ARAB JOURNAL OF UROLOGY
2024, VOL. 22, NO. 2, 89–95
https://doi.org/10.1080/20905998.2023.2287869

ORIGINAL ARTICLE

OPEN ACCESS Check for updates

Combined on-demand sildenafil citrate and tramadol hydrochloride is an effective and safe treatment for premature ejaculation: A randomized placebo-controlled double-blind clinical trial

Adel Kurkar, Ahmed Reda, Mahmoud Mohamad Shalaby, Mohammed Abdelhafez, Mahmoud Osman and Sherif Abulsorour

Urology, Assiut University, Assiut, Egypt

ABSTRACT

Background: Premature ejaculation (PE) is a common sexual dysfunction that harms both sex partners.
Aim: To evaluate the safety, efficacy and impact on sexual satisfaction scores of the combined use of tramadol HCl and sildenafil citrate for the treatment of PE.
Methods: One hundred and sixty otherwise healthy males complaining of PE (primary/secondary) were enrolled in this randomized, double-blind, placebo-controlled study. Only 155 patients (age range 22–48 years) completed the study. Of them, 81 patients had primary PE, and 74 had secondary PE. The comparative groups included the placebo group ($n = 34$), sildenafil citrate 50 mg group ($n = 39$), tramadol HCl 100 mg group ($n = 40$), and the combination therapy group ($n = 42$). The treatment duration for all groups was 10 weeks.
Outcomes: This combination is safe and effective.
Results: Five patients discontinued the study, all from the placebo group, due to a lack of improvement over the treatment course. No significant differences were reported between groups before treatment as regards Intravaginal ejaculatory Latency Time ($p = 0.8$), satisfaction score ($p = 0.7$), age ($p = 0.9$), or duration of marriage ($p = 0.9$). There was a significant improvement in IELT after treatment with a placebo ($p = 0.0001$), associated with an insignificant improvement in satisfaction score ($p = 1.0$). In the other three groups, there was a significant improvement in IELT after treatment ($p = 0.0001$ for all), which coincided with a significant improvement in satisfaction scores in all three groups ($p = 0.0001$ for all).
Clinical Implications: We recommend this combination in the treatment of premature ejaculation.
Strengths: It is a prospective randomized double-blind placebo-controlled clinical trial.
Limitations: Limited number of participants.
Conclusion: Combined therapy of PE, whether primary or secondary, with sildenafil citrate 50 mg and tramadol HCl 100 mg is safe and effective; and its therapeutic effect is superior to the utilization of either agent alone.

ARTICLE HISTORY
Received 7 July 2023
Accepted 21 November 2023

KEYWORDS
Sildenafil citrate; tramadol hydrochloride; premature ejaculation

Introduction

Premature ejaculation (PE) is a common form of ejaculatory dysfunction. However, there was lack of a global definition for PE has led to much controversy about its actual prevalence and, in turn, to underrating and under-treatment of PE, with the estimated prevalence varying in literature from 2 to 27.5% [1].

The International Society for Sexual Medicine (ISSM) has established the definition of PE as: 'ejaculation which always or nearly always occurs before or within 1 min of vaginal penetration; together with the inability to delay ejaculation on all/nearly all vaginal penetrations; and negative personal consequences e.g. distress, bother, frustration and/or the avoidance of sexual intimacy' [2]. PE can be classified as lifelong or acquired, and it can negatively impact the quality of life not only of the male but also his female partner as well causing interpersonal difficulties, sexual dissatisfaction, and distress [3–5].

Psychological factors such as anxiety, social phobia, interpersonal issues, infrequent sexual intercourse, and lack of sexual experience have been suggested to have a role in the etiology of PE [6]. Although pharmacotherapy switched to psychotherapy in the last 40 years, PE likely has a mixed etiology, both physiological and psychological. Several physiological factors have been implicated in the pathophysiology of PE, e.g. penile hypersensitivity, hyperexcitability of the ejaculatory reflex, high sexual arousability, endocrinopathy, genetic factors, and serotonergic receptor dysfunction [7,8].

