Effect of tramadol on the male reproductive system and sexual health

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Objectives
The aim of this study was to review the literature as regards the potential effects of chronic tramadol administration on the male reproductive system and sexual health in humans and experimental animals *in vivo* and *in vitro* in published studies.
Materials and methods
We searched electronic databases from 2006 to 2016, including PubMed MEDLINE, Medscape, EMBASE, EBCSO Academic Search Complete, Cochrane Systematic Reviews Database, and Google-Scholar.
Study selection
The articles that studied the effect of chronic tramadol administration on the male reproductive system and sexual health in both humans and laboratory animals were selected. The initial search selected articles that met the inclusion criteria. If the studies did not fulfill the inclusion criteria, they were excluded.
Data extraction
Study quality assessment included the following: whether ethical approval was gained, eligibility criteria specified, appropriate controls, adequate information, and defined assessment measures.
Data synthesis
Comparisons were made using a structured review with the results tabulated.
Conclusion
This review demonstrates a significant damage to testicular tissue with chronic tramadol administration. Tramadol was demonstrated to affect male reproductive hormones by decreasing serum testosterone and gonadotrophins and increasing estradiol and prolactin. As regards its effect on sexual function, it was demonstrated that it is neither more effective nor safer compared with other drugs used in the treatment of premature ejaculation. Moreover, it may be associated with erectile dysfunction.

Keywords:
epididymis, erectile dysfunction, histopathology, premature ejaculation, sex hormones, sperm, spermatogenesis, testis, tramadol

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Introduction

Despite the introduction of many new analgesics, opioid drugs remain the first choice for relief from moderate-to-severe pain conditions that require long-term treatment [1].

Tramadol is a synthetic centrally acting analgesic drug that was introduced in Germany in 1977. It has multimodal effect resulting from a dual mode of action: opioid and nonopioid mechanisms [2].

Tramadol has been included as a step 2 analgesic in the second edition of the World Health Organization's recommendations for the treatment of cancer pain [3].

Meta-analyses by Cochrane and others as well as evidence-based treatment recommendations by pain societies worldwide provide support that tramadol is an efficacious, versatile, and useful analgesic, particularly when paracetamol, NSAIDs, or cyclooxygenase (Cox)-II inhibitors provide insufficient analgesia, are not tolerated, or are contraindicated, and when there is hesitation to use strong opioids [4].

Tramadol has been prescribed off-label for the treatment of premature ejaculation (PE) when other therapies have failed because of the risk for addiction and side effects [5].

Epidemiological reports have showed that tramadol abuse has recently increased in many countries, including Egypt [6].

In an Egyptian study conducted to detect the prevalence of tramadol dependency among substance abusers, it was found that tramadol dependency is at the top of all substances abused in Egypt, at 49%, followed by polysubstances at 43%. The prevalence of tramadol dependency is higher in men than in women [7].

The effect of chronic tramadol use and addiction on the male reproductive system and sexual health has been studied in a number of published studies, which reported that it affects desire and ejaculation and causes hypogonadism. Others were conducted to demonstrate its effects on the structure of the male reproductive system.

Materials and methods

Search strategy

We reviewed papers on the influence of chronic tramadol administration on the male reproductive system and sexual health from Medline databases (PubMed, Medscape, and Science Direct), from EBCSO Academic Search Complete, Cochrane Systematic Reviews Database, and Google-Scholar.

We used tramadol/addiction/male reproductive system/testis/epididymis/sperm/erectile dysfunction/premature ejaculation/sexual satisfaction and histopathology as search terms. In addition, we examined references from the specialist databases EMF-Portal (*http://www.emf-portal.de*) reference lists in relevant publications. The search was performed in the electronic databases from 2006 to 2016.

Study selection and inclusion criteria

All studies were independently assessed for inclusion criteria. They were included if they fulfilled the following criteria:

(1) Published in English language
(2) Published in peer-reviewed journals
(3) Focused on tramadol administration and its effect on male reproductive health
(4) If a study had several publications on certain aspects, we used the latest publication giving the most relevant data.

Papers were preferred if they discussed the histopathological changes in the male reproductive system as regards the testicular and epididymal light and electron microscopic changes after tramadol administration.

Data extraction

If the studies did not fulfill the above criteria, they were excluded: studies of tramadol effects on systems other than the reproductive system, such as the liver or the brain; surveys about reproductive symptoms and sexual health without tramadol exposure assessment; and report without peer-review, not within national research program, and letters/comments/editorials/news.

The analyzed publications were evaluated according to evidence-based medicine (EBM) criteria using the classification of the US Preventive Services Task Force and UK National Health Service protocol for EBM in addition to the evidence pyramid (Fig. 1).

