PJSS Vol. 68, No. 3, July-December, 2013

PJSS PHILIPPINE JOURNAL OF SURGICAL SPECIALTIES

Meta-Analysis with Meta-Regression and Systematic Review of the Efficacy of On-Demand Tramadol for the Treatment of Lifelong Premature Ejaculation

Marlon P. Martinez, M.D.

Department of Surgery, University of Santo Tomas Hospital

This is a systematic review and meta-analysis on the efficacy of on-demand tramadol for the treatment of lifelong premature ejaculation.
Methods: A systematic review and meta-analysis with meta-regression of trials evaluating the use of tramadol to treat premature ejaculation using intravaginal ejaculation latency time as a measure. Relevant studies were identified using PubMed, Ebscohost, MEDLINE, EMBASE and the Cochrane Collaboration Library.
Results: This analysis included 8 publications. Study of the intravaginal ejaculation latency time (IELT) among 599 patients showed that tramadol was effective in subjects with premature ejaculation as seen by the significant difference in mean IELT of tramadol treated patients versus those receiving placebo (mean difference 2.43 minutes; 95% CI 0.93-3.93; P=0.002). The effect on IELT between tramadol and paroxetine was not statistically significant (mean difference -0.58; 95% CI -5.81 to 4.65; P=0.83) . Meta-regression analysis showed that the lower the dose of tramadol, the higher its benefit in the prolongation of IELT, however, there was no significant difference (95% CI regression coefficient -0.0956 to 0.0322). There was a significant difference in adverse effects profile of tramadol versus placebo (risk ratio 2.48; 95% CI 1.55-3.98; overall effect Z= 3.79; P<0.0002) and overall therapeutic effectiveness between tramadol compared to placebo (risk ratio 0.55; 95% CI 0.46-0.67; P<0.00001).
Conclusion: On-demand tramadol is an effective treatment for lifelong premature ejaculation. It significantly prolongs the intravaginal ejaculation latency time. The overall adverse events and overall therapeutic effectiveness are significantly greater during treatment with tramadol.

Key words: Premature ejaculation, tramadol, intravaginal ejaculation latency time (IELT)

Premature ejaculation (PE) is the most prevalent male sexual complaint a?ecting 20% to 30% of men.[1] Although erectile dysfunction affects older men more frequently than their younger counterparts, the prevalence of premature ejaculation is similar for men of all ages. It remains underdiagnosed and undertreated because of misconceptions by patients and physicians about its causes and lack of approved treatment.[2] In a comprehensive, internet-based survey done by Porst, et al. only 9.0% of men with premature ejaculation reported having consulted a physician for the condition; 81.9% had to initiate the conversation about premature ejaculation and 91.5% reported little or no improvement as a result of seeking treatment.[3]

Waldinger, et al. hypothesized that lifelong early ejaculation in humans may be explained by neurotransmitter serotonin or 5-hydroxytryptamine (5-HT) either a hyposensitivity of the 5-HT2C and 5-HT1B or hypersensitivity of the 5-HT1A receptors. Activation of post-synaptic 5-HT2C or 5-HT1B receptors prolongs ejaculatory latency, whereas activation of pre-synaptic 5-HT1A autoreceptors, which inhibits 5-HT release, decreases ejaculatory latency. They hypothesized that men with a low 5-HT neurotransmission and 5-HT2C receptor hyposensitivity may have their ejaculatory threshold genetically set at a lower point and ejaculate quickly with minimal stimulation.[4]

Several studies have shown that premature ejaculation has a marked effect on the quality of life of men. Both men and their partners affirm negative effects and interpersonal difficulty related to their PE and an overall reduction in their quality of life. In a multicenter, observational study by Patrick, et al. shorter intravaginal ejaculatory latency time (IELT), which was defined as the time between the start of intromission and

the start of intravaginal ejaculation, was significantly associated with reduced ejaculatory control and sexual satisfaction and increased distress and interpersonal difficulty.[5]

Premature ejaculation can be classified as either a lifelong condition which is present since the onset of sexual maturity or an acquired condition that develops after an interval of normal sexual function.[6] In the earlier years, the definition of PE is not standardized and a universally accepted definition has yet to be established. Different authorities [Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR), International Statistical Classification of Diseases and Related Health Problems (ICD-10), International Society for Sexual Medicine (ISSM), European Association of Urology (EAU) Guidelines, American Urological Association (AUA) Guidelines, International Consultation on Urologic Disease) have their own definitions. Because of the discontent with the existing definitions of premature ejaculation, last 2010, ISSM developed a definition grounded in clearly definable scientific criteria. Lifelong PE is defined as " a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and 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."[7] Two other experiences of ejaculation have been described that are sometimes mistaken for premature ejaculation which have been termed Natural Variable PE and Premature-like Ejaculatory Dysfunction; neither is a sexual dysfunction.[1]

Measurement of IELT might provide the most objective and quantitative method for assessing the severity and treatment response of PE in clinical studies.[8] In 2005, Waldinger, et al. published a multinational report involving Netherlands, United Kingdom, United States, Spain, and Turkey determining the stopwatch assessed IELT distribution. The median IELT was 5.4 minutes (range, 0.55-44.1 minutes) and the distribution of the IELT in all five countries was positively skewed. The median IELT decreased significantly with age, from 6.5 minutes in the 18-30 years group, to 4.3 minutes in the group older than 51 years. For all five countries, median IELT values were independent of condom usage and circumcision status.[9]

The proposed treatment modalities for PE include topical agents, creams, sprays, behavioral modification, and drug therapies.[10] Treatment of PE depends on its etiology.[11] Pharmacotherapy is the basis of treatment in lifelong PE but all medical treatments are off-label indications. An ideal pharmacologic treatment for PE would be an on-demand-dosed treatment with high rate of efficacy after early doses, have a quick onset of action, not to interfere with sexual spontaneity and not have sexual side effects.[12]

There are currently no Food and Drug Administration (FDA)-approved pharmacological therapies for treating PE. Selective serotonin reuptake inhibitors (SSRIs) are commonly used in a daily dosing schedule for the treatment of PE. In addition to the potentially desirable side-effect of delaying ejaculation, this dosing regimen for long-acting SSRIs is associated with a number of undesirable side-effects, such as decreased libido and erectile dysfunction.[13] Pharmacokinetic profiles of SSRIs provide constant systemic concentration with long-term administration, and it takes about 2-3 weeks to reach a maximum steady-state concentration in order to exhibit efficacy.[14]

Among the SSRIs, paroxetine has shown the best effects on prolongation of IELT. Two studies have reported contrasting results comparing its superior efficacy against tramadol.[15,16] Recently, dapoxetine, a new SSRI with a favourable pharmacokinetic profile, has been evaluated and reported in four published pivotal phase III randomised, placebo-controlled, multicentre studies for safety and efficacy in the treatment of men with PE of both lifelong and acquired aetiology.[17,18]

