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The Analysis Study of Efficacy, Effectiveness, and Clinical Risk of Tramadol as Treatment of Premature Ejaculation : A Comprehensive Systematic Review

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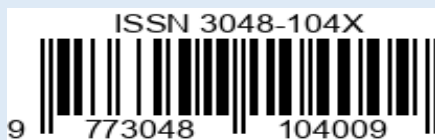
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ABSTRACT

Background: Premature ejaculation is a common sexual dysfunction affecting 20%-30% of men. Understanding the effectiveness and potential dangers of tramadol in treating premature ejaculation can help develop efficient treatment protocols. **Methods:** In accordance with the PRISMA 2020 principles, this systematic review focused specifically on comprehensive English literature published from 2013 to 2024. **Result:** The study examined over 2000 papers from respectable sources such as Science Direct, SagePub, and PubMed. Following the decision to subject eight publications to further scrutiny, a comprehensive examination of the complete body of literature was conducted. **Conclusion:** Tramadol, an analgesic derived from opioids, effectively suppresses premature ejaculation (PE) and enhances sexual satisfaction during sexual intercourse. Nevertheless, the efficacy and safety of its use in treating PE are still a subject of discussion due to a lack of solid empirical evidence. Additional investigation is required to ascertain the effectiveness of the medication and its possible adverse effects.

Keyword: Premature ejaculation, tramadol, effectiveness, efficacy, safety

INTRODUCTION

Premature ejaculation (PE) is a common cause of male sexual dysfunction, affecting approximately 20% to 30% of men in the sexually active age group.¹ Premature ejaculation may harm the overall well-being of patients and their spouses, as stated by Althof in 2010.² In the past, there was a lack of detailed information on this medical condition and the underlying processes causing it. However, in 2014, a comprehensive and standardized description of PE was introduced based on evidence.³

As per the recommendations of the International Society for Sexual Medicine (ISSM), premature ejaculation is characterized by three main features: (i) ejaculation occurring within the first minute after vaginal penetration during initial sexual encounters, or a very short ejaculation latency time (ELT) of less than 3 minutes; (ii) inability to delay ejaculation in most instances of vaginal penetration; and (iii) negative psychological effects on the affected individual, leading to feelings of distress, frustration, and avoidance of sexual intercourse.^{4,5}

The primary pharmaceutical methods involve prescribing selective serotonin reuptake inhibitors (SSRIs), such as sertraline, fluoxetine, dapoxetine, and paroxetine, phosphodiesterase type 5 (PDE5) inhibitors, such as tadalafil or sildenafil, and alternative medications like tramadol.⁵ Providing patients with the ability to use a specific drug whenever needed is more convenient. This approach also helps to decrease the occurrence of tachyphylaxis (a decrease in drug effectiveness over time) and minimize the negative effects that can result from daily usage of the drug.⁶

Instantaneous Tramadol has been utilized for the management of premature ejaculation. The precise mechanism of action of tramadol remains uncertain, although it has been postulated that tramadol stimulates opioid receptors and hinders the reuptake of serotonin and noradrenaline. Tramadol has been administered at different doses and for varying periods. The medicine has demonstrated efficacy in multiple studies. However, its use is limited due to its side effect profile and propensity for addiction.⁷ Gaining

insight into the correlation between the effectiveness and potential dangers of tramadol as a treatment for PE can assist in formulating efficient treatment protocols. This systematic literature review aims to investigate the correlation between the effectiveness, efficacy, and clinical risk of tramadol in patients with premature ejaculation (PE), using research conducted in the last ten years.

METHODS

Protocol

The study's author diligently adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 criteria to guarantee full compliance with all requirements. A meticulous and thoughtful methodology was employed to provide precise and compelling research results.

Criteria for Eligibility

This article offers a comprehensive review of research conducted in the last decade on the effectiveness, efficiency, and clinical risks of tramadol as a treatment for premature ejaculation. This program aims to elucidate and optimize patient

care methods through thorough data analysis. The main aim of this thesis is to highlight important themes that are found in a range of literary works.

