Use of Dapoxetine in Premature Ejaculation Management: Review Article

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ABSTRACT
Background: Premature ejaculation (PE) isn’t life-threatening, but it has a negative influence on the lives of both the patient and their partners. Varied researches have employed different definitions of PE, which include, for example, the number of intra-vaginal thrusts and the duration of male voluntary control. Dapoxetine is a selective serotonin reuptake inhibitor (SSRI) medication, one of many commonly prescribed for depressive symptoms. Cognitive behavioral therapy (CBT) has been widely utilised to treat PE prior to the availability of dapoxetine. Other than dapoxetine, other Off-label usage of SSRIs in the treatment of PE has increased in recent years.

Objective: Assessment of possible role of dapoxetine in premature ejaculation management.

Methods: Dapoxetine, serotonin reuptake inhibitors, and premature ejaculation were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete studies from February 2001 to May 2021 were included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: Clinical evidence demonstrated that treatment for people with long-term or acquired PE, dapoxetine is highly effective as well as safe, and the unique properties of dapoxetine make it an appropriate choice for on-demand dosage.

Keywords: Dapoxetine, Serotonin reuptake inhibitors, Premature ejaculation.

INTRODUCTION
Patients and their partners are affected by PE in a substantial way, even though it is not life-threatening. PE has been defined in several ways by various researchers, including the length of ejaculatory latency, the sum of intra-vaginal thrusts, and the degree of male voluntary control (1).

Althof et al. (2) reported that ejaculation, which is always or nearly always occurring before or within one minute of vaginal penetration, in men with erectile dysfunction, was classified as "premature ejaculation" as well as term for vaginal penetrations and the inability to delay ejaculation with unfavourable personal repercussions like distress or trouble or dissatisfaction and/or the avoidance of sexual relations (3).

Some researchers predict that as many as seventy percent of all men will develop PE at some point in their lives. Based on the results of a recent study, it was reported that 20 to 30% of men have the condition. Most people in the age range of 18 to 59 never bring up the matter with their doctors. The Global Study on Sexual Attitudes and Behaviors polled over 13,000 men aged 40 to 80 from 19 countries (4).

PE has been linked to a variety of issues, including those involving the mind, body, hormones, and brain. A number of neurotransmitters are involved in neuronal control of ejaculation at the supraspinal level, the most studied of which is serotonin (5-hydroxytryptamine, 5-HT). In the pathophysiology of PE, at least three 5-HT receptor subtypes (5-HT1a, 5-HT1b, and 5-HT2c) have been identified (5).

The current treatment options:
Sex therapy and cognitive therapy have both been utilised traditionally to treat PE because of the disorder's stigma as a mental health issue. It is hoped that this type of treatment may help patients with PE gain more self-confidence and intimacy with their partners, therefore increasing their performance and lowering the stress associated with sexual encounters. Squeezing the penis glans or intermittent penetration are two other behavioural ways for reducing the need to ejaculate urgently, albeit the latter may lead to longer periods of sexual frustration rather than more penetrative duration (2).

Selective serotonin reuptake inhibitors (SSRIs): Depressions are routinely treated with SSRIs. Clomipramine, a tricyclic antidepressant, was found to extend ejaculatory latency in rats by inhibiting serotonin reuptake in the central nervous system. In contrast, SSRI medicine only mildly activates 5-HT1C receptors after a few hours, therefore on-demand SSRI treatment is expected to have only a small ejaculation-postponing effect because of this (5).

Even yet, SSRIs have been employed in numerous trials, and Waldinger et al. (6) were the first to do methodological assessments of these studies in

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accompanying with standards based on scientific evidence.

After reviewing 79 papers on medication treatment for PE, the results showed that 35 included studies using serotonergic antidepressants. Accordingly, there was a large degree of heterogeneity in the degree of ejaculatory latency reported in both single-blind and open-design investigations employing questionnaires and subjective reports. Only 8 research (18.5%) met all evidence-based medicine criteria, for example, real-time stopwatch evaluations at each intercourse, both at baseline and during the drug trials, are used in prospective double-blind experiments (6). It has been found that the most effective SSRIs for everyday usage include Clomipramine, paroxetine, sertraline, and Fluoxetine (6).