A sudden reduction or cessation of long-term treatment of SSRIs can lead to the "SSRI discontinuation syndrome," a group of symptoms including nausea, vomiting, dizziness, headache, ataxia, drowsiness, anxiety, and insomnia. These symptoms begin 1 to 3 days after the drug cessation and may continue for more than a week in some patients. This syndrome is usually reversible by SSRI reintroduction. Thus it is recommended that SSRI agents should be gradually withdrawn over a 2- to 4-week period, and all patients using SSRI for PE should be forewarned about this.[19]

In 2009, Salonia, et al. reported the "fear" of using antidepressant for treatment of PE as the main cause for refusal of start of therapy and also the "treatment effect below expectations" as the main cause of discontinuation of treatment.[20]

The effect on sexual function of patients taking Tramadol for analgesia was observed. The fact that many of these patients had delayed ejaculation or anejaculation inspired the use of tramadol empirically since 2000 in patients with PE. These findings led to the hypothesis that tramadol produces its treatment effects on PE by multimodal mechanisms. These mechanisms are inhibition of neuronal reuptake of serotonin, inhibition of neuronal reuptake of noradrenaline, enhancing serotonin efflux, antinociceptive effect, and inhibition of spinal somatosensory-evoked potentials.[21]

Similar to dapoxetine, tramadol is rapidly absorbed and eliminated, which are desirable properties for an as needed dosing regimen.[22] After oral administration, tramadol is absorbed almost completely and quite rapidly after a lag time of 0.5 hour. Peak plasma concentrations are attained within 1.6 to 1.9 hours. Tramadol is rapidly distributed in the body, with a distribution half-life in the initial phase of 6 minutes, followed by a slower distribution phase with a half-life of 1.7 hours.[23] Tramadol is mainly excreted approximately 90% via kidneys. The mean elimination half-life is approximately 5 to 6 hours.[24] As a result of its short half-life, tramadol can be used in an on-demand dosing protocol.[25]

A review was performed on all available drug treatment studies and a meta-analysis was conducted on studies using tramadol for on-demand treatment of PE. This study aimed to conduct a meta-analysis with meta-regression and systematic review investigating the efficacy of on-demand tramadol for treatment of lifelong PE.

Methods

Literature Search Strategy

A literature search was performed using PubMed, Ebscohost, MEDLINE, EMBASE and the Cochrane Collaboration Library from January 2000 - January 2012 on the efficacy of tramadol in the treatment of PE. The following keywords were used: "Tramadol", "Intravaginal ejaculation latency time", "Premature Ejaculation" and "treatment". All matches were appraised by titles and abstracts and those relevant to the study were initially included for the appraisal. Articles were initially retrieved and those with missing or unpublished data were excluded. Risk of bias and validity of each retrieved article were addressed and graded using the risk of bias assessment feature of RevMan 5.0 and the Jadad scoring.

Inclusion and Exclusion Criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: studies evaluating the use of tramadol in treating PE, parameters measured included the IELT, randomized controlled trials and prospective study designs. Studies were excluded if one of the following existed: participants received tramadol treatment prior to the study for whatever reason stated or not stated in the article, there was insufficient information for extraction of data, or results were unpublished.

Analyzed Studies

The authors reviewed results of trials evaluating the role of tramadol in the treatment of PE. Data sources included randomized controlled trials and prospective studies published between January 2000 to January 2012, as described previously.

Data Extraction

All data were extracted independently by 2 reviewers according to the inclusion criteria listed above. Disagreements were resolved by discussion between all the researchers. Subject demographics were compared and checked for homogeneity. The following characteristics were also collected from each study: first author, year of publication, country of the first or corresponding author, definition of premature ejaculation used, number of cases and controls, treatment methods, outcomes, and adverse events.

Statistical Analysis

The meta-analyses evaluated the role of tramadol in the treatment of PE compared with patients who received other treatment alone. Effect estimates for mean difference (MD) and risk ratio (RR) along with the corresponding confidence intervals (CIs) were derived from RevMan 5.0 and calculated with random-effects models. Forest plots were generated using the same platform. All statistical tests were 2-sided and effect estimates were deemed statistically significant when $P \leq .05$.

Assessment of Methodological Quality

The Jadad scoring (Table 1) introduced in 1996 by Alejandro Jadad has been used as the gold standard in assessing the methodological quality of studies.[28,29] This validated score lies in the range of 0-5 and studies are scored according three main criteria: Randomization, blinding, and accountability of all patients, including withdrawals. Studies are rated as high quality if they receive a Jadad score of 4 or 5 and low quality if equal to or less than three.

Risk of Bias Assessment

The risk of bias assessment, a feature of RevMan 5.0, was used to appraise the quality of included studies in the meta-analysis similar to the more widely accepted Jadad scoring system.[33] Here, included studies are arranged in vertical columns and corresponding bias assessment criteria plotted horizontally. Green symbols denote a positive point or a low risk for bias grade, yellow symbols mean that the item has unclear risk, while red symbols denote a negative point or a high risk for bias grade for a particular criteria. Grading is author dependent and subjective based on the author's appraisal.

Methodological quality was also assessed using a risk of bias summary graph which takes together all the studies and plots the corresponding assessment bias in a horizontal spectrum ranging from 0% to 100%. Similar to the risk of bias assessment graph; green denotes low risk of bias, yellow for unclear risk of bias, and red for high risk of bias then stratifies the overall grade in percentage. Newcastle-Ottawa Scale for non-randomized controlled trials.

For non-randomized controlled trials the Newcastle-Ottawa scale was used. It takes into account the following criteria in order to determine the quality of non-randomized controlled trials.[36] Four stars under this criteria means that the study has fulfilled all the categories mentioned in the scoring system. Similarity in the study design or analysis has a maximum of two stars under the comparability criteria; one for the most important factor and another star for any additional factor.

Table 1. Jadad scoring system.

Jadad Scoring	Safarinejad (2006)	Alghobary (2010)	Xiong (2011)	Bar-Or (2012)
Was the study described as randomized?	+1	+1	+1	+1
Was the method used to generate the sequence of randomisation described and appropriate?	+1	+1	+1	+1
Was the study described as double blind?	+1	0	0	+1
Was the method of double blinding described and appropriate?	+1	0	0	+1
Was there a description of withdrawals and dropouts?	+1	+1	0	+1
Deduct one point if the method used to generate the sequence of randomisation was described and it was inappropriate.	0	0	0	0
Deduct one point if the study was described as double blind but the method of blinding was inappropriate.	0	0	0	0
Total	5	3	2	5

Results

Study Selection

A total of 55 studies were identified and appraised based on the inclusion and exclusion criteria described in the Methods section. From the 55 studies, 46 were then excluded. One recent meta-analysis[26] was retrieved and appraised. However, the study was not able to include similar study done by Mohammadi-Jazi, et al.[27] Furthermore, no dose-response analysis and overall therapeutic effectiveness was done. The remaining 9 articles were assessed for eligibility and 1 article was further discarded due to inability to obtain information required to make an assessment leaving a total of 8 similar studies analyzed (Figure 1 & Table 2).

