

ORIGINAL ARTICLE

Safety and efficacy of tramadol hydrochloride on treatment of premature ejaculation

Bayoumy I Eassa¹ and Mohamed A El-Shazly²

Premature ejaculation (PE) is the most common sexual disorder. It affects 20%–30% of adult men; the aetiology of this condition has not yet been elucidated. The aim of this study is to evaluate the efficacy, safety, tolerability, undesirable effects and improved satisfaction with sexual intercourse with tramadol hydrochloride at different dosages for the treatment of PE. A total of 300 patients who presented with lifelong (primary) PE were included in this study. The study was performed for 28 weeks, in which placebo (starch tablet) was given for 4 weeks, and active ingredient (tramadol hydrochloride) was administered at different therapeutic dosages for 24 weeks. Patients were divided into three equal groups, each consisting of 100 patients. The first group (A) was given tramadol hydrochloride capsule 25 mg. The second group (B) was given tramadol hydrochloride capsule 50 mg. The third group (C) was given tramadol hydrochloride capsule 100 mg. All of the 300 participants included completed the study voluntarily. The age of the patients varied from 25 to 50 years. After the treatment period, the recorded data were collected for each group and analysed. The results showed a highly significant increase in the mean intravaginal ejaculatory latency time (IELT) in all groups compared to baseline data ($P < 0.0001$). We concluded that using tramadol hydrochloride at different doses on demand for the treatment of PE is effective, safe and tolerable, with minimal undesirable effects, and approval for this indication should be sought.

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INTRODUCTION

Ejaculatory dysfunction is a common and distressing cause of male sexual difficulties. It also represents a significant cause of male factor subfertility, posing distinct reproductive challenges for couples attempting to conceive. Ejaculatory dysfunction can be classified along a spectrum ranging from premature ejaculation (PE), retarded or delayed ejaculation (DE), to complete anejaculation (AE), along with retrograde ejaculation (RE).¹

PE is the most common male sexual dysfunction, affecting approximately 20%–30% of the male population at any given time.²

Masters and Johnson³ first suggested the concept that first intercourse experiences that were rushed and associated with nervousness at the time of inexperienced sex led to PE.

The medical literature contains several definitions of PE. The lack of agreement on what constitutes PE has hampered basic and clinical research into the aetiology and management of this condition. Quantitative measures of intercourse, such as the intravaginal ejaculatory latency time (IELT), the number of thrusts between penetration and ejaculation, the extent of partner sexual satisfaction, and the patient's assessment of his voluntary control over ejaculation, have been described. Each of the four criteria above has been operationalized, although not always with consistency.⁴

The International Society of Sexual Medicine (ISSM) recently published an evidence-based definition of lifelong (primary) PE as a male

sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within approximately 1 min of vaginal penetration, 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.⁵

In 1994, the concept of IELT was introduced.⁶ IELT has been defined as the length of time between vaginal entry (IELT), anal (anal ejaculatory latency time) or oral penetration (oral ejaculatory latency time) and the initiation of masturbation (masturbatory ejaculatory latency time) and ejaculation.⁷ IELT forms the basis of most current clinical studies on PE.⁸

Based on Dutch data,⁹ the baseline IELT defining ejaculation that occurred prematurely was estimated at less than 1 min. Some publications stated that any ejaculation occurring within 1, 2, 3, or even 7 min of penetration is considered premature; others specify the number of penile thrusts, considering 8–15 thrusts as a criterion for PE. Still others consider partner satisfaction, suggesting that a man experiences PE if he is unable to delay his ejaculation until his partner is sexually satisfied in at least 50% of their coital connections.¹⁰

Anteportant ejaculation is the term for men who ejaculate prior to vaginal penetration and is considered the most severe form of PE. Such men/couples typically present when they are having difficulty conceiving children. It is estimated that 5% of lifelong PE men suffer from anteportant PE.¹¹