In order to guarantee the precision of the data utilized in this analysis, rigorous criteria for inclusion and exclusion were enforced. Any material that has been officially released or made available in the English language from 2013 to 2024 is considered eligible for inclusion. The exclusion criteria encompass published reviews, editorials, submissions lacking a DOI, and duplicate entries within the same journal.

Search Strategy

The study's keywords include "premature ejaculation, tramadol, efficacy, effectiveness, clinical risk, outcome, effect". For this research, the following Boolean MeSH keywords were entered into the databases: (((“premature ejaculation”[MeSH Terms] OR “tramadol”[All Fields] AND “efficacy”[All Fields]) OR (“premature ejaculation”[MeSH Terms] OR “tramadol”[All Fields] AND “effectiveness”[All Fields])

AND (“premature ejaculation”[MeSH Terms] OR “tramadol”[All Fields] OR “clinical risk”[All Fields] OR “outcome”[MeSH Subheading] OR “risk”[All Fields] OR “effect”[All Fields]))).

Data retrieval

Prior to commencing this comprehensive investigation, the authors meticulously assessed the relevance of each publication by analyzing its title and abstract. Only research that fulfilled the aims and met the inclusion criteria of the article were given greater significance. A distinct and uniform pattern became evident after conducting repeated searches. Only English was permitted for full-text submissions. The screening method was thorough and resulted in content that was directly relevant to the study's topic and met all planned inclusion criteria. Research that did not meet these criteria was typically ignored and its findings were not considered significant. The examination encompassed a diverse array of data, comprising factors, titles, authors,

publication dates, places, and study methodologies.

Quality Assessment and Data Synthesis

The authors themselves meticulously review the abstract and title of each article to identify those that necessitate additional examination. Subsequently, every document that was initially under consideration had to undergo a meticulous examination. The assessment outcomes influenced the choice of the review papers. This criterion facilitated the expedited selection of publications for further examination, so enabling a more comprehensive evaluation of previous research and the context in which it was assessed.

