy alone or in combination	Experimental study (3 groups comparison)	Simple random	January 2012 to December 2012	279 male outpatients	Lifelong PE measured with IELT ≤ 2 minutes and PEDT >9	Presence of psychiatric disorders requiring medical treatment, drugs and alcohol	Group Psychotherapy is an alternative method of treatment for PE. Group Psychotherapy plays a significant role in the treatment of PE, determining a better improvement of symptoms than Dapoxetine alone even if not statistically significant.
Safarinejad MR. Safety and Efficacy of Dapoxetine in the Treatment of Premature Ejaculation: A Double-Blind, Placebo-Controlled, Fixed-Dose, Randomized Study	Randomized control trial	Simple random	12 weeks February 2004 to March 2006	212	Only patients without any obvious organic cause of PE and possible sexual intercourse equal to or greater than 1 per week were included	Those with erectile dysfunction according to IIEF; an organic cause of PE including anatomical abnormalities; low libido; chronic depression, psychiatric, or physical illness; alcohol, drug, or substance abuse; organic illness causing limitation in SSRI use; use of psychotropic and antidepressant medication; and serious relationship problems	Dapoxetine has moderately better results in terms of IELT and intercourse satisfaction vs placebo without long-term benefit for the patient after it is withdrawn. Further studies are necessary to draw final conclusions on the efficacy of this drug in PE.
Ridwan Shabsigh. Perceived control over ejaculation is central to treatment benefit in men with premature ejaculation: results from phase III trials with Dapoxetine	Randomized control trial	Simple random	12 weeks	2614	Men aged ≥18 years who were in a stable, heterosexual relationship for ≥6 months, who met DSM-IV-TR criteria for PE,	Not provided	A two-category or greater increase in control (5-point scale) is useful for assessing the treatment benefit in men with PE; it corresponds with improvements in the man's perception of his condition, substantially greater prolongation of IELT, and higher levels of satisfaction with sexual intercourse.
Abdul Muttalip Simsek. Comparison of paroxetine and Dapoxetine, a novel selective serotonin reuptake inhibitor in the treatment of premature ejaculation	Experimental study (3 groups comparison)		October 2011 and May 2013	150	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	Erectile dysfunction; low libido; major psychiatric or psychological illness, organic diseases causing limitation in using SSRIs; and use of other treatments for PE within the previous 3 months.	On demand dapoxetine is a novel effective treatment modality for PE. Although a lower dose of dapoxetine (30 mg) does not outperform the currently used paroxetine treatment, 60 mg dapoxetine 1–3 h before planned intercourse produces a greater increase in IELT for men with PE, compared to paroxetine. We propose that in cases of severe PE (e.g., IELT <30 s), 60 mg dapoxetine should be given directly.

The mean IELT score recorded at baseline of each study is much lower than recorded after treatment with Dapoxetine (Table 2). The difference between baseline IELT and post treatment IELT is significant in all studies (Table 2).

Table 2: Difference of IELT before and after treatment with Dapoxetine.

#	Author	Number of participants	IELT (seconds) Mean scores (SD;95%CI) (Baseline)	IELT(seconds) Mean scores (SD;95%CI) (Post treatment)	p value
1	Carlo Pavone	62	50.77(13.52;48.02 - 53.52)	231.86(39.97;221.91 - 241.81)	<0.001
2	Abdul Muttalip Simsek	50	46.1 ± 23.2	100.2 ± 24.5	<0.001
3	Mohammad R Safarinejad	106	28	193	<0.001
4	Shabsigh R	1569	54 ± 30	282 ± 264	<0.001

DISCUSSION

Although nonlethal, Premature Ejaculation can severely negatively affect quality-of-life. Despite the high prevalence of this condition, there is little research regarding its causation, and it is likely that there are both biological and psychological factors. Penile hypersensitivity, hyper-excitable ejaculatory reflex, increased sexual arousability, endocrinological problems, genetic predisposition and serotoninergic receptor dysfunction have been proposed as biological factors.[25] Psychological risk factors for PE include social phobia, anxiety, relationship problems, infrequent sexual intercourse, and lack of sexual experience.[26] Before the past decade, the major approach to treating PE was behavioral and psychotherapy, relying on such techniques as the 'pause' and 'squeeze' methods.[28] However, the application of principles of evidence-based medicine shows that there is little evidence to support the psychological approach and behavioral treatment.