¹Department of Dermatology, Venereology and Andrology, Al-Azhar University, Cairo 11884, Egypt and ²Department of Urology, Menoufiya University, Cairo 32511, Egypt
Correspondence: Dr BI Eassa (bayeassa@yahoo.com)

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PE has been classified as either primary (lifelong), which begins when a male first becomes sexually active, or secondary (acquired), meaning that a male previously had an acceptable level of ejaculatory control and developed the condition later in life,¹² and it has been associated with chronic prostatitis and specific endocrinopathies, including diabetes mellitus and hyperthyroidism.¹³ In these instances, PE is usually reversed when the underlying disorder is treated.¹⁴

The second international consultation on erectile and sexual dysfunctions recommends the use of the term early ejaculation rather than PE; however, PE will continue to be used for the near future.¹⁵

Tramadol hydrochloride was developed in the late 1970s.¹⁶ It possesses weak agonist action at the μ -opioid receptor, releases serotonin and inhibits the reuptake of norepinephrine.¹⁷ Its mode of action is not completely understood. From animal tests, at least two complementary mechanisms appear applicable: the binding of parent and M1 metabolites to μ -opioid receptors (antinociceptive effect), and the inhibition of the reuptake of norepinephrine and serotonin (5-HT), which may account for its effect on delaying ejaculation.¹⁸

Tramadol undergoes hepatic metabolism *via* the cytochrome P450 isozyme CYP2D6 and is *O*- and *N*-demethylated to five different metabolites. Of these, M1 (*O*-desmethyltramadol) is the most significant metabolite, because it has 200 times the μ -affinity of tramadol and has an elimination half-life of 9 h compared with 6 h for tramadol. In the 6% of the population who have slow CYP2D6 activity, there is a slightly reduced analgesic effect. Phase II hepatic metabolism renders the metabolites water soluble, and they are excreted by the kidneys; thus, reduced doses may be used in renal and hepatic impairment.¹⁹

The objective of this study was to evaluate the efficacy, safety, tolerability, undesirable effects, improved satisfaction with sexual intercourse and control over ejaculation with tramadol hydrochloride at different dosages for the treatment of PE.

PATIENTS AND METHODS

Subjects

A total of 300 heterosexual men complaining of lifelong (primary) PE were recruited from the outpatient clinic of Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt, from January 2009 to December 2011. The study was approved by the local medical ethics committee. The enrolled men aged 25–50 years had been in a stable, monogamous, heterosexual relationship with regular sexual intercourse at least twice per week with a cooperative female partner and had been married for at least 2 years. The study was performed for 28 weeks, during which the placebo was given for 4 weeks, and the active ingredient (tramadol hydrochloride) (Grünenthal GmbH, Aachen, Germany) was administered at different therapeutic dosages for 24 weeks.

Study design

Patients were randomly divided through a simple (complete) randomisation process into three groups, each consisting of 100 patients, and administered placebo tablets (starch) for 4 weeks before being administered active ingredient (tramadol hydrochloride). The first group (A) was given tramadol hydrochloride capsule 25 mg. The second group (B) was given tramadol hydrochloride capsule 50 mg. The third group (C) was given tramadol hydrochloride 100 mg. All of the patients were instructed to take the drug with a cup of water 2–3 h before intercourse. All of the patients were asked about their satisfaction and control of ejaculation before and after treatment, in addition to their tolerance to the drug and whether there were any side effects. No specific validated questionnaire was used in this study.

Investigations

Routine laboratory investigations were performed for all patients and included complete blood count, urine analysis, liver function test, renal profile, lipid profile, blood sugar, hormonal profile (follicle-stimulating hormone, luteinizing hormone, testosterone, and prolactin and thyroid profile (thyroid-stimulating hormone, T3 and T4).

Assessment method (IELT)

The duration of IELT is the time from penetration (vaginal penetration) until ejaculation (release of semen) and was timed on a stopwatch by 'start' (penetration) to 'stop' (ejaculation). Either of the partners was allowed to handle the stopwatch; however, it was requested that the same person remain responsible for every IELT measurement for the duration of the study, and they were asked to be honest in recording the time. They were instructed to calculate and record the exact time after ejaculation.