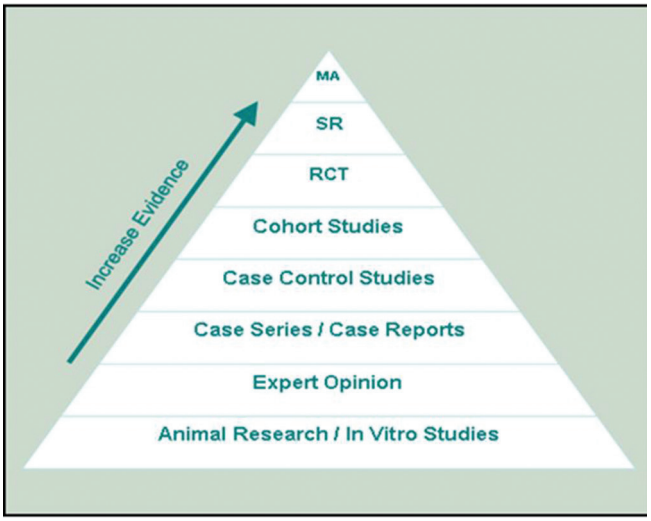
US Preventive Services Task Force:

(1) Level I: Evidence obtained from at least one properly designed randomized controlled trial
(2) Level II-1: Evidence obtained from well-designed controlled trials without randomization
(3) Level II-2: Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group
(4) Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence
(5) Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Quality assessment

The quality of all studies was assessed. Important factors included study design, attainment of ethical approval, specified eligibility criteria, appropriate controls,

Figure 1



The pyramid of evidence-based medicine. MA, meta-analysis; RCT, randomized controlled trial; SR, systematic reviews.

adequate information, and specified assessment measures.

Data synthesis

A structured systematic review was performed with the results tabulated.

Results

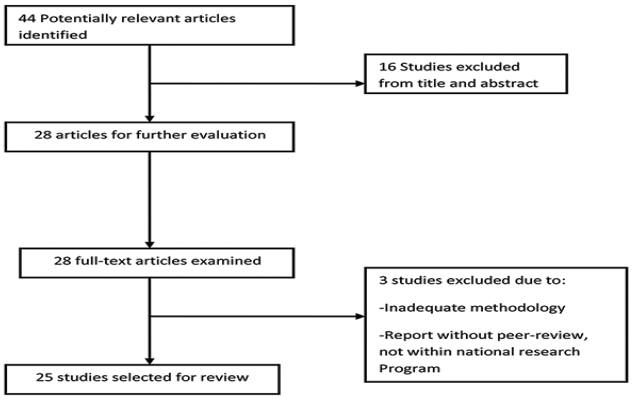
In total, 41 potentially relevant publications were identified; 16 articles were excluded as they did not meet our inclusion criteria. A total of 25 studies were included in the review as they were deemed eligible as they fulfilled the inclusion criteria (Fig. 2). Of these 25 studies included in this review, 17 were human studies and eight were animal studies. The selected studies examined the effects of chronic tramadol administration on the male reproductive system as regards histopathological and functional aspects. Histopathological assessment included the assessment of tramadol effect on testes, epididymes, and spermatogenesis using light or electronic microscopy. Some of the included studies discussed the effect of tramadol administration on the reproductive hormones. Others discussed tramadol effect on premature ejaculation and erectile dysfunction, which are major sexual health problems.

The selected studies were analyzed with respect to the study design using the classification of the US Preventive Services Task Force and UK National Health Service protocol for EBM.

Effect of tramadol on the reproductive hormones according to evidence-based medicine

The effect of chronic tramadol administration on male reproductive hormones was discussed in five experimental animal studies (which come in the base of the evidence pyramid and provide the least strength of evidence) (Table 1) [8–15].

Figure 2



Flow chart of study selection.

All these animal studies showed a significant decrease in the mean values of testosterone, luteinizing hormone (LH), and follicular stimulating hormones (FSH) in tramadol-treated rats when compared with control groups.

Of these five animal studies, four (studies 8, 9, 10, and 15) showed a significant increase in the mean values of estradiol and prolactin levels in tramadol-treated rats when compared with control groups.

Two of the previously mentioned studies [8,9] reported that these effects are dose dependent.

Effect of tramadol on the structure of the male reproductive system and spermatogenesis according to evidence-based medicine

Studies involving light microscopic examination for tramadol effects on the male reproductive system

We identified seven animal studies discussing light microscopic changes in the testicular tissue and epididymal sperms after chronic tramadol administration in male rats.