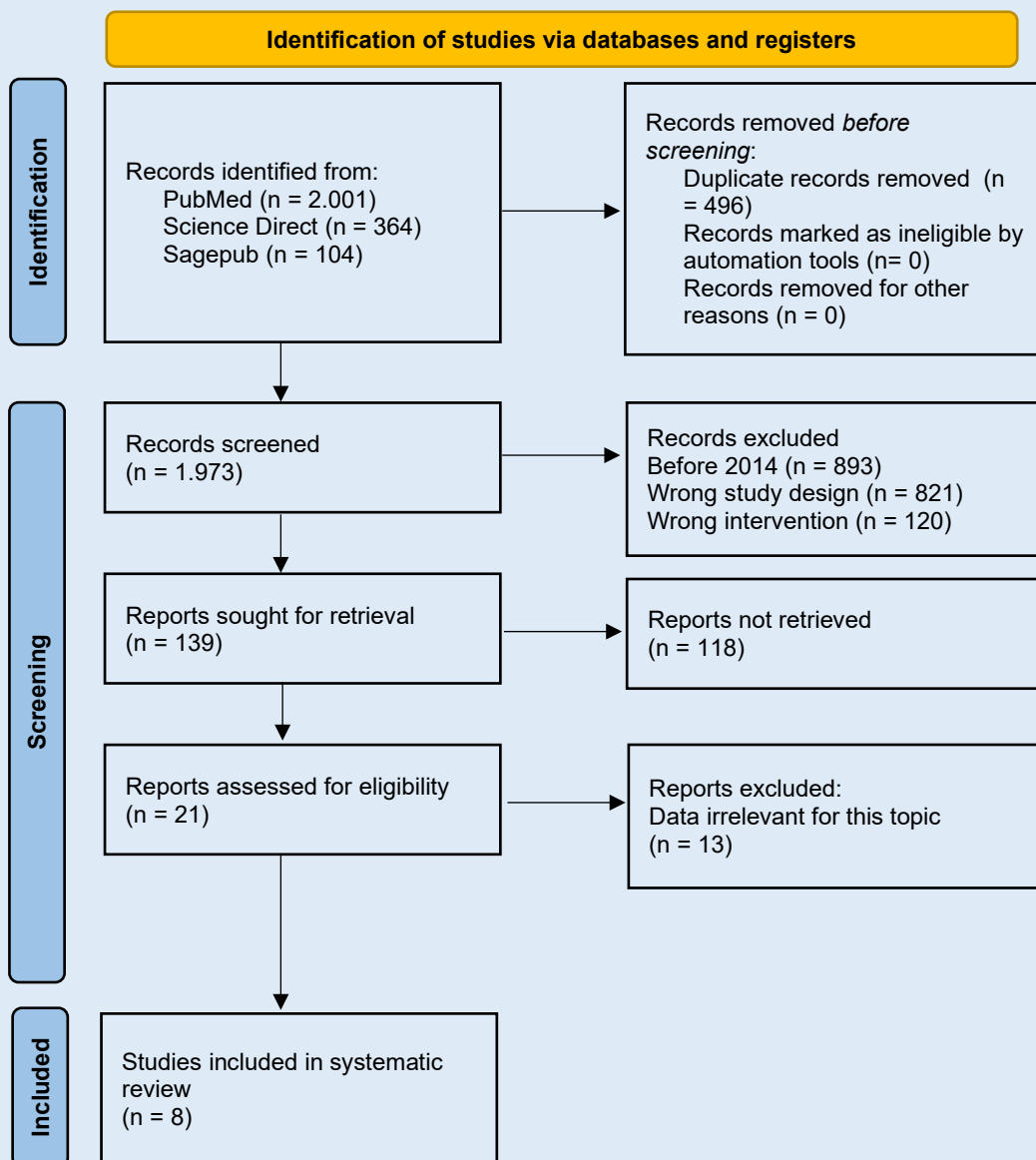


Figure 1. Article search flow chart

RESULT

To initiate the inquiry, our team diligently gathered a considerable assortment of papers from reputable sources such as Science Direct, PubMed, and SagePub. After a thorough three-stage screening process, we selected eight papers that were considered highly relevant to our ongoing systematic inquiry. Subsequently, we selected certain topics for further examination and meticulously evaluated each report. In order to expedite our inquiry, we have furnished a concise summary of the evaluated information in Table 1.

Yang's research suggests tramadol as a promising new treatment for PE, particularly when SSRIs and other therapeutics have failed. However, caution should be exercised before or after chronic use, and future research should focus on high-quality, long-term RCTs with a large number of PE patients to address this issue.⁸

Castiglione's research on pharmacologic treatment of PE revealed high risk of bias in RCT data, with Dapoxetine being the only drug confirmed in meta-analysis,

indicating larger, better-designed clinical trials rather than superior effectiveness.⁹

Gur & Sikka's study highlights the complexity of PE treatment, highlighting the need for standardized evidence-based studies and a clear definition of the disease. They emphasize the importance of considering etiology, pathobiology, and treatment approaches, and the need for large randomized clinical trials.¹⁰

Martyn-St. James et al. found tramadol effective in treating PE, but caution should be exercised due to between-trial heterogeneity and the lack of evaluation of long-term effects and side effects, including addiction potential, in the current evidence base. The variability across placebo-controlled trials limits the assessment of safe and effective minimum daily doses.¹¹

Jian recommends dapoxetine 30 mg OD for PE treatment due to its effectiveness in clinical trials. Tramadol 50 mg OD can be used as an alternative to oral treatment with SSRIs. PDE5is combined with SSRIs is more effective but has more side

effects, making it suitable for PE patients with ED.¹²

Tan et al.'s study revealed that on-demand therapy of tramadol or paroxetine significantly improved IELT and sexual satisfaction scores in patients with PE, with both groups showing good tolerance and better effects compared to placebo.¹³

Sharma et al. discovered tramadol as an effective drug for PE management, with low adverse events. However, effective duration and dose are unknown. Further studies are needed to determine dosage, duration, and side effects

profile, and compare tramadol to other drugs before recommending widespread use.⁷