After explanation of the purpose of the study, all of the patients agreed to participate in the study, and written informed consent was requested from all patients and signed before starting treatment. They were provided with a stopwatch and a sexual events diary, were carefully instructed on how to measure the IELT and were reminded and confirmed during the follow-up visits (every 2 weeks).

Exclusion criteria

Exclusion criteria included patients with secondary (organic) PE; sexual dysfunction (decreased sexual interest, erectile dysfunction according to the International Index of Erectile Function, painful intercourse, urinary tract infection, or female sexual dysfunction that affected the sexual relationship); current physical illness (e.g., diabetes mellitus, liver diseases, dyslipidaemia, hypertension, heart diseases, renal diseases, thyroid diseases and hormonal disorders); history of a psychiatric or neurological disorder; substance abuse (alcohol or drug); previous pelvic trauma or surgery; spinal cord injury; or currently taking a drug known to affect sexual function, including either topical penile applications or systemic drugs. All male patients had been circumcized at birth and were asked to avoid condom use.

Statistical analysis

The computer software Stat View 5 (SAS Institute Inc., Cary, NC, USA) was used for data analysis. Paired *t*-test was used for comparison between the mean values. A $P < 0.05$ was considered significance.

RESULTS

All 300 participants included in this study completed the period voluntarily. The age of the patients varied from 25 to 50 years (mean 34.47 ± 8.16 , 33.86 ± 8.31 and 33.15 ± 7.24 years in groups A, B and C, respectively). No changes in hormonal profile were recorded before and after treatment.

At the end of the first 4 weeks (placebo period), recorded data were collected from all patients and analysed by paired *t*-test. The results showed that the mean IELT was ≤ 4 min. The mean baseline of IELT before treatment was 2.82 ± 0.89 in group A, 2.79 ± 0.95 in group B, and 2.99 ± 0.86 in group C (**Table 1**).

At the end of the study, i.e., after 24 weeks of treatment with tramadol hydrochloride, the recorded data were collected from each group and analysed. As shown in **Table 1**, the mean IELT in all groups was significantly different compared to baseline data ($P < 0.0001$). The IELT was 13.17 ± 1.83 min (range 8.00–15.00 min) in group A, 23.43 ± 1.78 min (range 18.00–25.00 min) in group B and 36.49 ± 3.25 (range 29.00–40.00 min) in group C (**Table 1**). All of the patients

Table 1 Statistical comparison between all groups

	IELT pre-treatment (placebo) (min)	IELT post-treatment (min)	P value
Group A	2.82±0.89	13.17±1.83	<0.0001
Group B	2.79±0.95	23.43±1.78	<0.0001
Group C	2.99±0.86	36.49±3.25	<0.0001

treated with tramadol hydrochloride at different dosages gained satisfactory control over ejaculation compared to baseline data in each group, and the drug was well tolerated (Figure 1).

Regarding undesirable effects, patients in all groups complained of somnolence (light sleeping or insomnia) and pruritus (itching without skin lesions), and the severity and intensity were dose-dependent. However, the patients in groups B and C complained of additional undesirable effects, including dizziness (18% and 38%, respectively), light headache (heaviness) (16% and 30%, respectively), and dryness of mouth (13% and 28%, respectively). Nausea (20%) and vomiting (17%) were only reported in group C (Table 2). All of these undesirable effects usually resolved approximately 10 h after ingestion of the drug.

Most of the patients (90% (270/300)) treated with tramadol hydrochloride reported an increase in penile rigidity during intercourse throughout the treatment period, and this claim was confirmed by their partners.