Various aspects and degrees of degenerative changes in testicular tissue were observed in different tramadol-treated rat groups when compared with control groups in all these seven studies. These changes included the following:

(1) Focal testicular degeneration [15]
(2) Disruption of seminiferous tubules' basement membranes. This was observed in studies [10–13]
(3) Desquamation of the germinal epithelium in seminiferous tubule lumen as observed in studies [11,12,14]
(4) Dissociation of spermatogenic cells from each other and from the basement membrane as observed in studies [11–13]
(5) Vacuolation in spermatogenic and Sertoli cells as observed in studies [11–13,15]
(6) Decreased spermatocytes and spermatids as observed in studies [9,11–14]
(7) Formation of spermatogenic and spermatid giant cells as observed in studies [9,13]
(8) Tubular calcification (observed in one study) [9,15]
(9) Decreased and malformed Leydig cells as observed in studies [10,11,13,14]
(10) Interstitial tissue changes, such as hemorrhage, deposition of acidophilic material as observed in studies [10,11,13,14]
(11) A significant decrease in the epididymal sperm count, motility, and vitality in tramadol-treated groups [10,12].

Table 1 Animal studies investigating the effects of tramadol administration on the male reproductive system

References	Type	Level of EBM	Effects
El-Gaafarawi [8]	Animal study	Comes in the base of the evidence pyramid and provides the least strength of evidence	Significant biochemical (hormonal) changes induced by tramadol in rats
Abou-Elfatoh *et al.* [9]	Animal study	Comes in the base of the evidence pyramid and provides the least strength of evidence	Significant hormonal and histopathological changes after tramadol administration in rats
Ahmed and Kurkar [10]	Animal study	Comes in the base of the evidence pyramid and provides the least strength of evidence	Significant hormonal, histopathological (light) and immunohistochemical changes after tramadol administration in rats
Abdellatief *et al.* [11]	Animal study	Comes in the base of the evidence pyramid and provides the least strength of evidence	Significant hormonal and histopathological (light and electron microscopy) changes after tramadol administration in rats
Azari *et al.* [12]	Animal study	Comes in the base of the evidence pyramid and provides the least strength of evidence	Significant histopathological (light microscopy) changes after tramadol administration in rats. Changes are reversible after tramadol withdrawal
Ghoneim *et al.* [13]	Animal study	Comes in the base of the evidence pyramid and provides the least strength of evidence	Significant histopathological (light and electron microscopy) and immunohistochemical changes after tramadol administration in rats. Changes are reversible after tramadol withdrawal
El-Ghawet [14]	Animal study	Comes in the base of the evidence Pyramid and provides the least strength of evidence	Significant histopathological (light microscopy) changes after tramadol administration in rats
Youssef and Zidan [15]	Animal study	Comes in the base of the evidence pyramid and provides the least strength of evidence	Significant histopathological (light microscopy) changes after tramadol administration in rats

EBM, evidence-based medicine.

Only two studies reported reversibility of the changes after withdrawal of tramadol treatment [12,13].

Two of those studies reported that the changes were dose dependent [9,12].

Although one study [11] reported a significant decrease in epithelial height and seminiferous tubule diameter in tramadol-treated groups, another study [10] denied this significant change.

Studies involving electron microscopic examination for tramadol effects on the male reproductive system

Electron microscopic examination of testicular tissue after tramadol treatment was carried out in two studies [11,13] and revealed different changes:

(1) A study conducted by Ghoneim *et al.* [13] showed the presence of a wavy thickened basement membrane. Spermatogonia in that study showed disrupted mitochondria and irregular hyperchromatic nuclei with irregular clumps of heterochromatin. Primary spermatocytes were disrupted with less peripheral mitochondria, which were ruptured. Early spermatid had vacuolation and ruptured nuclei

Of note, that study showed that these changes were absent in tramadol-treated rat groups after withdrawal of tramadol.

(2) A study conducted by Abdellatief *et al.* [11] showed the deteriorating effects of tramadol on Sertoli cells where their cytoplasm was rarified and contained electron-dense mitochondria and lipid droplets. The Sertoli cell junction structure was absent or interrupted at some sites. Tramadol also affected primary spermatocytes, which demonstrated lost intercellular bridges, separation from spermatogenic lineage, ill-defined nuclear envelope, and nuclear and cytoplasmic vacuolation. Wide separations between spermatogenic cells were observed. Ultrastructural adverse effects of tramadol on the spermatids were the most encountered, wherein they showed irregular outlines, euchromatic nuclei, and vacuolated cytoplasm with few mitochondria

The process of metamorphosis was affected when the postacrosomal sheath of late spermatids were defective.

(3) Leydig cells were affected in both studies [11,13]; they had irregular outlines and contained numerous dilated smooth endoplasmic reticulum cisternae, electron-dense mitochondria, and euchromatic nucleus.

Studies involving immunohistochemical analysis for study of tramadol effects on the male reproductive system

We identified two animal studies [10,13] that used immunohistochemical analysis for the assessment of tramadol effects on the male reproductive system.