Lee et al.'s review explores various strategies for treating PE, including behavioral, drug, and surgical interventions. Dapoxetine, an approved as-needed preparation, is the exception. Alternative therapeutic strategies include tramadol, clomiphene, topical treatments, PDE5 inhibitors, and SSRIs, with dapoxetine being the most effective and well-tolerated.⁵

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Yang et al.⁸ (2013)	China	Systematic Review	5 studies	A study of 5 trials involving 715 patients found that tramadol significantly increased IELT values post-therapy, with more pronounced changes in the tramadol group. Patients in the tramadol group also reported improved satisfaction with sexual intercourse and control of ejaculation. However, the incidence of side effects (SEs) was significantly higher in the tramadol group compared to the control group, with most SEs being mild or moderate and transient.
Castiglione et al.⁹ (2015)	Italy	Meta Analysis	22 studies	Tramadol, a medication used to treat IELT, has been found to be more effective than placebo in increasing the duration of epilepsy-induced labor (IELT). However, the interpretation of these meta-analyses may be impaired due to frequent heterogeneity in the pooled analyses.
Gur & Sikka¹⁰ (2015)	Turkey	Review	-	Premature ejaculation (PE) is a prevalent male sexual dysfunction, requiring treatment with antidepressants, local anesthetic agents, and phosphodiesterase type 5 inhibitors.

				Dapoxetine, a short-acting SSRI, is effective and safe.
Martyn-St James et al.¹¹ (2015)	United Kingdom	Meta Analysis	8 studies	Tramadol is an effective therapy for PE, with evidence showing it is more effective than placebo in increasing IELT over eight to 12 weeks. However, it is associated with more adverse events than other treatments, such as erectile dysfunction, constipation, nausea, headache, and vomiting. Addiction problems and breathing difficulties are not assessed in the current evidence base.
Jian et al.¹² (2018)	China	Meta Analysis	48 studies	A review of 48 studies revealed that topical anaesthetic creams (TAs), tramadol, selective serotonin reuptake inhibitors (SSRIs), and phosphodiesterase type 5 inhibitors (PDE5is) are more effective at prolonging IELT compared to placebo. TAs and PDE5is plus SSRI had the highest SUCRA, making them the most likely effective intervention.
Tan et al.¹³ (2021)	China	Meta Analysis	7 studies	A study of 663 patients found that on-demand tramadol or paroxetine therapy significantly improved intravaginal ejaculatory latency time (IELT) and sexual satisfaction scores compared to placebo. On-demand tramadol had a better effect than paroxetine. Safety concerns included sleep disturbance and headache, with no serious adverse events observed in both groups.
Sharma et al.⁷ (2021)	India	Meta Analysis	9 studies	Tramadol significantly improved IELT with a mean difference of 139.6 seconds, out of 9 randomized controlled trials. All dosages except 25mg performed well compared to the placebo. Tramadol fared better at 1 month, 2 months, and 3 months after therapy initiation. However, the Tramadol group reported a significantly higher number of adverse events compared to the placebo.
Lee et al.⁵ (2024)	Korea	Meta Analysis	59 studies	Tramadol, a commonly prescribed pharmaceutical agent for patients with PE, ranked first in terms of ELT after analyzing 143 effect sizes with 43 treatments from 59 direct comparison trials. Among these, 9 mono treatments and 4 combination treatments were statistically significant.

DISCUSSION

Tramadol has the potential as a drug for avoiding premature ejaculation and improving sexual satisfaction during intercourse. The administration of tramadol has demonstrated substantial enhancements in the duration of intravaginal ejaculation latency time (IELT), as observed in a study conducted by Mulhall in 2006.¹⁴ This study provides fresh evidence supporting the potential utilization of tramadol in the management of premature ejaculation. Nevertheless, the efficacy and safety of tramadol in the treatment of PE are still a subject of discussion due to a lack of solid evidence supporting its use over an extended period.⁸ In May 2009, the US Food and Drug Administration issued a warning letter about the addictive nature of tramadol. The letter acknowledged that tramadol was believed to have a lower likelihood of dependence compared to conventional opioids. However, it emphasized the importance of recognizing the potential risk of addiction when using tramadol as an on-demand treatment for premature ejaculation.¹⁵