Table 2. Characteristics of included studies.

Author Year Country	Design	PE Definition	Treatment (*n*) Control (n)	Treatment methods	Outcomes	Adverse events
Safarinejad et. al [31] 2006 Tehran, Iran	Double-blind, placebo – controlled, randomized study	IELT of <2 mins in >90% of coitus	Tramadol 50 mg n=29 Placebo n=28	2 hours before sexual activity for 8 weeks	Mean IELT pretreatment placebo 21 s tramadol 19 s Mean change IELT post treatment placebo 0.22 mins tramadol 3.73 mins no. coitus/wk: placebo 1.1 tramadol 1.07 posttreatment: placebo 1.3 tramadol 2.3 intercourse satisfaction domain values of the IIEF: placebo 11 tramadol 10 post treatment: placebo 10 tramadol 14	Placebo:5 (15.6%) patients: 1 (3.1%) nausea, 2 (6.2%) vomiting, 2 (6.2%) dizziness Tramadol: 9 (28.1%) patients: 5 (15.6%) nausea, 2(6.2%) vomiting, 1 (3.1%) dizziness , 1 (2.6%) constipation;
Mohammadi-Jazi et. al.[27] 2007 Isfahan, Iran	Single-blind, placebo-controlled, crossover prospective study	IELT of <1 min on at least 50% of coitus	Tramadol 100mg n=32 Placebo n=32	1 tablet daily treatment for 4 weeks 7 days washout period, then crossover	Mean IELT pretreatment: 43+16 s Mean change IELT post treatment placebo 1.68mins tramadol 2.08mins	Placebo: 5 patients (15.6%) Tramadol: 11 patients (34.3%) nausea and dizziness: most common
Salem et. al [34] 2008 New Orleans, LA,USA	Single-blind, placebo-controlled, crossover prospective study	IELT of <2mins in 80% of coitus	Tramadol 25 mg n=30 Placebo n=30	1-2 hours before sexual activity for 8 weeks 7 days washout period, then crossover	Mean IELT pretreatment: 1.17 +0.39 minutes Mean change IELT post treatment placebo 0.84 mins tramadol 6.2mins Tramadol: 98% reported increased in their control over ejaculation and benefits in their sexual satisfaction	Tramadol: 8 patients (13.3%): 5 mild dyspepsia , 3 mild somnolence
Alghobary et. al. [15] 2010 Mansoura, Egypt	Single-blind, placebo controlled, crossover, prospective, randomized study	IELT of <2 mins in >90% of coitus	Tramadol 50 mg n=35 Paroxetine 20mg n=35 No placebo	Tramadol: 2-3 hours before sexual activity Paroxetine: single daily dose after breakfast To take for 6 and 12 weeks 2 weeks washout period, then crossover	Mean IELT pretreatment: 36.14 s after 6 weeks: Mean change IELT: paroxetine 3.23 mins tramadol 2.4 mins, both AIPE score improved after 12 weeks: Mean change IELT: paroxetine 6.63 mins tramadol 1.62mins, AIPE score further improved for paroxetine while no significant improvement for tramadol	No adverse events stated
Xiong et. al.[30] 2011 Jiangxi, China	Prospective, randomized study	IELT of <2mins	Tramadol 50mg with behavioral modification n=36 Behavioral modification only n=36	2 hours before sexual activity for 12 weeks	Mean IELT pretreatment treatment group 1.13+0.32 min control group 1.14+0.31 min Mean change IELT post treatment behavioral modification only 1.67 mins tramadol + behavioral modification 3.33mins Total rate of effectiveness of 72.2% and improvement of IIEF in tramadol group	Tramadol + behavioral modification: 10 (27.8%) patients: 4 (11.1%) nausea, 1 (2.8%) vomiting,3 (5.6%) dry mouth, 2 (8.3%) dizziness
Eid et. al. [16] 2011 Cairo, Egypt	Single-blind, placebo controlled, crossover, prospective study	IELT of <2 mins in 80% of coitus	Tramadol 50mg n=44 Paroxetine 20mg n=44 Placebo n=44	3-4 hours before intercourse for 3 weeks for at least 10 successive intercourses of paroxetine followed by placebo and then tramadol in the same manner	Mean IELT pretreatment: 1.05+0.51 mins Mean change IELT post treatment paroxetine 2.27 mins placebo 1.27 mins tramadol 6.32 mins	Tramadol: nausea 13%, constipation 7%, vomiting 4.5% Paroxetine: minimal in the form of mild nausea, headache, dry mouth
Kaynar et. al [35] 2012 Konya, Turkey	Single-blind, placebo controlled, crossover, prospective randomized study	IELT of <1 min in 90% of coitus	Tramadol 25mg n=30 Placebo n=30	2 hours before sexual activity for 8 weeks	Mean IELT pretreatment: placebo 30.66+18.56 s tramadol 38.83+15.69 s Mean change IELT post treatment placebo 0.42 mins tramadol 1.93 mins AEC and SSS improved in both groups	Tramadol: 8 (26.5%) patients: 6 (20%) mild nausea and headache , 2 (6.5%) mild somnolence
Bay-or et al [32] 2012 CO, USA	Double-blind, placebo-controlled, randomized study	IELT of <2 mins in >90% of coitus	Tramadol 62mg n=206 Tramadol 89mg n=198 Placebo n=200	2-8 hours before sexual activity for 12 weeks	Mean IELT pretreatment: placebo 1.03 min, tramadol 62mg 0.98 min, tramadol 89mg 1.02min Mean change IELT post treatment placebo 1.64mins, tramadol 62mg 2.3 mins, tramadol 89mg 2.36 mins Improvement in all measures (satisfaction with sexual intercourse, control over ejaculation, ejaculation related distress, interpersonal difficulty) of Premature Ejaculation Profile (PEP) scores	overall adverse event rate was 11.8%: placbo6.7%, tramadol 62mg 12.4%, and tramadol 89 mg 16.4% 6 (<1.0%) erectile dysfunction 5 (0.9%) vertigo, 3 (0.5%) dizziness,3 (0.5%) headache, 3 (0.5%) drowsiness, 3 (0.5%) common cold