DISCUSSION

Human sexual function includes sexual *libido*, penile erection, ejaculation and orgasm. Patients with PE can be divided into primary and secondary PE. Primary (lifelong) PE patients are patients who have suffered chronically from the beginning of their sexual lives, and secondary PE patients have suffered from PE after years of normal sexual functioning.²⁰

PE is the most common form of male sexual dysfunction, affecting 30% of men, and it is defined as an inability to exert voluntary control over the ejaculatory reflex, resulting in rapid orgasm.²¹ Currently, available data suggest that only 1%–12% of males self-reporting PE receive treatment for their dysfunction.² In a recent study conducted in Korea, the self-reported prevalence rate was 27.5%.²²

PE, unlike ED, affects men of all ages equally. However, both PE and ED coexist, and PE can often be misdiagnosed as ED in many men.

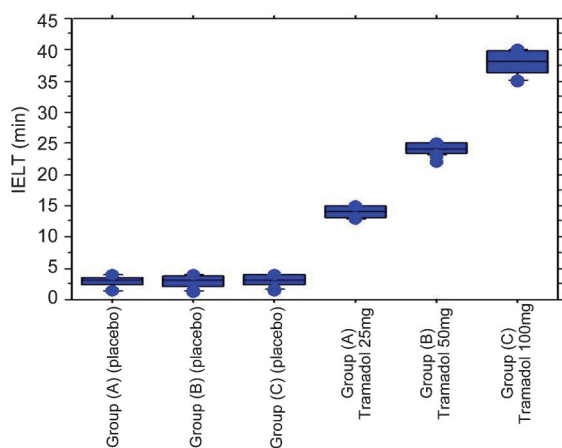


Figure 1 Mean IELT in all groups before and after treatment. IELT, intravaginal ejaculatory latency time.

Table 2 Undesirable side effects in all groups

Symptoms	Group A	Group B	Group C
Somnolence	100% (100/100)	100% (100/100)	100% (100/100)
Pruritus	100% (100/100)	100% (100/100)	100% (100/100)
Dizziness	—	18% (18/100)	38% (38/100)
Headache	—	16% (16/100)	30% (30/100)
Mouth dryness	—	13% (13/100)	28% (28/100)
Nausea	—	—	20% (20/100)
Vomiting	—	—	17% (17/100)

This is, in part, due to the lack of knowledge about PE, the absence of performing a careful history, and the nonexistence of diagnostic tools for PE.²³

The diagnostic criterion for many authors is the time between penetration and ejaculation, and this time is agreed to be 1 min.²⁴ Rowland *et al.*⁴ suggested that an IELT of 2 min or less may serve as an adequately sensitive criterion for defining PE. Other authors concluded that any ejaculation occurring within 1, 2, 3, or even 7 min of penetration should be considered premature,¹⁰ but none of the definitions offer any supportive rationale for their proposed cut-off time.⁸ Waldinger *et al.*²⁵ published multinational reports of IELT (The Netherlands, United Kingdom, United States, Spain and Turkey), and they found that the median IELT was 5.4 min (range 0.55–44.1 min) and that the distribution of IELT in all five countries was positively skewed.

The exact aetiology of PE is unknown, but it is believed to include neurobiological and/or psychological components and/or penile hypersensitivity.²⁶

There are multiple reports in the literature on the use of a variety of drugs in the treatment of PE. These drugs facilitate ejaculation through either a central dopaminergic or anti-serotonergic mechanism of action.^{27,28}

PE has been treated with various modalities, including behavioural therapy,³ topical anaesthetic creams or sprays,²⁹ and off-label use of oral pharmacotherapy, such as phosphodiesterase-5 inhibitors,³⁰ selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, citalopram and duloxetine),³¹ and a tricyclic antidepressant (clomipramine) that blocks serotonin, dopamine and norepinephrine transporters.³² These modalities are associated with variable rates of success when taken daily,^{33,34} and intracavernosal vasoactive drug injection has also been reported.³⁵ In contrast, some reports suggest that these drugs may be effective when received as needed.^{36,37}