The current lines implicated in the treatment of PE include behavioral therapy, psychotherapy, pelvic floor exercise, topical agents, sprays, and systemic medications

CONTACT Ahmed Reda Ahmedreda_leo@yahoo.com Urology, Assiut Urology University Hospital, Assiut, Egypt

This article was originally published with errors, which have now been corrected in the online version. Please see Correction http://dx.doi.org/10.1080/20905998.2024.2303240

e.g. SSRIs, tramadol HCl, α-blockers & PDE-5 inhibitors with average stopwatch-clocked IELT was almost 1 min [3,7–19]. To our knowledge, the use of the combination of tramadol HCl and sildenafil citrate for the treatment of PE is considered new [20].

Our aim of this study is to evaluate the safety, efficacy and impact on sexual satisfaction scores of the combined use of tramadol HCl and sildenafil citrate for the treatment of PE.

Patients and methods

During 2 years from January 2016 to January 2018, 160 patients were enrolled in a prospective randomized double-blind placebo-controlled clinical trial, in which the patients were randomized to four treatment groups. Only 155 patients (age range 22–48 years) completed the study, as five patients missed the follow-up. Of them, 81 patients had lifelong PE, and 74 had acquired PE. Randomization was simply done by the coin method (heads or tails). The first group (P, n = 39) received a placebo, the second group (S, n = 39) received sildenafil citrate 50 mg, the third group (T, n = 42) received tramadol HCl 100 mg, while the fourth group (S+T, n = 40) received a combination of sildenafil citrate 50 mg and tramadol HCl 100 mg. All the pills were identical (they were specially made for the study by the faculty of Pharmacy, Assiut University). The trial was independent, with no sponsorship but it is a part of the research program at our university. The paper was funded by the university research committee. The patients were not asked to pay for their medications. The placebo was manufactured at the lab of the faculty of pharmacy for free. All the patients provided their informed consent. All the patients were insured. This manuscript was approved by our ethical committee, and our clinical trial number is NTC05183334.

All the patients had a history of premature ejaculation (PE), lifelong or acquired, and a maximum IELT of 2 min before treatment. All included patients had no previous medical treatment for PE. The exclusion criteria were known drug non-compliance, positive history of diabetes mellitus, psychological problems, neurological disorders, erectile dysfunction, chronic illnesses, interpersonal troubles with the spouse, as well as long-term medications that could affect the patient's condition.

All patients underwent a detailed interview and a thorough physical examination. Each patient received 10 doses of the assigned medication for a period of a maximum of 10 weeks (frequency of intercourse was 2–3 times/wk.). The baseline IELT values were measured 1 month before the commencement of the study. The stopwatch was provided by the department of urology and calibrated before the commencement of the study. Patients were instructed to ingest medication doses (both drugs together for the S+T group) 1 h before intercourse as on-demand therapy and to record IELT in seconds for each intercourse using a stopwatch held by the spouse. The inability to control ejaculation and eventually the increased control ability after treatment were measured by stopwatch.

Each couple received detailed information and training about the process and how to record IELT. Follow-up visits were established weekly. Patients were asked to record their degree of satisfaction, with treatment using The Sexual Satisfaction Score for PE and to record any encountered side effects of the assigned medication. The investigators were third parties and not oriented by which group they were investigating.

Five patients were lost to follow-up, and their data were discarded from the study, all of them were found to be from the placebo group. Statistical analysis was done using IBM SPSS software V.25 (Statistical Package for Social Sciences, IBM Corporation, New York City, New York, United States). Data were examined at first for the normality of distribution using Kolmogorov-Smirnov and Shapiro–Wilk tests.

Statistical tests used for data analysis were as follows: For parametric data, we used independent samples T-test, one-way ANOVA, Pearson's correlation, Levine's homogeneity of variance test, and Post Hoc LSD test. For non-parametric data, we used Mann Whitney U test, Kruskal–Wallis test, Wilcoxon signed ranks test, chi-square test, Fisher's exact test, Spearman's correlation, Yates continuity correction, contingency coefficient, and Phi and Cramer's V tests. Finally, we performed regression analysis using a linear regression model. The confidence level for all tests was 95%, and a p-value ≤0.05 was considered significant. Power analysis was also done for the sample size.