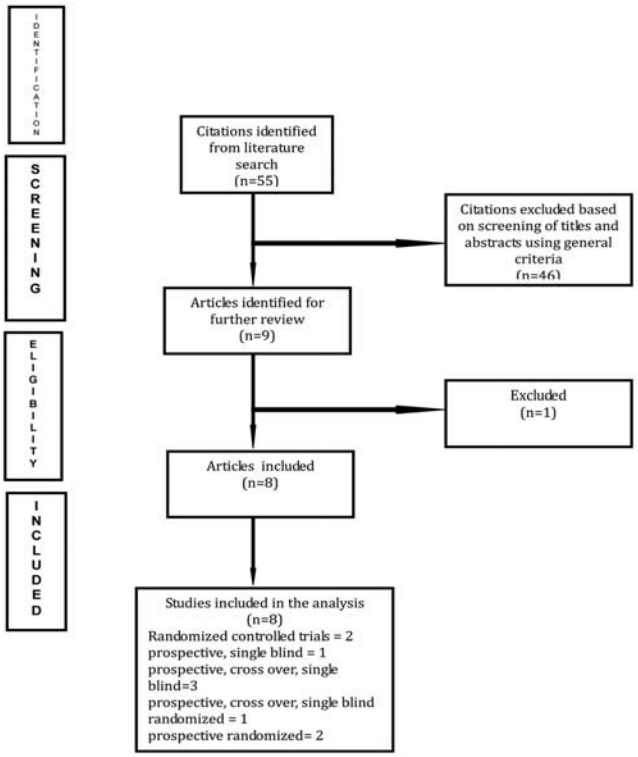
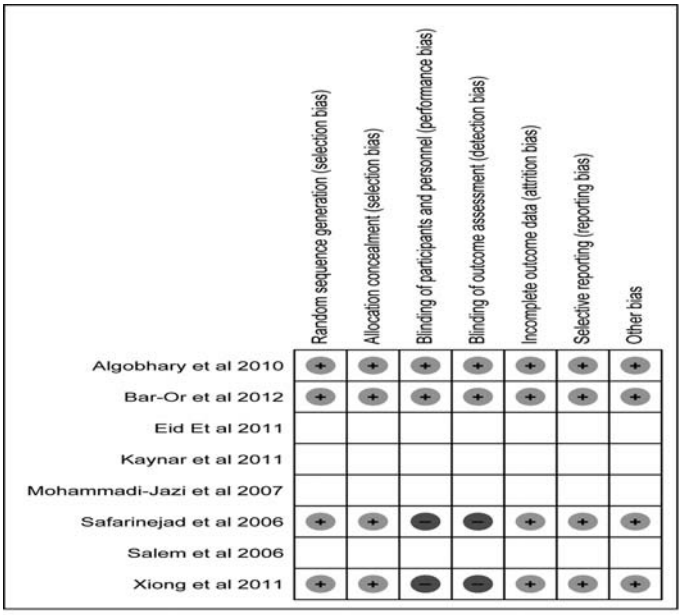


Figure 1. Search strategy flowchart.

Two of the four randomized studies included had poor quality. Alghobary et. al. and Xiong, et al.[30] failed to report the method of blinding used and in addition, there were no withdrawals or dropouts reported in both studies. Safarinejad, et al.[31] and Bar-Or, et al's.[32] studies described appropriately their methods of randomization, blinding, and withdrawals or dropouts and were thus graded as high quality randomized controlled trials on the Jadad system.

The risk of bias assessment was performed with a risk of bias assessment graph (Table 3) and risk of bias summary graph (Figure 2). These showed that half of the studies were randomized trials. Safarinejad, et al. [31] and Bar-or, et al.[32] had low risk of bias in contrast to Xiong, et al.[30] and Alghobary, et al.[15] which failed to describe their method of blinding. Four other studies[16,27,34,35] included were not randomized studies and were therefore not appraised through this graph and was left blank.

Table 3. Risk of bias assessment graph.



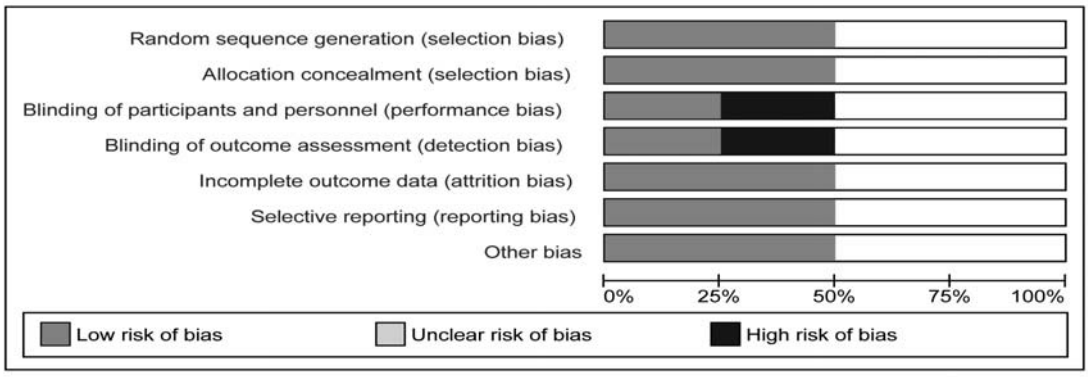


Figure 2. Risk of bias Summary graph.

Assessment of the studies by Salem, et al.[34], Kaynar, et al.[35], Mohammadi-Jazi et. al.[27], and Eid, et al.[16] carried out using the Newcastle-Ottawa scale shown in Table 4. In this meta-analysis, two non-randomized studies[16,34] only had one important factor and were hence graded with one star. Finally, the outcome criterion assesses for blinding, adequacy of length of follow-up and if all followed-up completely in the cohort. In our analysis of the 4 articles, only that of Mohammadi-Jazi, et al.[27] had no mention of blinding and was hence graded with one star.

Table 4. Newcastle-Ottawa Scale.

Newcastle-Ottawa Scale	Selection	Comparability	Outcome/ Exposure
Salem, et al. (2006)	****	*	**
Mohammadi-Jazi, et al. (2007)	****		*
Eid, et al. (2011)	****	*	**
Kaynar, et al. (2012)	****		**

Evaluation of Intravaginal Ejaculatory Latency Time

Our analysis of the IELT among 599 patients showed that tramadol was effective in increasing the IELT of subjects with PE as seen by the significant difference in mean IELT of tramadol treated patients versus those receiving placebo, MD 2.43 (95% CI 0.93, 3.93; P=0.002)(Figure 3) compared to MD 2.77 done by Wu, et al.[26] Among the studies, Bay-or et. al. had the most significant weight in the overall effect (29.3%) and Safarinejad, et al. the lowest contribution (11.9%). In the study by Eid, et al. the highest mean difference of 6.32 minutes was achieved using tramadol 50 mg while in the study by Alghobary, et al. the lowest mean difference of 1.62 minutes was achieved at 12 weeks of intake.

