TRAMADOL IN THE MANAGEMENT OF PREMATURE EJACULATION: A PRAGMATIC REVIEW

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ABSTRACT
Premature ejaculation (PE) is the most common sexual disorder affecting 20%-30% of adult men; its etiology still remains idiopathic. Tramadol is a synthetic codeine derivative with a weak agonistic activity on the mu-opioid receptor. It is a unique centrally acting analgesic which also inhibits the neuronal reuptake of nor-adrenaline and serotonin. This review is presented to evaluate efficacy, safety, tolerability, addiction liability on-demand dosing tramadol that is effective in lengthening intra vaginal ejaculation latency time (IELT) in men with varying degrees of PE disorder following treatment.

KEYWORDS: Tramadol, analgesic, opioid, IELT, Premature ejaculation.

INTRODUCTION
Premature ejaculation is the normal sexual problem in common population nearing as high as 20-30%,[1] associated with lowering the quality of life consequent to morbidly.[2] The precise definition of PE is unsettled since historic period that confirms diagnosis but now the international society of sexual medicine (ISSM) has clarified PE for the diagnosis criteria as ‘a male sexual dysfunction’ characterized by ejaculation that always exhibited before or within a minute of vaginal penetration (IELT) that led to instigation of negative personification such as distress, bothersome, frustration, and then avoidance of sexual intimacy.[3] Further this definition does not gained consensus, although, it provided subjective as well as objective benefits, and hence, arose another statement which is perfectly based on subjectivity defining as a persistent or recurrent ejaculation with minimal sexual
stimulation before or shortly after penetration as the subject doesn’t desire of the event that is associated with marked frustration, distress and interpersonal difficulty,\(^4\) though this definition has to be taken in mind as an old version of Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Text Revision (DSM-IV-TR) but revised DSM--V utilizes IELT measures to address the definition of PE.\(^5\)

Management and treatment of PE include both psychological or behavioral modification and topical or systemic medications.\(^6,7,8,9\) The common applications are SSRI, TCI, Phospodiestrase-5 inhibitor or opioid receptor agonist and 5- HT1A receptors agonist.\(^9,10,11,12\) Of the mentioned, tramadol is a centrally acting opioid mu-receptor agonist that also has activity of reuptake inhibitor of serotonin and noradrenaline,\(^13\) hence taking into consideration of all these functions, this review aims to explore the mechanism of action, efficacy, safety, physical & psychological dependence of tramadol in the management and treatment of PE.

**Mechanism of action of tramadol in the management of PE**

Tramadol acts centrally as a mu-receptor agonist and inhibits both sensory and motor transmissions acting as a moderate analgesic that suppresses conduction in the spinal cord, hence producing anesthetic effects on the peripheral nerves and declines ejaculation as well as also it inhibits reuptake of serotonin and noradrenaline.\(^13,14\)

**Clinical efficacy**

Efficacy of tramadol for the treatment of PE is perpetually observed since last decade, although the dosage and timing of use varied across studies, there was universal reports on improvement in PE symptoms measured both objectively and subjectively. Specifically, IELT was shown to improve to varying degrees regardless of dose, and patient satisfaction improvement with the treatment.\(^15-20\)

In 2006, Safarinejad and Hosseini reported the results of their randomized control trial on the basis of DSM-IV-TR definition for PE, patient used a stopwatch to measure IELT whereby baseline IELTs of 19–21 s and were randomized to either placebo or tramadol HCL 50 mg to be taken 2 h prior to intercourse. The tramadol group experienced an average 3.73-min improvement in IELT relative to 0.22 min in the control \((P<0.001)\) where the efficacy of tramadol was proved to be significant, Furthermore, studies evaluating a 25-mg dose of tramadol in an on-demand manner,\(^19,20\) or placebo 1–2 h prior to intercourse and the
recorded average baseline of IELT was 1.17 min. The results showed a significantly greater improvement in IELT in the treatment group relative to the placebo arm, 6.20 versus 0.84 min, respectively ($P<0.0001$). More recently in 2012, Kaynar et al.\textsuperscript{19} found a result where tramadol HCL 25 mg or placebo was utilized with finding of 38.83 and 30.66 s, respectively. Although this represented a less robust absolute response with respect to IELT, it should be noted that the baseline IELT in the cohort of Kaynar et al. was less than that in the study by Salem et al.\textsuperscript{20} approximately 34 s versus 1.17 min. For each of these assessments, the tramadol group exhibited a significant improvement relative to placebo ($P<0.001$).