Results

The patient's age range was 22–48 years. (Mean 32.07 ± 6.9SD). The intercourse frequency per week range was 1–4 times. The duration of the marriage range was 1–9 years. Pre-treatment Satisfaction score range was 0–1. Pre-treatment IELT range was 32–102 s (mean 64.4 ± 16.03 SD). The following table summarizes the main pre-treatment group characteristics (Table 1).

The Kruskal–Wallis test (Table 2) showed no statistically significant differences among study groups regarding age (p = 0.9), pre-treatment satisfaction score (p = 0.7), and the duration of marriage (p = 0.9); but the fourth group (S+T, combined therapy) showed significantly less frequent intercourse episodes per week in comparison to other groups (p = 0.27). One-way ANOVA test showed no significant difference between groups concerning the pre-treatment IELT (Mean Square = 68.511, F = 0.263; p = 0.8).

The chi-square test showed no significant difference among groups concerning the type of PE whether lifelong or acquired (p = 0.7). Independent samples

Table 1. The main pre-treatment group characteristics.

Variable	Group	Mean	SD	Minimum	Maximum	Range
Age	P	31.32	6.59	22	46	24
	S	32.13	7.15	22	48	26
	T	32.17	7	22	48	46
	S+T	32.55	7.16	23	48	25
Marriage duration	P	3.24	1.63	1	7	6
	S	3.49	1.97	1	8	7
	T	3.57	2.26	1	9	8
	S+T	3.48	2.21	1	9	8
Pre-treatment IELT	P	62.24	14.04	32	90	
	S	65.08	16.59	32	102	70
	T	65	16.42	33	100	67
	S+T	64.98	17.04	32	100	68

Table 2. Kruskal Wallis test (SS = satisfaction score).

	Mean rank (sum of all freq. of all pt.)				
Variable	P	S	T	S+T	Kruskal–Wallis H
Intercourse frequency/week	84.07	88.91	78.82	61.34	9.178
Pre-treatment SS	74.59	78.68	82.51	75.50	1.081
Age	73.65	77.95	78.71	81.00	0.511
Marriage duration in years	77.01	79.54	78.44	76.88	0.095

T-test showed no significant difference between the two types of PE as regards the mean pre-treatment IELT (1ry type: Mean pre-treatment IELT = 65.23, SD = 15.79 - 2ry type: Mean pre-treatment IELT = 63.50, SD = 16.34; $p = 0.5$). Similarly, no significant differences were found between 1ry and 2ry PE regarding the pre-treatment satisfaction scores using the Mann-Whitney U test ($p = 0.5$, U = 2858.5).

The Kruskal–Wallis test (Table 3) showed a more significant improvement in both post-treatment IELT and satisfaction scores in the fourth group (G4, the combined therapy group) compared to the other three groups ($p < 0.001$ for both variables).

Wilcoxon signed ranks test showed a statistically significant improvement of post-treatment IELT in all groups. However, post-treatment satisfaction scores showed only significant improvement in the treatment groups but not in the placebo group (Table 4).

Independent samples T-test showed no significant differences between the two types of PE concerning the mean post-treatment IELT (lifelong type: Mean post-treatment IELT = 270.56, SD = 189.294 – acquired type: Mean post-treatment IELT = 262.88, SD = 194.717; $p = 0.8$). Similarly, the Mann-Whitney U test showed no significant differences between lifelong and acquired PE as regards to the post-treatment satisfaction score ($p = 0.8$, U = 2934). The chi-square test also showed no significant effect of the frequency of intercourse per week on the degree of post-treatment sexual satisfaction ($p = 0.089$).

Spearman's correlation showed no significant correlation between the patient age and the post-treatment IELT (Correlation Coefficient = 0.02, $p = 0.8$), nor did it show a significant correlation between the intercourse frequency per week and the post-treatment IELT (Correlation Coefficient = –.021, $p = 0.7$). On the contrary,

Table 3. Kruskal Wallis test (SS = satisfaction score).