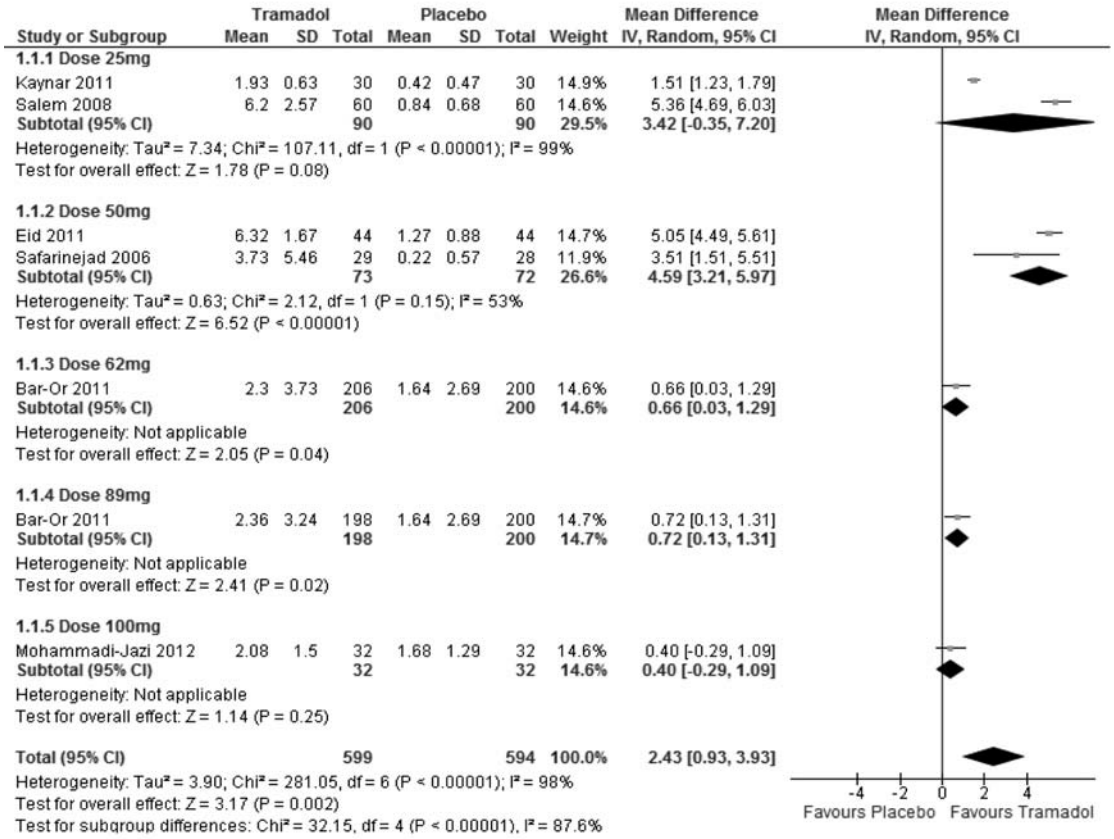


Figure 3. Comparison of mean change in IELT among different dosages of tramadol versus placebo.

Two studies[15,16] provided a comparison using between tramadol and paroxetine. These showed conflicting superiority between the two different medications. In this analysis, MD -0.58 (95% CI -5.81, 4.65; P=0.83) (Figure 4). The middle of the lowest diamond in the Forrest plot sits on the value for the overall effect estimate. Its confidence interval crossed the line of no effect proving no statistically significant difference in the effects of the two interventions.

Meta-regression Analysis

Meta-regression analysis (Figure 5) aims to relate the size effect to one or more characteristics of the studies involved. Various statistical methods for meta-regression have been published. A random effects model was used in this analysis. There was no clear agreement of the optimal dose of tramadol in this situation, and one of the principal aims of this paper was to determine the effect of the different doses of tramadol to prolongation of the IELT. The data points and the weighted regression are shown. The size of the dots represents the relative weight and hence the importance of the study. The line of best fit has a downward slope to the right. In this analysis, it showed that the lower the dose of tramadol the higher its benefit in the prolongation of IELT. However, the results revealed that the 95% CI of the regression coefficient is -0.0956 to 0.0322 which traversed the zero value, and therefore not statistically significant.

Evaluation of Adverse Effects

There were more adverse effects reported among those receiving tramadol with total of 104 out of 599 participants as compared to 36 out of 594 in the placebo group. However, the reported adverse events were only mild and limited mainly to nausea, vomiting, and dizziness and others. Bar-or et al had the most significant weight in the overall effect at 29.0%. The results showed a significant difference in adverse effects profile of tramadol versus placebo, overall effect Z= 3.79, P<0.0002. RR 2.48 (95% CI, 1.55, 3.98) (Figure 6). This showed that the treatment with tramadol increases the risk of adverse events to 248% compared to control.

Evaluation of Overall Therapeutic Effectiveness

Asides from IELT and adverse events, different outcomes were measured in different studies with risk ratio 0.55 (95% CI 0.46-0.67; P=0.0002) (Figure 7). This showed

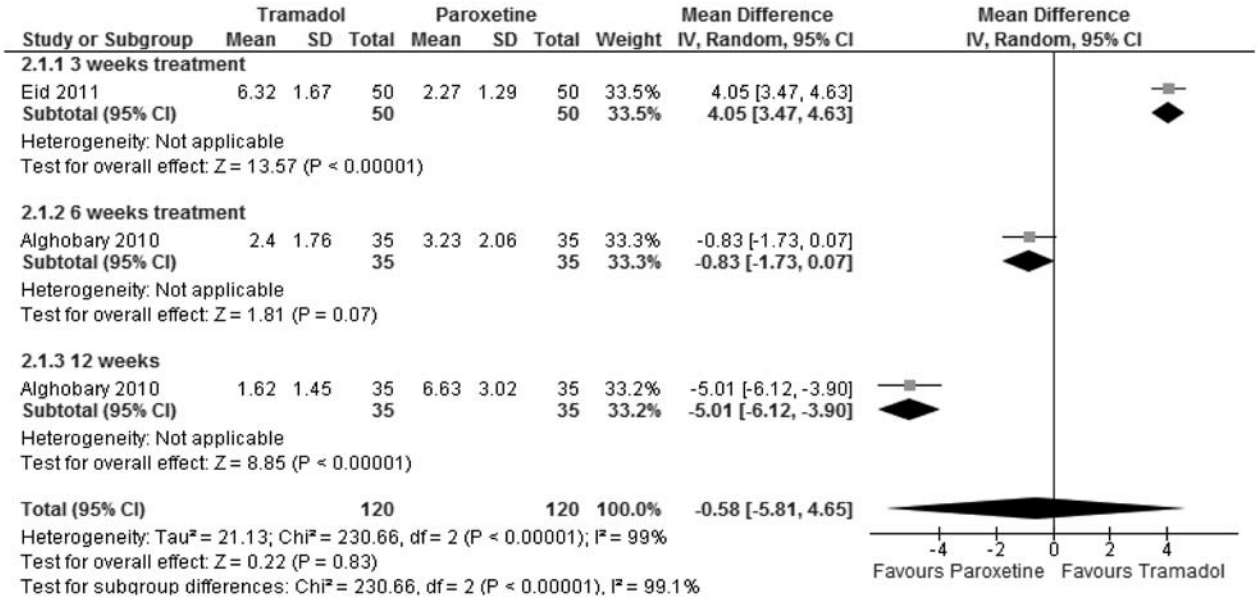


Figure 4. Comparison of mean change in IELT between tramadol versus paroxetine after different durations of administration