In another study with mean baseline IELTs 2.79–2.99 min, each patient was given a placebo for 4 weeks as a lead-in and 25, 50 or 100 mg, of tramadol was given on-demand 2–3 h before intercourse, the result obtained were 25-, 50- and 100-mg groups demonstrated significant increase in IELT of 10.4, 20.6 and 33.5 min respectively. Although this study illustrated the most robust absolute response to treatment, the groups also had IELTs upwards of threefold higher than the other studies, this supports the notion that baseline dysfunction may predict response to treatment.\textsuperscript{16}

Kahn and Rasaily\textsuperscript{21} control trial performed, according to the DSM-IV-RT criteria, taking an average baseline IELT of 60 patient was between 58.7 and 59.2 s., each patient utilized a stopwatch to measure IELT. Compared tramadol 100 mg in both a daily and on-demand dose with placebo. Administered daily tramadol and then on-demand dosing for the next 4 weeks. The results observed was mean IELT increased in the daily tramadol group from 59.2 to 202.5 s and in the on-demand group IELT to 238.2 s. Each of these increases was significantly greater than that seen in the placebo arms, which escalated to 94.8 s in the daily group and 96.6 s in the on-demand group.\textsuperscript{15}

**Tramadol versus Paroxetine in the management of PE**

Although the above studies specifically evaluated tramadol versus placebo, others have compared tramadol with an alternative therapy, specifically paroxetine.\textsuperscript{16, 18} SSRIs such as paroxetine antidepressants as its used patient has reported side effect of delayed ejaculation therefore evaluated for use in treating PE,\textsuperscript{16, 22, 23} Alghobary et al.\textsuperscript{16} were the first to report on this in their prospective, single-blind study of 35 men randomized to either on-demand tramadol HCL 50 mg 2–3 h prior to intercourse or daily paroxetine 20 mg in a cross-over manner, Only those with lifelong PE were included, and each patient utilized a stopwatch to
record IELT. DSM-IV-TR criteria were used to define PE, and average baseline IELT was equal to 36.13 s. Outcomes were evaluated at 6- and 12-weeks end points. At 6 weeks, both the tramadol and paroxetine groups experienced improvements in IELT relative to baseline, 111 s and 180 s, respectively (P<0.001). At 12 weeks, the two treatment groups continued to experience overall improvement, but the tramadol response declined to 84 s longer than baseline, while in the paroxetine group the IELT time further increased to 379 s relative to baseline. The improvements in IELT were significantly greater at both 8 and 12 weeks relative to baseline for each of the groups (P<0.001). With respect to patients’ satisfaction, this study reported the interesting finding that while the Arabic index of premature ejaculation improved for both the tramadol and paroxetine group at 6 weeks, this improvement was not durable for the tramadol group, losing significance at 12 weeks whereas the paroxetine group remained significantly improved.\cite{16}

A study involving 44 men with tramadol HCL 50 mg 3–4 h prior to intercourse, paroxetine 20 mg prior to intercourse or placebo, and average baseline recorded for IELT was 0.51 s. Both the tramadol and paroxetine groups experienced increases in IELT relative to baseline that surpassed those of the placebo, with tramadol exhibiting the greater effect. Tramadol increased 6.33 min, paroxetine increased 2.23 min and placebo increased 1.23 min, representing significant improvement for both interventions relative to baseline and placebo. It is important to note that in this study the paroxetine group was only followed for 3 weeks while on that treatment.\cite{18}