	Mean rank				
Variable	P	S	T	S+T	Kruskal–Wallis H
Post-treatment IELT	17.69	55.46	96.55	131.76	135.763
Post-treatment SS	21.38	53.95	108.64	117.40	1.081

Table 4. The difference between the mean pre-treatment and post-treatment IELT/satisfaction score results among treatment groups.

Wilcoxon signed ranks test				
		Mean		
Variable	Group	Pre-treatment	Post-treatment	*p*
IELT	P	62.24	66.44	*0.0001*
	S	65.08	146.33	*0.0001*
	T	65.00	300.57	*0.0001*
	S+T	64.98	519.45	*0.0001*
Satisfaction Score	P	0.59	0.59	*1*
	S	0.64	1.95	*0.0001*
	T	0.69	3.76	*0.0001*
	S+T	0.60	3.97	*0.0001*

Table 5. Treatment side-effects distribution among treatment groups.

Side effect	Group: Sildenafil citrate ($n = 39$)	Group: Tramadol HCl ($n = 42$)	Group: Combination ($n = 40$)	*Total ($n = 155$)*
Difficult urination	-	4/42 (9.52%)	-	4/155 (2.58%)
Blurred vision	1/39 (2.56%)	3/42 (7.14%)	4/40 (10%)	8/155 (5.16%)
Dizziness	1/39 (2.56%)	3/42 (7.14%)	3/40 (7.5%)	7/155 (4.52%)
Constipation	-	3/42 (7.14%)	-	3/155 (1.94%)
Dyspepsia	3/39 (7.69%)	-	3/40 (7.5%)	6/155 (3.87%)
Nausea	1/39 (2.56%)	2/42 (4.76%)	3/40 (7.5%)	6/155 (3.87%)
Headache	4/39 (10.26%)	-	1/40 (2.5%)	5/155 (3.23%)
Flushing	4/39 (10.26%)	-	2/40 (5%)	6/155 (3.87%)
Nasal congestion	3/39 (7.69%)	-	2/40 (5%)	5/155 (3.23)
No. of Patients	7/39 (17.95%)	8/42 (19.05%)	8/40 (20%)	23/155 (14.84%)

Pearson's correlation showed a moderate, yet highly statistically significant, positive (direct) correlation between the pre-treatment IELT and the post-treatment IELT ($r = 0.4$, $p = 0.0001$). However, a linear regression model was conducted, and it showed that the only factor that had an actual and important significant impact on the post-treatment IELT was the type of medication used in each treatment group (B = 153.07, $t = 34.33$, $p = 0.0001$). It is important to mention that there is no reported hypotension in the combination group.

The incidence of side effects was low and all of them were in active treatment groups (Group S, T, S+T). The encountered side effects were mild and did not necessitate stopping treatment in any of the patients, with no significant difference in their frequency of occurrence among different treatment groups. The results are summarized in the following table (Table 5)

Discussion

PE poses much burden not only on the patient's sexual life but also on all aspects of the life of both the patient and his partner [21]. Several treatment options have been proposed for the treatment of PE, including tramadol HCl and PDE5 inhibitors [22]. Tramadol HCl is thought to exert its therapeutic action in PE patients by one or more of the following mechanisms: weak μ-opioid effect [3,8,23], 5-HT2 receptor antagonist effect [16,24], N-methyl-D-aspartate receptor antagonist effect [25], serotonin and norepinephrine reuptake inhibitory effect [8,23,26,27], and acetylcholine receptor antagonist effect [28–30]. On the other hand, PDE5 inhibitors are thought to play a therapeutic role in treating PE through the following mechanisms: peripheral delay of ejaculation through modulation of contractions of the vas deferens, seminal vesicles, prostate, and urethra, increasing the duration of erection [31,32], a central decrease in the sympathetic output via modulation of NO activity in the medial preoptic area [33], peripheral analgesic effect, peripheral analgesic effect, increasing patient confidence, and improving the perception of ejaculation control and sexual satisfaction [34].