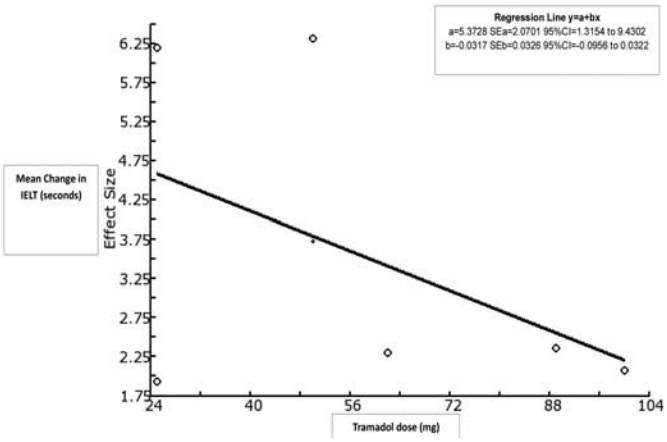


Figure 5. Meta-regression analysis. Random Effect Model.

that the treatment with tramadol increases the overall therapeutic effectiveness to 55% compared of the control.

Mean weekly intercourse episodes and mean intercourse satisfaction domain values of International Index of Erectile Function (IIEF) sexual satisfaction rates of the patients and wives showed improvements with the corresponding $P<0.05$ each.[31] These were increased from 1.07 to 2.3 and 10 to 14 respectively during 8 weeks duration of the tramdol group. IIEF was likewise used by Xiong, et al. showing significant difference ($P<0.01$).[30] Hepatic and renal functions were evaluated before and after treatment but showed no statiscally significant differences.[30] Men saw significantly greater improvement in all four measures (satisfaction

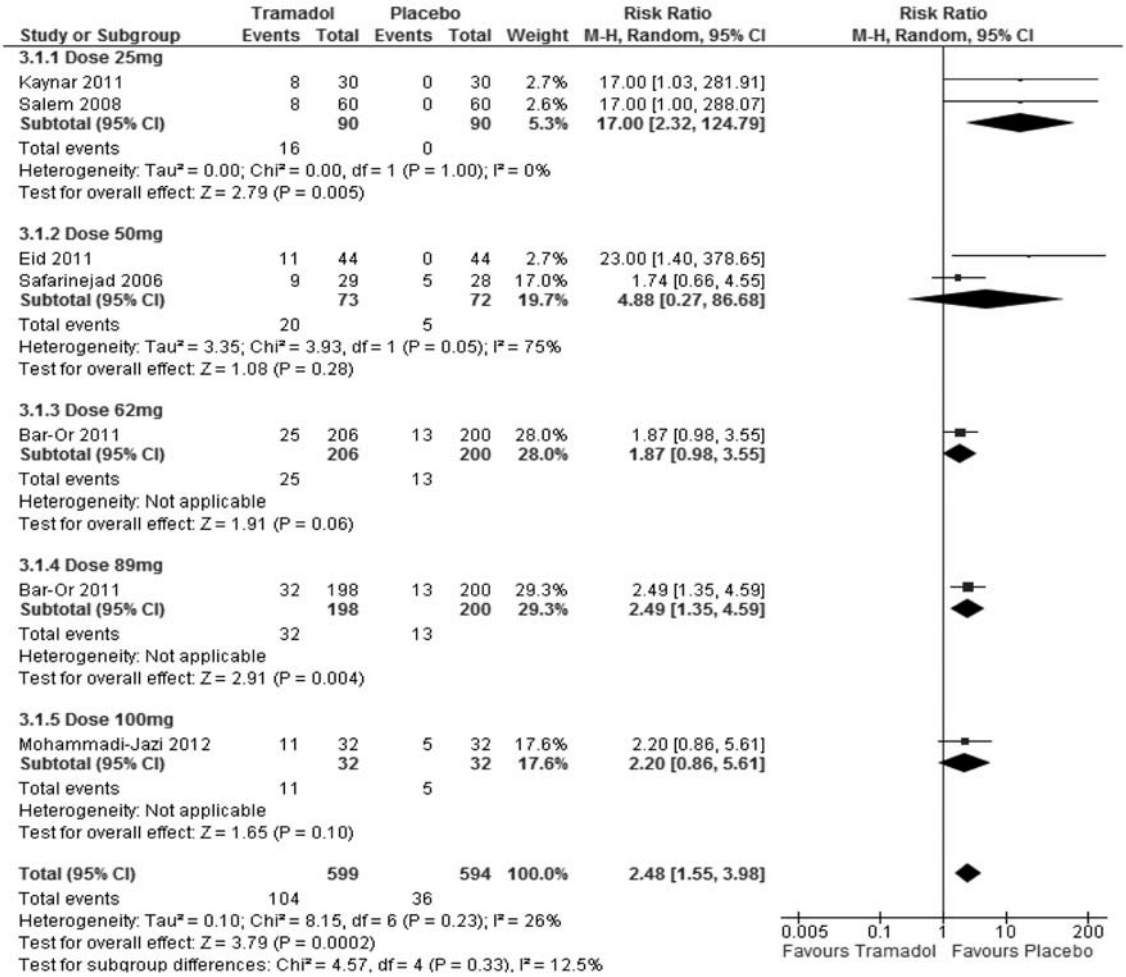


Figure 6. Comparison of occurrence of over-all adverse effects among different doses of tramadol versus placebo.