Other agents, including α -adrenoreceptor antagonists (terazosin and alfuzosin)³⁸ and an analgesic opioid receptor agonist and norepinephrine reuptake inhibitor (tramadol), have also been investigated for treating PE.³⁹ Psychotherapy and behavioural therapy also have a role, although well-designed, controlled trials that use such approaches are lacking.⁴⁰

PE management is dependent upon aetiology. When secondary to ED, aetiology-specific treatment is employed. When PE is lifelong, initial pharmacotherapy (SSRI, topical anaesthesia, or phosphodiesterase-5 inhibitors) is appropriate. When PE is associated with psychogenic/relationship factors, behavioural therapy is indicated. When PE is acquired, pharmacotherapy and/or behavioural therapies are preferred.² Melnik *et al.*⁴¹ concluded that there is weak and inconsistent evidence regarding the effectiveness of psychological interventions for the treatment of PE.

Currently, there is no US Food and Drug Administration (FDA)-approved pharmacological therapies for treating PE.⁴² To date, the largest trials of a treatment for PE have been conducted with dapoxetine, a

short-acting SSRI that is the only oral agent approved for the treatment of PE in several European, Asia-Pacific and South American countries.⁴³

Tramadol is almost completely absorbed when given orally, and it has an apparent elimination half-life of 6 h in humans. Its bioavailability of 70% after a single administration can be entirely attributed to first-pass metabolism. After multiple dosing, the bioavailability increases to almost 100%. Twenty percent of the drug is bound to plasma proteins. Approximately 90% of the administered dose is recovered in urine either unchanged (30%) or as metabolites (60%), and the remainder is eliminated in the faeces.⁴⁴

Safarinejad and Hosseini⁴⁵ published a double-blind, placebo-controlled, fixed-dose study indicating that the on-demand use of 50 mg tramadol exerted a significant ejaculation-delaying effect in men with PE. Additionally, Salem *et al.*,⁴² in a single-blind, placebo-controlled study in men with PE, concluded that the on-demand use of 25 mg tramadol showed impressive results in delaying ejaculation.⁴²

In an open-label crossover comparative study of daily paroxetine (20 mg) and on-demand tramadol (50 mg) in 35 subjects with lifelong PE, superior IELT fold increases and responses were demonstrated with paroxetine (22 fold vs. fivefold for tramadol) after 12 weeks of treatment.³⁹

Hellstrom⁴⁶ stated that tramadol for the treatment of PE showed promise, but the data available from small trials need to be corroborated. In addition, long-term studies are warranted to investigate the risk of opioid addiction. Bar-Or *et al.*⁴⁷ concluded that using the tramadol orally disintegrating tablet on demand is an effective treatment for PE at a small (62 mg) and safe therapeutic dose, and it provides a new option for managing mild to severe PE.

Xiong *et al.*⁴⁸ found that the treatment of PE with tramadol hydrochloride with behavioural modification showed positive effects in prolonging IELT and improving partners' intercourse satisfaction. More multicentre and double-blind studies are required to evaluate its efficacy and safety as a routine therapy for PE. Kaynar *et al.*⁴⁹ also stated that the use of low-dose tramadol on demand is effective for lifelong PE.

In our study, we concluded that the use of tramadol hydrochloride at 25, 50 or 100 mg, 2–3 h on demand before sexual activity showed a highly significant delay in ejaculation and a 10- to 20-fold increase in IELT compared to mean baseline data. At the same time, the drug was well accepted and tolerated regarding its side effects, especially at low dosage (25 and 50 mg). This result is in agreement with previous studies.^{39,42,45–49}

Tramadol has long been considered to have a low abuse potential. Although it is an opioid agonist, it has not been classified as a scheduled substance. According to the US FDA, the rate of addiction was 1 in 100 000 during the last 18-month period of surveillance.⁵⁰ Because the M1 metabolite is the principal agonist for μ -opioid receptors, the delayed agonist activity reduces dependence liability. The noradrenalin reuptake effects may also play a role in reducing dependence.⁵¹