**Safety, Efficacy and physical & psychological dependence of tramadol**

In general, tramadol was well tolerated with relatively few adverse events. The most common of these were somnolence and gastrointestinal (GI) upset (nausea, dyspepsia, vomiting), escalation in AEs is dose dependent tramadol, overall rate of AEs with 12.4% in the 62 mg group and 16.4% in the 89 mg group. 13.3% rate among patients taking 25 mg and 28.0% with 50 mg.\cite{18-22} 100-mg group experiencing more GI-related AEs than those taking 50 mg who in turn had more AEs than the 25 mg cohort.

Comparision of 50-mg group with 100 mg group, the preceding experienced dizziness and pruritus with an incidence of 18% and 16%, respectively, compared with 38% and 30%, respectively, in the 100-mg group. The 100-mg group experienced nausea and vomiting at an incidence of 20% and 17%, the resolution of these symptoms, reported was on average < 10 h.\cite{17}
As tramadol is an opioid analgesic prescribed to manage moderate to moderately severe pain, its area of primary concern that worries later is its physical dependence and addiction, physical dependence of tramadol is only reported in chronic user with in high dose generally between 50 to 200 mg per day and the frequency on these doses are also very rare just 1 in 100000 patient. Specifically dose equals to 400 mg did show withdrawal effect explaining the dose less than 50 mg is effective in the treatment of PE.[23-28]

Comparision of tramadol in PE: Sporadic versus continuous use
Anxiety is common in the patient with IELT less than 1 min.[29] tramadol is better option to reduce this disorder. Besides this, considering the economical aspects, tramadol has greater advantage over other drugs used in the treatment of PME. A recent study demonstrated mean IELT was 202.5 s after continued tramadol treatment and 238.2 s after sporadic treatment in Group A. Coital frequency increased to 4.32 times /week with daily tramadol treatment and 4.86 times with sporadic treatment. Thus the results of PME treatment with tramadol are similar with both continued and sporadic administration. The sex life of patients improved and they reported greater satisfaction with the sporadic treatment. Hence, tramadol has shown relatively higher degree of efficacy in PME when used as sporadic basis. [30]

CONCLUSION
Tramadol is generally well tolerated, particularly in the groups taking 25 mg and 50 mg doses. A dose related response was observed with respect to both groups with prolongation of IELT and incidence of side effects. There are minor common side effects & it exhibits very low addiction liability only when used for prolonged period as in case of chronic cancer pain. Tramadol lowers seizure threshold, it should not be used in epileptic patients, it should not be given to patients taking SSRI & TAD for danger of producing epilepsy, epilepsy is also produced in over doses, it should not be administered to patients who are already on therapy of MAOIs as it may precipitate Hypertensive crisis, hence, the above mentioned facts should be first taken care of while prescribing tramadol to PE patients. On the basis of risk & benefit, it is strongly suggested that tramadol has worth of administering to PE patient safely intermittently in a daily dose of 25 mg to 50 mg on-demand dose basis & it should be taken 2–4 h prior to sexual activity. This will certainly improve quality of sexual satisfaction of both the partners by lengthening period / time of intercourse in PE patients, but maximum dose should not exceed 50 mg once daily, it is well tolerated in such recommended therapeutic doses of 25 mg to 50 mg with acceptable very minor side effects. Therefore, it is
an effective oral therapy for patients of PE being overall safe and well tolerated but it should not be used on regular basis, only on-demand dose basis.

Therefore, it is concluded that using tramadol hydrochloride on doses usually less than 50 mg on-demand for the treatment of PE is quite effective, safe and tolerable, with minimal undesirable side effects, lengthening mean intravaginal ejaculatory latency time (IELT), hence, it is now recommended to be used as effective remedy for the temporary solution of PE.

REFERENCES


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