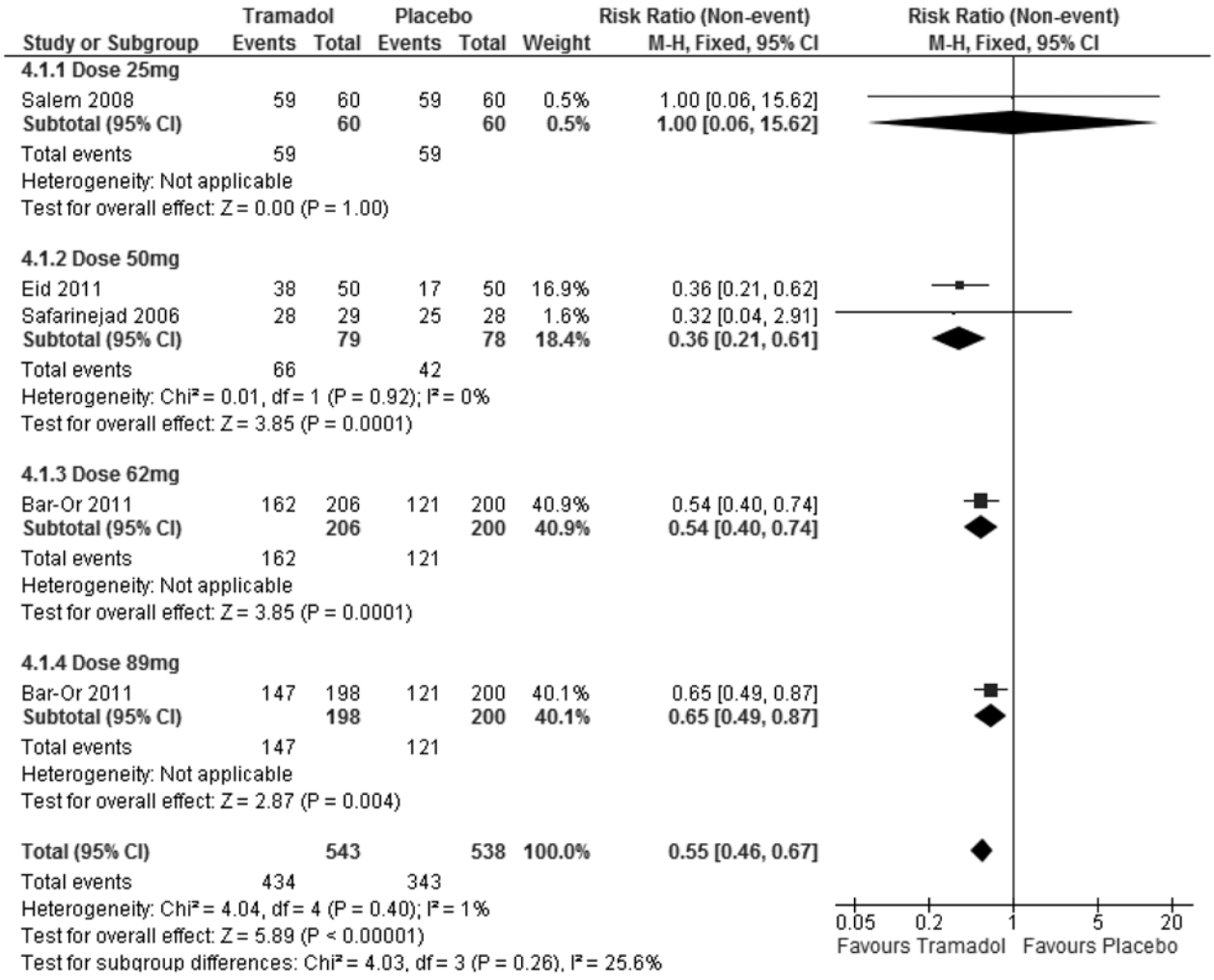


Figure 7. Comparison of therapeutic effectiveness between tramadol and placebo

with sexual intercourse, control over ejaculation, ejaculation related distress, interpersonal difficulty) of Premature Ejaculation Profile (PEP) scores with P<0.05 for all comparisons.[32] Another validated questionnaire was used by Alghobary, et al. Tramadol improved Arabic Index of Premature Ejaculation (AIPE) score significantly after 6 weeks but not after 12 weeks versus baseline. However, paroxetine increased the AIPE score after 6 and 12 weeks compared to baseline (P<0.05).[15] In the study of Kaynar, et al. Ability of ejaculation control (AEC) and Sexual Satisfaction score (SSS) were both significantly greater statistically from 0.83 to 2.83 (P<0.01) and from 0.96 to 2.77 (P<0.01) respectively compared with the placebo group.[35] Three authors[16,27,34] did not use other parameters for evaluation of premature ejaculation.

Discussion

A recent meta-analysis evaluating the efficacy and safety of tramadol for the treatment of PE was done by Tao Wu, et al.[26] However, they did not include the article done by Mohammadi-Jazi, et al.[27] working on the similar study. The evaluation done by the former contributed to

14.6% and 17.6% overall study weight to the comparison of mean change in IELT and occurrence of over-all adverse effects among different dosages of tramadol (25, 50, 62, 89, and 100 mg) compared to placebo. Another analysis evaluating the overall therapeutic effectiveness was performed in this study favoring the use of tramadol. Meta-regression analysis was likewise done to know the effect of different dosages of tramadol to prolongation of IELT. This showed that the higher the dosage of tramadol, the shorter its effect on IELT, however, it is not statistically significant. Eight trials[15,16,27,30,31,32,34,35] were included in our systematic reviews compared to 7 studies done by Tao Wu, et al.

Measurement of IELT has provided the most objective and quantitative method for assessment of premature ejaculation in clinical trials.[8] In a multinational report, the median IELT was 5.4 minutes.[9] This present day study showed that tramadol, compared to placebo, was effective in increasing the IELT of patients with premature ejaculation by a mean change of 2.43 minutes which was statistically significant.

In contrast, comparing tramadol and paroxetine, the mean change was 0.58 minute showing no significant difference between the two intervention. In one of these studies[15], tramadol and paroxetine increased IELT significantly after 6 weeks by 7 and 11 folds respectively compared with baseline. However, the efficacy of tramadol on IELT declined to five-folds after 12 weeks of treatment compared with baseline.

In 1997, a postmarketing surveillance study was performed comparing the acute intravenous, acute intramuscular, acute oral and multiple dose oral admistration of everyday use of tramadol in general medical practice.[37] This revealed that the most commonly observed side effects were nausea, dizziness, drowsiness, tiredness, sweating, vomiting and dry mouth, with an overall incidence of between 1 and 6%. In this study, it also showed the same adverse events from using tramadol. The computed risk ratio was 2.48 indicating that more side effects were encountered in tramadol compared to placebo.

Standardized assessment measures for PE include the use of questionnaires and patient reported outcome measures, asides from measuring the IELT. Intercourse episodes, IIEF, PEP, AIPE, AEC, SSS were used as parameters to determine the response of patients to interventions in the studies included in our analysis. All of which showed superior results for use of tramadol.

In a study by Xiong, et al.[30], tramadol with behavioral modification showed positive effects in delaying ejaculation in patients with PE and improving partner's intercourse satisfaction (pre-treatment IELT 1.13±0.32 minutes to post-treatment 4.46±3.31 minutes, $P<0.05$) compared to behavioral modification alone.

More well- designed studies on larger scale and longer duration of treatment are needed in order to determine the true effect of tramadol on IELT, adverse events and other parameters.