Several studies in the literature have shown the efficacy and safety of both tramadol HCl [20,35–41] and PDE5 inhibitors [11,42,47]. However, this study examines the efficacy of combined Tramadol HCl and PDE5 inhibitors which has not been examined in previous research. The new combination therapy of Tramadol HCl with Sildenafil Citrate showed significantly better results than either of therapies alone or placebo in terms of increased IELT and improved subjective sexual satisfaction and without a significant difference in the incidence or severity of the side effects. The increased cost of combination therapy has not been reported by most of the patients to be a problem. It is important to mention that the known lower urinary tract symptoms caused by tramadol were found to be ameliorated by the effect of Sildenafil used in our combination as Sildenafil is known to improve the lower urinary tract symptoms. No reported life-threatening complications with no need for hospitalization and all are reported in the literature.

Many studies tried the use of combination drugs in the treatment of premature ejaculation and proved the efficacy of the combination over the single drug like that of Salonia et al. who proved that Paroxetine combined with sildenafil appears to provide significantly better results in terms of ejaculatory latency time and intercourse satisfaction versus paroxetine alone in potent patients with premature ejaculation. This study showed an improvement in satisfaction scores from pre-treatment to post-treatment which is comparable to our study. However, their combined treatment is associated with a mild increase in drug-related side effects [43, 48]. (Table 6).

Previous studies such as Gameel et al. used an on-demand treatment of Tramadol, Sildenafil, Paroxetine, and Local anaesthetics for the management of Premature Ejaculation. Tramadol-treated patients had a significantly longer mean (SD) IELT, of 351 (119) s, than the other groups [45]. On the other hand, our combination improved posttreatment IELT to 519 s with improvement in sexual satisfaction score and minimal side effects, Table 6.

Table 6. Different drugs used in previous studies.

Study	Used drugs	Satisfaction score	IELT/sec.	Side effects	P value
Salonia et al. [49]	Paroxetine with sildenafil	Improved to 9	-	Increased	<0.05
Gameel et al. [20]	Tramadol, Sildenafil, Paroxetine, and Local Anaesthetics	-	119, 111, 65 respectively	Minimal	<0.05
Hosseini et al. [44]	Fluoxetine with sildenafil	Improved to 9	-	Tolarable	<0.05
Our study	Tramadol with sildenafil	Improved to 9	519	Minimal	<0.0001

Another study, Hosseini et al. proved that fluoxetine combined with sildenafil seems to provide significantly better ejaculatory latency time and intercourse satisfaction as compared with fluoxetine alone in patients with premature ejaculation with $p < 0.05$. Such a study confirms our point regarding the efficacy of combined over single-drug treatment [44, 46], Table 6.

However, there are limitations in our study which include the lack of long-term follow-up to assure the sustainability of the therapeutic results and to rule out the worsening of the side effects or the emergence of new ones. In addition, the small number of the study group and the diverse nature of the participants both necessitate proceeding with further studies on a larger scale.

It is important to mention that our specially designed satisfaction score for this work was from 0 to 4 where zero means very unsatisfied and four means very satisfied.

To our knowledge, our study is a new one as this combination has not been used before. Only one study used a combination of Paroxetine and Sildenafil for the treatment of PE [49].

Comparing our study with recent monotherapy-based studies like Shariev et al. (Lidocaine spray-based treatment) and Krishnappa et al. (Sildenafil-based treatment), we still have better outcomes concerning the success rate [49–51].

It is important to mention that Tramadol addiction was not reported in our study because of the on-demand use of the drug and the short duration of treatment.

One of the limitations of our study is the lack of questionnaires. More future studies use the PEDT questionnaire to discriminate the presence of PE or not and the PEP questionnaire to determine the applied treatment effect.