PE has been historically treated with alpha adrenergic blocking agents and monoamine oxidase inhibitors; side-effects limited the use of these treatments. More recently, newly developed drugs such as antidepressants, local anesthetic agents and phosphodiesterase type 5 inhibitors have been applied as treatments.

All the studies included in this systematic review indicate a significant increase in IELT after the use of Dapoxetine for PE. In several studies Dapoxetine has been shown to significantly improve the IELT compared with baseline and placebo levels; IELT 1.66, 3.03 and 3.15 min with placebo, 30 mg Dapoxetine and 60 mg respectively, when the drug was taken 30–60 min before intercourse. When taken 3-4 hours prior to intercourse the IELT was 1.79, 3.06 and 3.97 min with placebo, for 30 and 60 mg Dapoxetine respectively.[27] These findings are in agreement with all the studies included in our systemic review.

Dapoxetine is a novel SSRI that is stereo chemically similar to many other described SSRIs.[18] Pharmacological studies have shown Dapoxetine to be a potent inhibitor of the 5-HT transporter and that its pharmacokinetics are unaffected by age, ethnicity or dosing frequency (for 30 & 60 mg doses).[23] Dapoxetine demonstrates rapid absorption and elimination with minimal accumulation following daily dosing and is extensively metabolized by multiple enzymes.[29,30] As a short acting SSRI Dapoxetine is probably better suited as an on-demand treatment for PE. Doses of 30 and 60 mg have been used and peak plasma concentrations observed 1.01 and 1.27 h after administration. Elimination is also rapid, with a half-life of 1.3–1.4 hours.[21,29]

Dapoxetine gave chronically improved latencies over baseline. However, even at 60 mg, the latencies were still <2 min in most of the patients. We doubt whether greater than this dose is suitable for large-scale use. Prolongation of the ejaculatory interval within few days of treatment suggests that this acute effect is due to direct blocking of central serotonergic reuptake by Dapoxetine. Ejaculation is a reflex comprising different sensory pathways, motor centers, and nerve pathways. This ejaculatory reflex has been shown to be controlled primarily by both serotonin and dopamine.[31] Among the different subtypes of 5-HT receptors, the most important ones on ejaculation are 5-HT1A, 5-HT1B, and 5-HT2C receptors.[32] Because the rapid onset of postponement of ejaculation by some of the SSRIs has a similar time course as their synaptic effect on 5-HT, it is suggested that the effect on ejaculation is mediated by acute enhancement of 5-HT neurotransmission or by differential activation of different 5-HT receptor populations, notably 5-HT1A and 5-HT2C receptors.[33] Dapoxetine's mechanism of action is the inhibition of neuronal reuptake of serotonin. It was also shown to bind and inhibit the reuptake transporters of dopamine and norepinephrine.[34]

Safarinejad found Paroxetine to be more effective in terms of satisfaction and IELT. Safarinejad's study divided 340 potent male patients into paroxetine (20 mg) and Dapoxetine (60 mg) groups. Intercourse satisfaction and IELT increment was higher in the paroxetine group.[35] Though Paroxetine proved more effective but the safety profile of Dapoxetine regarding adverse effects makes it more suitable drug for PE than paroxetine.

CONCLUSION

On demand Dapoxetine is a novel effective treatment modality for Premature Ejaculation. The evidence suggests that Dapoxetine may be a safe and effective drug for these patients. More research is required to establish whether greater doses are suitable for large-scale use.

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