Conclusion

On-demand tramadol is an effective treatment for lifelong premature ejaculation. It significantly prolongs the IELT. The overall adverse events and overall therapeutic effectiveness are significantly greater during treatment with tramadol. There were no differences on the effect on IELT between tramadol and paroxetine. The lower the dose of tramadol, the longer the IELT, however, this is not statistically significant.

References

1. Marcel D. Waldinger .Premature Ejaculation: State of the Art. Urol Clin North Am 2007; 591-9.
2. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA 1999; 281:537-44.
3. Porst H, Montorsi F, Rosen RC, Gaynor L, Grupe S, Alexander J. The premature ejaculation prevalence and attitudes (PEPA) survey: Prevalence, comorbidities and proessionalhelp-seeking. Eur Urol 2007; 51: 816-24.
4. Waldinger M. The neurobiological approach to premature ejaculation.J Urol 1998; 168: 2359-67.
5. Patrick DL, Althof SE, Pryor JL, Rosen R, Rowland DL, Ho KF, et al. Premature ejaculation: an observational study of men and their partners. J Sexual Med 2005; 2: 358-67.
6. Rosen RC, McMahon CG, Niederberger C, et al. Correlates to the clinical diagnosis of premature ejaculation: results from a large observational study of men and their partners. J Urol 2007; 177: 1059-64.
7. Althof SE, Abdo CHN, Dean J, Hackett G, McCabe M, McMahon CG, Rosen RC et al. International Society for Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation. J Sexual Med 2010; 7: 2947-69.

8. Pryor JL, Althof SE, SteidleC Ef?cacy and tolerability of dapoxetine in the treatment of premature ejaculation: integrated analysis of two randomized, double-blind, placebo-controlled trials. Lancet 2006; 368 : 929-37
9. Waldinger M, Quinn P, Dilleen M, Mundayat R, Schweitzer D, Boolell M. A multinational population survey of intravaginal ejaculation latency time. J Sexual Med 2005; 2: 292-7.
10. Linton KD, Wylie KR, et al. Recent advances in the treatment of premature ejaculation. Drug Des Devel Ther 2010;4:1-6.
11. Waldinger MD, Premature ejaculation: different pathophysiologies and etiologies determine its treatment, J Sex Marital Ther 2008; 34:1-13.
12. Mulhall JP, et al. Current and future pharmacotherapeutic strategies in treatment of premature ejaculation. Urology 2006; 67: 9-16.
13. Montague DK, Jarow J, Broderick GA, et al. AUA guideline on the pharmacologic. management of premature ejaculation. J Urol 2004, 172: 290-4.
14. Hiemke C, Hartter S. Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol Ther 2000; 85:11-28.
15. Alghobary M, El-Bayoumy Y, Mostafa Y, et al. Evaluation of tramadol on demand vs daily paroxetine as a long term treatment of lifelong premature ejaculation. J Sexual Med. 2010; 7:2860-7.
16. Eid MA, Ahmed HH, Ismail NN, et al. Comparative study between tramadol (50mg) on demand and paroxetine HCl (20mg) on demand in the treatment of premature ejaculation. Human J Androl 2011; 1:69-73
17. Buvat J, Tesfaye F, Rothman M, et al., Dapoxetine for the treatment of premature ejaculation: results from a randomized, double-blind, placebo-controlled phase 3 trial in 22 countries. Eur Urol 2009 21 (Epub ahead of print).
18. Pryor JL, Althof SE, Steidle C, et al. Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. Lancet, 2006; 368(9539): 929-37.
19. Giuliano F, Clement, P. Neuroanatomy and physiology of ejaculation. Annual Rev Sex Res 2005; 16: 190-216.
20. Salonia A, Rocchini L, Sacca A, Pelluchi F et. al. Acceptance of and discontinuation rate from paroxetine treatment in patient with lifelong premature ejaculation. J Sex Med 2009; 6: 2868-77.
21. Lantz MS, Bruchalter EN, Giambanco V. Serotonin syndrome following the administration of tramadol with paroxetine. Int J Geriatr Psychiatr 1998; 13: 343-5.
22. Eradiri O, Sista S, Lai JC-K, Danyluk A, Brett V. Bioavailability of extended releaseand immediate-release formulations of tramadol HCl. J Clin Pharmacol 2006; 46:1091
23. Lee CR, McTavish D, Sorkin EM. Tramadol: a preliminary review of its pharmaco- dynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. Drugs. 1993; 46: 313-40.
24. Lintz W, Erlacin S, Frankus E, et al. Biotransformation of tramadol in man and animal. Arzneimittel-Forschung. 1981;31:1932-43.
25. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet 2004; 43: 879-923.
26. Wu T, Yue X, Duan X, Luo D, Cheng Y, Tian Y, Wang K. Efficacy and safety of tramadol for premature ejaculation: A systematic review and meta-analysis. Urology 2012: 80(3):618-24.
27. Mohammadi-Jazi A, Nori K, Salehi S. Study of efficacy and safety of oral tramadol in the treatment of premature ejaculation. J Urol. 2007: 3:7: 217
28. Olivo, SA, Macedo LG, Gadotti IC, Fuentes J, Stanton T, Magee DJ. Scales to assess the quality of randomized controlled trials: A systematic review. Physical Therapy. 2008.
29. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clinical Trials 1996; 17:1-12.
30. Xiong GG, Wu FH, Chen SH, et al. [Safety and efficacy of tramadol hydrochloride with behavioral modification in the treatment of premature ejaculation]. Zhonghua Nan Ke Xue. 2011;17: 538-41.
31. Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. J Clin Psychopharmacol. 2006; 26:27-31.
32. Bar-Or D, Salottolo KM, Orlando A, et al. A randomized double blind, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of the tramadol orally disintegrating tablet for the treatment of premature ejaculation within less than 2 minutes. Eur Urol. 2012;61:736-43.
33. Cochrane Handbook for Systemic Reviews of Interventions Version 5.1.0. In: Higgins JPT, Green S, eds. The Cochrane Collaboration; 2011.
34. Salem EA, Wilson SK, Bissada NK, et al. Tramadol HCl has promise in on-demand use to treat premature ejaculation. J SexMed 2008;5:188-93.
35. Kaynar M, Kilic O, Yurdakul T. On-demand tramadol hydrochloride use in premature ejaculation treatment. Urology 2012;79(1): 145-9.
36. Wells G, Shea B, O'connell D, et. al. The Newcastle-Ottawa scale for assessing the quality of nonrandomized studies in meta-analysis. Available from:URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm [cited 2009 October 19]
37. Cossmann M, Kohnen C, Langford R, et al. [Tolerance and safety of tramadol use: results of international studies and data from drug surveillance]. Drugs. 1997;53 Suppl 2:50-62.