Conclusion

Combined Tramadol HCl and Sildenafil Citrate therapy is a safe and cost-effective therapy for the treatment of PE with better patient satisfaction than either of the therapies alone.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Ahmed Reda http://orcid.org/0000-0003-3699-5735

References

[1] Wang J, Wang D. The diagnosis and treatment of ejaculatory dysfunction. Transl Androl Urol. 2018;7 (Suppl S5):AB028–AB028. doi: 10.21037/tau.2018.AB028

[2] McMahon CG, Althof SE, Waldinger MD, et al. An evidence-based definition of lifelong premature ejaculation: report of the International society for sexual medicine (ISSM) ad hoc committee for the definition of premature ejaculation. J Sex Med. 2008;5 (7):1590–1606. doi: 10.1111/j.1743-6109.2008.00901.x

[3] 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(4):736–743. doi: 10.1016/j.eururo.2011.08.039

[4] Giuliano F, Patrick DL, Porst H, et al. Premature Ejaculation: Results from a Five-Country European Observational Study. Eur Urol. 2008;53(5):1048–1057. doi: 10.1016/j.eururo.2007.10.015

[5] Patrick DL, Althof SE, Pryor JL, et al. Original research—ejaculatory disorders: premature ejaculation: An observational study of men and their partners. J Sex Med. 2005;2(3):358–367. doi: 10.1111/j.1743-6109.2005.20353.x

[6] Wylie KR, Ralph D. Premature ejaculation: The current literature. Curr Opin Urol. 2005;15(6):393–398. doi: 10.1097/01.mou.0000186844.40506.98

[7] McMahon C. Premature Ejaculation: Past, Present, and Future Perspectives. J Sex Med. 2005;2:94–95. doi: 10.1111/j.1743-6109.2005.20368.x

[8] Xin Z-C, Zhu Y-C, Yuan Y-M, et al. Current therapeutic strategies for premature ejaculation and future perspectives. Asian J Androl. 2011;13(4):550–557. doi: 10.1038/aja.2010.130

[9] Kurkar A, Abulsorour S, Gamal R, et al. Treatment of premature ejaculation: a new combined approach. Egypt Rheumatol Rehabil. 2015;42(1):39–44. doi: 10.4103/1110-161X.155649

[10] Linton KD, Wylie KR. Recent advances in the treatment of premature ejaculation. Drug Design Develop Therapy. 2010(4).

[11] James M M-S, Cooper K, Kaltenthaler E, et al. Tramadol for premature ejaculation: a systematic review and meta-analysis. BMC Urol. 2015;15(1):6. doi: 10.1186/1471-2490-15-6

[12] McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. J Urol. 1999;161(6):1826–1830. doi: 10.1016/S0022-5347(05)68816-7