Tramadol hydrochloride therapy has proven to be an effective treatment for PE, as studies have demonstrated its efficacy in cases with lifelong PE while causing little short-term negative effects. Nevertheless, data are scarce regarding long-term safety, potential for abuse, and drug dependence. Tramadol hydrochloride medication is highly effective in treating PE, particularly when administered at low dosages of 25 and 50 mg. Additional research is required to determine the effectiveness of treatment and any possible adverse effects. This should include follow-up and long-term studies that use a placebo control group.^{16,17}

The 2014 Guidelines of the European Association of Urology for male sexual dysfunction suggest various pharmacological treatment options. These options include using dapoxetine as needed, taking a longer-acting selective serotonin reuptake inhibitor (SSRI) daily, taking clomipramine daily, using topical local anesthetic agents, and using tramadol as needed (which is not officially approved for this use).¹⁸ Nevertheless, the existing body of

information on tramadol does not offer more definitive assessments of the connection between tramadol-induced improvements in IELT, ejaculatory control, and sexual satisfaction.¹¹

Tramadol is a potent analgesic derived from opioids that is prescribed for the management of moderate to severe pain. The administration of three different dosages (25, 50, and 100 mg once a day) resulted in a substantial increase in the IELT as compared to the placebo. The SUCRA was deemed average when compared to other regimens. Nevertheless, administering a high dosage of 100 mg did not provide a notable benefit. The low-dosage regimens were widely accepted and well tolerated, and the lower confidence interval (CI) for a daily dose of 25 mg was near zero. Hence, a daily dosage of tramadol 50 mg may be an appropriate treatment for premature ejaculation, but it should be carefully considered in light of the potential hazards of drug dependence.^{12,19}

A study conducted from the perspective of evidence-based medicine compared the effectiveness

of on-demand tramadol and on-demand paroxetine in treating patients with prostate-erectile dysfunction (PE). The results indicated that both tramadol and paroxetine significantly improved the condition of patients compared to a placebo, as measured by IELT (intravaginal ejaculatory latency time) and sexual satisfaction scores. The US Food and Drug Administration (FDA) has approved Tramadol, a synthetic opioid that has a central analgesic effect and is known for its safety.^{13,20} It is appropriate for immediate use, with the highest amount present in the body 95-110 minutes after taking it orally.²¹ Sleep disturbance was the most prevalent adverse event associated with tramadol, whereas headache was the most prevalent adverse event reported in the paroxetine group. There were no significant negative events reported in either group.^{16,22-24}

The precise mechanism by which Tramadol affects premature ejaculation (PE) is not well understood, however, it is believed to reduce sensitivity and postpone ejaculation.⁵ According to Salem

(2008), the frequency of adverse events and the safety data of tramadol are satisfactory.²⁵ Research has demonstrated that administering a dosage of 50 mg two hours before engaging in sexual activity enhances ejaculatory latency time (ELT) and sexual satisfaction in individuals diagnosed with PE. Nevertheless, an additional longitudinal study is necessary to determine the probability of opioid addiction in this particular environment.⁵

CONCLUSION

Tramadol, a powerful pain reliever derived from opioids, has the capacity to inhibit premature ejaculation and enhance sexual gratification during sexual intercourse. Research has demonstrated that the use of tramadol hydrochloride is an effective treatment for premature ejaculation (PE), especially when given in small doses of 25 and 50 mg. Nevertheless, the effectiveness and safety of tramadol in the treatment of PE are still a matter of debate due to insufficient empirical evidence substantiating its long-term usage. In 2009, the US Food and Drug Administration issued a warning

letter on the addictive properties of tramadol. The letter acknowledged that tramadol had a lesser probability of causing dependency compared to traditional opioids. Tramadol hydrochloride medicine is highly efficacious in the treatment of PE, especially when given at low doses of 25 and 50 mg. However, further research is necessary to ascertain the efficacy of the treatment and any potential negative consequences, including conducting follow-up and long-term trials with a placebo control group.

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