The ejaculatory-delaying effect of paroxetine on-demand for PE was shown to be more pronounced in subsequent investigations. Ejaculation was delayed by four times when Abdel-Hamid and colleagues (7) administered an on-demand dose of 20 mg paroxetine 3–4 hours before coitus. Also, McMahon and Touma (8) discovered in their single-blinded research, 20 mg of paroxetine administered three to four hours before coitus delayed ejaculation 11 times without having substantial serotonergic side effects.

A large delay in therapy without serotonergic side effects does not appear to be possible with on-demand medicine, which has superior effects than previously reported daily treatment with 20 mg paroxetine (9).

On-demand SSRI use will not delay ejaculation within the first 1–2 hours of taking the medicine, according to animal studies and current scientific understanding (9,10). If normal SSRIs aren’t effective enough for treating PE when it occurs suddenly, animal studies suggest that 5-HT1A receptor antagonists or other serotonin-releasing interventions may be required (9).

Dapoxetine (DAP):

Dapoxetine is the sole SSRI licenced for the treatment of PE, in contrast to the other SSRIs previously listed. The pharmacokinetics of dapoxetine distinguish it from other SSRIs currently being used off-label to treat PE. Dapoxetine's pharmacology can be summed up in the following way:

- In contrast to other SSRIs, which can take days or even weeks to reach steady-state concentrations in the blood after oral treatment, dapoxetine is rapidly absorbed.
- A 30 mg or 60 mg dosage of dapoxetine reaches peak plasma concentrations in roughly one hour.
- For all doses, the half-life of dapoxetine is around 1.4 hours compared to the 21-hour to 4-day half-life of other SSRIs.
- Dapoxetine's half-life is 18.7 hours for 30 mg and 21.9 hours for 60 mg.
- Pharmacokinetic properties of DAP are not affected by successive doses, and it does not appear to build up considerably (11).

On demand Dapoxetine:

However, even though SSRIs are meant to be used on a long-term basis for the treatment of depression, to be effective over the long haul, they may require many days or even weeks to reach steady-state levels in the body (11).

PE is typically treated with an SSRI in a daily dosage regimen. Taking long-acting SSRIs may postpone ejaculation, but it's also been linked to other negative effects, such as diminished libido and erectile dysfunction (ED) (12).

For certain people with bipolar disorder, it may be more convenient and less likely to cause serotonergic side effects to use SSRIs with short half-lives and low Tmax on-demand rather than daily (9).

Therefore, a medicine that is quickly absorbed and rapidly removed is suitable for the treatment of PE since it reduces total drug exposure while lowering the risk of side effects (13).

There are 341.88 molecular weight dapoxetine hydrochloride molecules in this water-soluble powder, which is mostly charged at physiological pH levels. Its pKa value is 8.6. There are distinct differences in the pharmacokinetics of typical SSRIs because of these pharmacological properties (13).

At a peak plasma concentration of around 1.5 hours after a dose, Dapoxetine is a fast-acting drug, which is significantly faster than fluoxetine, paroxetine, or sertraline (14).

Dapoxetine is quickly absorbed from the gastrointestinal tract and then rapidly depletes the blood of its active ingredient. Because of these features, dapoxetine is a great candidate to be administered only when needed where the dangers of continual medication are avoided. As the most common side effect, nausea was reported by 5.6% of patients who took 60 mg, 16.1% of individuals who took 100 mg, and 0.7% of patients who got placebo. Dapoxetine 100 mg was given to nine participants who dropped out of the study due to side effects, while a placebo was given to one (15).

In the second phase II clinical studies, dapoxetine was evaluated at 20 mg, 40 mg, 60 mg, and 100 mg in order to determine the appropriate on-demand dosage for large-scale phase III clinical trials (16). Men with PE took part in double-blind, multi-center, randomized, and placebo-controlled phase II investigations, each of which included three periods of crossover.

Subjects were instructed to consume a study drug (1–3 hours in study 1 and 1–2 hours in study 2) and attempt sexual contact up to twice weekly before the intended sexual encounter (16). The most important
result was the time the female partner took to complete her intravaginal ejaculatory latency time (IELT). There were 128 individuals in the first study who took 20 mg and 40 mg of dapoxetine, while 130 patients (60 mg and 100 mg) completed the second research's trials. All four doses of dapoxetine were found to improve IELT scores considerably over placebo (16).

**CONCLUSION**

Clinical evidence demonstrates that as a treatment for people with long-term or acquired PE, dapoxetine is highly effective as well as safe, and the unique properties of dapoxetine make it an appropriate choice for on-demand dosage.

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**REFERENCES**