[13] Morales A. Evolving therapeutic strategies for premature ejaculation: the search for on-demand treatment – topical versus systemic. CUAJ. 2012;6(5):380–385. doi: 10.5489/cuaj.12002
[14] Pastore AL, Palleschi G, Leto A, et al. A prospective randomized study to compare pelvic floor rehabilitation and dapoxetine for the treatment of lifelong premature ejaculation. Int JAndrology. 2012;35 (4):528–533. doi: 10.1111/j.1365-2605.2011.01243.x
[15] La Pera G, Nicastro A. A new treatment for premature ejaculation: the rehabilitation of the pelvic floor. J Sex & Marital Therapy. 1996;22(1):22–26. doi: 10.1080/00926239608405302
[16] Salem EA, Wilson SK, Bissada NK, et al. ORIGINAL RESEARCH–EJACULATORY DISORDERS: Tramadol HCL has promise in on-demand use to treat premature ejaculation. J Sex Med. 2008;5(1):188–193. doi: 10.1111/j.1743-6109.2006.00424.x
[17] Serefoglu EC, Saitz TR, Trost L, et al. Premature ejaculation: do we have effective therapy? Transl Androl Urol. 2013;2(1):45–53. doi: 10.3978/j.issn.2223-4683.2013.01.02
[18] Serefoglu EC, Saitz TR. New insights on premature ejaculation: a review of definition, classification, prevalence and treatment. Asian J Androl. 2012;14 (6):822–829. doi: 10.1038/aja.2012.108
[19] Waldinger MD. Emerging drugs for premature ejaculation. Expert Opin Emerg Drugs. 2006;11 (1):99–109. doi: 10.1517/14728214.11.1.99
[20] Gameel TA, Tawfik AM, Abou-Farha MO, et al. On-demand use of tramadol, sildenafil, paroxetine and local anaesthetics for the management of premature ejaculation: a randomised placebo-controlled clinical trial. Arab J Urol. 2013;11(4):392–397. doi: 10.1016/j.aju.2013.05.003
[21] Sotomayor M. The burden of premature ejaculation: the patient's perspective. J Sex Med. 2005;2(SUPPL. 2):110–114. doi: 10.1111/j.1743-6109.2005.20371.x
[22] Althof SE, McMahon CG, Waldinger MD, et al. An update of the international society of sexual medicine's guidelines for the diagnosis and treatment of premature ejaculation (PE). Sex Med. 2014;2(2):60–90. doi: 10.1002/sm2.28
[23] Frink MC, Hennies HH, Englberger W, et al. Influence of tramadol on neurotransmitter systems of the rat brain. Arzneimittelforschung. 1996;46(11):1029–1036.
[24] Ogata J, Minami K, Uezono Y, et al. The inhibitory effects of tramadol on 5-hydroxytryptamine type 2C receptors expressed in xenopus oocytes. Anesthesia & Analgesia. 2004;98(5):1401–1406. doi: 10.1213/01.ANE.0000108963.77623.A4
[25] Hara K, Minami K, Sata T. The effects of tramadol and its metabolite on glycine, ??-Aminobutyric AcidA, and N-Methyl-d-aspartate receptors expressed in xenopus oocytes. Anesthesia & Analgesia. 2005;100 (5):1400–1405. table of contents. doi: 10.1213/01.ANE.0000150961.24747.98
[26] 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 (1):27–31. doi: 10.1097/01.jcp.0000195110.79027.3f
[27] Szkutnik-Fiedler D, Kus K, Balcerkiewicz M, et al. Concomitant use of tramadol and venlafaxine - evaluation of antidepressant-like activity and other behavioral effects in rats. Pharmacol Rep. 2012;64 (6):1350–1358. doi: 10.1016/S1734-1140(12)70932-5
[28] Shiga Y, Minami K, Shiraishi M, et al. The inhibitory effects of tramadol on muscarinic receptor-induced responses in xenopus oocytes expressing cloned M (3) receptors. Anesth Analg. 2002;95(5):1269–1273. doi: 10.1097/00000539-200211000-00031
[29] Shiraishi M, Minami K, Uezono Y, et al. Inhibition by tramadol of muscarinic receptor-induced responses in cultured adrenal medullary cells and xenopus laevis oocytes expressing cloned M1 receptors. J Pharmacol Exp Ther. 2001;299(1):255–260.
[30] Shiraishi M, Minami K, Uezono Y, et al. Inhibitory effects of tramadol on nicotinic acetylcholine receptors in adrenal chromaffin cells and in xenopus oocytes expressing alpha 7 receptors. Br J Pharmacol. 2002;136(2):207–216. doi: 10.1038/sj.bjp.0704703
[31] Abdel-Hamid IA. Phosphodiesterase 5 inhibitors in rapid ejaculation: potential use and possible mechanisms of action. Drugs. 2004;64(1):13–26. doi: 10.2165/00003495-200464010-00002
[32] Medina P, Segarra G, Torondel B, et al. Inhibition of neuroeffector transmission in human vas deferens by sildenafil. Br J Pharmacol. 2000;131(5):871–874. doi: 10.1038/sj.bjp.0703657
[33] Pfaus JG. Neurobiology of sexual behavior. Curr Opin Neurobiol. 1999;9(6):751–758. doi: 10.1016/S0959-4388(99)00034-3
[34] Aversa A, Francomano D, Bruzziches R, et al. Is there a role for phosphodiesterase type-5 inhibitors in the treatment of premature ejaculation? Int J Impot Res. 2011;23(1):17–23. doi: 10.1038/ijir.2010.34
[35] Eassa BI, El-Shazly MA. Safety and efficacy of tramadol hydrochloride on treatment of premature ejaculation. Asian J Androl. 2013;15(1):138–142. doi: 10.1038/aja.2012.96
[36] Kaynar M, Kilic O, Yurdakul T. On-demand tramadol hydrochloride use in premature ejaculation treatment. Urology. 2012;79(1):145–149. doi: 10.1016/j.urology.2011.09.031
[37] Kirby EW, Carson CC, Coward RM. Tramadol for the management of premature ejaculation: a timely systematic review. Int J Impot Res. 2015;27(4):121–127. doi: 10.1038/ijir.2015.7
[38] Kurkar A, Elderwy AA, Abulsorour S, et al. A randomized, double-blind, placebo-controlled, crossover trial of? on-demand? tramadol for the treatment of premature ejaculation. Urol Ann. 2015;7 (2):205. doi: 10.4103/0974-7796.150481
[39] Wong BLK, Malde S. The use of tramadol "on-demand" for premature ejaculation: a systematic review. Urology. 2013;81(1):98–103. doi: 10.1016/j.urology.2012.08.037
[40] Wu T, Yue X, Duan X, et al. Efficacy and safety of tramadol for premature ejaculation: a systematic review and meta-analysis. Urology. 2012;80 (3):618–624. doi: 10.1016/j.urology.2012.05.035
[41] Yang L, Qian S, Liu H, et al. Role of tramadol in premature ejaculation: a systematic review and meta-analysis. Urol Int. 2013;91(2):197–205. doi: 10.1159/000348826
[42] El-Hamd M A. Efficacy and safety of daily use of tadalafil in treatment of patients with premature ejaculation: a randomised placebo-controlled clinical trial. Andrologia. 2018;50(5). doi: 10.1111/and.13005
[43] Aversa A, Pili M, Francomano D, et al. Effects of vardenafil administration on intravaginal ejaculatory latency time in men with lifelong premature ejaculation. Int J Impot Res. 2009;21(4):221–227. doi: 10.1038/ijir.2009.21