A trial in a chronic pain population of 11 352 enrolled subjects, 8139 of whom completed the trial and 68.2% of whom were female, identified that the rate of abuse with tramadol (2.7%) was not significantly greater than nonsteroidal anti-inflammatory drugs (2.5%) and less than oxycodone (4.9%).⁵²

Regarding addiction to tramadol hydrochloride, we believe that the use of this drug on demand is safe and tolerable, especially within the therapeutic dose range from 50–400 mg daily (mentioned in the package insert). According to the US FDA, the rate of addiction was low and mostly reported in patients with a prior history of substance abuse.^{49,50}

Although the mechanism by which tramadol delays ejaculation has not been elucidated, numerous laboratory studies have shown that tramadol acts as a mild μ -opioid agonist,²³ *N*-methyl-D-aspartate

receptor antagonist.⁵³ 5-hydroxytryptamine type 2C receptor antagonist,⁵⁴ 5-nicotinic acetylcholine receptor antagonist,⁵⁵ M1 and M3 muscarinic acetylcholine receptor antagonist,⁵⁶ and a serotonin and norepinephrine modulator.²³ It is possible that one or a combination of these effects leads to a delay in ejaculation.

Safarinejad and Hosseini⁴⁵ hypothesized that tramadol affects PE through a multimodal mechanism, including inhibiting the neuronal reuptake of serotonin, inhibiting the neuronal reuptake of noradrenaline, enhancing serotonin efflux, antinociceptive effects and inhibiting spinal somatosensory evoked potentials; thus, it has anaesthetic-type effects on peripheral sensory nerves.

Most of the patients included in this study reported that the drug reduced penile sensitivity, especially the gland penis, and this result is in agreement with Safarinejad and Hosseini, who mentioned the anaesthetic-type effect on peripheral sensory nerves,⁴⁵ and in disagreement with Paick *et al.*,⁵⁷ who failed to identify any penile hypersensitivity factors in patients with PE.

Tramadol has been used off-label and empirically since 2000 for the treatment of PE, because of its acceptable safety profile and because patients taking tramadol for analgesia reported delayed ejaculation.⁴⁸ As a result of its short half-life, tramadol can be used in an on-demand dosing protocol.⁵⁸

The inability to control and defer ejaculation until the female partner is sexually satisfied in at least 50% of intercourse attempts was proposed as a definition of PE by Masters and Johnson.³ An inherent problem exists in defining a man as dysfunctional based on the sexual response of his partner, as only 30% of women achieve orgasm during sexual intercourse, regardless of the extent of their partner's ejaculatory control and latency.²

The undesirable effects reported from the patients in this study were minimal, temporary and not serious compared to other medications used for the treatment of PE, especially SSRIs, in which delayed ejaculation occurs at the expense of a decrease in *libido* and a moderate decrease in penile rigidity.⁵⁹ In our study, most of the patients reported an increase in penile rigidity during intercourse throughout the treatment period.

Zin *et al.*⁶⁰ stated that the most important priorities that need to be addressed in the research of PE are the lack of a standard animal model and adequately powered aetiological studies enrolling both PE patients and unaffected control males. There remains a long way to go in terms of future research.

The ideal treatment for PE should meet the following criteria: on-demand treatment with quick onset of action so as not to interfere with sexual spontaneity, high rates of efficacy after early doses and minimal sexual and other adverse effects.⁶¹ We met the above criteria in our study, with minimal adverse effects and no reduction in sexual activities.

CONCLUSIONS

We concluded that using tramadol hydrochloride on demand at small dosages (25 and 50 mg) for the treatment of PE is acceptable for managing PE because it is effective, safe, and tolerable, with non-serious side effects, and approval for this indication should be sought.

AUTHOR CONTRIBUTIONS

BIE contributed to conception, design, acquisition, analysis and interpretation of data, drafting the manuscript, revising it critically for important intellectual content, and giving final approval of the version to be published. MAE contributed to conception, interpretation of data, and final approval of the version to be published.

COMPETING FINANCIAL INTERESTS

All authors declare that there are no competing financial interests.

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