[44] Hosseini MM, Yarmohammadi H. Effect of fluoxetine alone and in combination with sildenafil in patients with premature ejaculation. Urol Int. 2007;79(1):28–32. doi: 10.1159/000102909

[45] Karabakan M, Keskin E, Akdemir S, et al. Effect of tadalafil 5mg daily treatment on the ejaculatory times, lower urinary tract symptoms and erectile function in patients with erectile dysfunction. Int Braz J Urol. 2017;43(2):317–324. doi: 10.1590/s1677-5538.ibju.2016.0376

[46] Men C, Yu L, Yuan H, et al. Efficacy and safety of phosphodiesterase type 5 inhibitors on primary premature ejaculation in men receiving selective serotonin reuptake inhibitors therapy: a systematic review and meta-analysis. Andrologia. 2016;48(9):1066–1073. doi: 10.1111/and.12540

[47] Wang WF, Wang Y, Minhas S, et al. Can sildenafil treat primary premature ejaculation? A prospective clinical study. Int J Urol. 2007;14(4):331–335. doi: 10.1111/j.1442-2042.2007.01606.x

[48] Chen J, Keren-Paz G, Bar-Yosef Y, et al. The role of phosphodiesterase type 5 inhibitors in the management of premature ejaculation: a critical analysis of basic science and clinical data. Eur Urol. 2007;52(5):1331–1339. doi: 10.1016/j.eururo.2007.08.005

[49] Salonia A, Maga T, Colombo R, et al. A prospective study comparing paroxetine alone versus paroxetine plus sildenafil in patients with premature ejaculation. J Urol. 2002;168(6):2486–2489. doi: 10.1016/S0022-5347(05)64174-2

[50] Sun Y, Luo D, Yang L, et al. Efficacy of phosphodiesterase-5 inhibitor in men with premature ejaculation: a New systematic review and meta-analysis. Urology. 2015;86(5):947–955. doi: 10.1016/j.urology.2015.06.051

[51] Krishnappa P, Fernandez-Pascual E, Carballido J, et al. Sildenafil/Viagra in the treatment of premature ejaculation. Int J Impot Res. 2019;31(2):65–70. doi: 10.1038/s41443-018-0099-2