One of those two studies [10] showed strong positive endothelial nitric oxide synthase (eNOS) activity in the cytoplasm of myoid cells, primary spermatocytes,

apoptotic cells, and Leydig cells in tramadol-treated rats compared with the control group, whereas the other [13] showed a significant decrease in the gene expression of the antioxidant enzymes (Cu–Zn SOD, Mn-SOD, catalase, and glutathione peroxidase) in testicular tissues in tramadol-treated rats.

Effect of tramadol on the male sexual function according to evidence-based medicine

Role of tramadol in premature ejaculation

We identified 15 human studies discussing the role of tramadol as a therapeutic agent for the treatment of premature ejaculation. Eleven of these 15 studies [16–26] are case–control studies, Whereas the others [27-29] are systematic reviews (Table 2).

Seven studies [16,17,19,21,23,25,26] compared the on-demand tramadol use versus placebo, whereas one study [22] compared on-demand tramadol treatment versus continued treatment. Two other studies reported on-demand tramadol versus paroxetine, either daily [18] or on demand [20]. Another study [24] compared on-demand tramadol with three other on-demand PE potential therapies (sildenafil, paroxetine, and local lidocaine gel).

All these studies found a significant improvement in intravaginal ejaculatory latency time and showed that tramadol can be used as a useful intervention for the treatment of premature ejaculation.

However, two of the aforementioned studies [5,28] recommended additional rigorous well-designed controlled trials to investigate the potential long-term risks of tramadol and to determine the safe and the effective minimum daily dose.

Moreover, the study conducted by Al-Ghobary *et al.* [18] found that daily paroxetine is more effective compared with on-demand tramadol for the treatment of premature ejaculation and stated that, although effective, tramadol should not be recommended as a long-term treatment.

Effect of tramadol on sexual satisfaction and erection

We identified four human studies [16,21,22,24] (case–control studies) that reported improvement in sexual satisfaction score and an increase in coital frequency after tramadol administration.

However, the study conducted by El-Hadidy and El-Gilany and Kirby E and Carson C [29,30] showed a significant increase in the subscales of the Arabic version of the Self-Esteem and Relationship questionnaire so that there were improved sexual relationships, sexual self-esteem, and overall sexual satisfaction 6 months after treatment of tramadol dependency more than that before treatment of dependency. Moreover, the study conducted by Giuliano and Droupy [31] showed that tramadol is potentially deleterious to sexual satisfaction. Moreover, Al-Ghobary *et al.* [18] in their study observed that all cases of PE in their study showed significantly less erection measured using the Arabic Index of Premature Ejaculation score after 6 and 12 weeks of tramadol treatment compared with the baseline level (Table 3).

Discussion

Tramadol dependency has risen in the last years as a major health problem with the need for many research studies to investigate its various side effects on different organs and systems of the body. Research about the effects of tramadol dependency on the male reproductive system and sexual health had gained a rising importance lately. This may be attributed to the widespread use of tramadol as an easily accessible illicit drug within different population categories and the increasing use of tramadol as a treatment in cases of premature ejaculation. Many significant studies are ongoing in both national and international research programs, in both public and private laboratories.

Different studies (both animal and human) have searched into the effect of tramadol on the testicular tissue, spermatogenesis, reproductive hormones, and sexual function.

During our systematic review article, we found that all studies of tramadol effect on the reproductive hormones and testicular structure were animal studies. These animal studies used different types of laboratory rats with different periods of tramadol administration, ranging between 1 and 3 months, after which different protocols for the assessment of tramadol effects were used, either light microscopic or electron microscopic examination.

Almost all studies concerning the histopathological effects of tramadol showed that tramadol caused structural damage to different testicular cells, spermatogonia, Sertoli cells, primary spermatocytes, spermatids, and Leydig cells, and caused a significant decrease in spermatogenesis [9–15].

This effect of tramadol may have been due to the effect of tramadol on the expression of eNOS in the testicular tissues and nitric oxide, which were postulated to be involved in the analgesic effect of tramadol. Nitric oxide is known to inhibit testosterone secretion [32].

Table 2 Human studies investigating the effects of tramadol administration on the male reproductive system

References	Type	Level of EBM	Number of patients	Dose	Duration (weeks)	Effects (fold increase in IELT)
Safarinejad and Hosseini [16]	Randomized control trial	Level I or level A	29	50 mg on demand	8	13-fold increase in IELT69% high sexual satisfaction
Salem *et al.* [17]	Prospective, crossover, single blind	Level I or level A	60	25 mg on demand	16	6.3-fold increase in IELT
Al-Ghobary *et al.* [18]	Prospective, cross-over, single-blind, randomized trial	Level I or level A	35	50 mg on demand Paroxitine daily	6-12	7.3-5.7-fold increase in IELT after tramadol treatmentDaily paroxetine was effective compared with on-demand tramadol
Bar-Or *et al.* [19]	Blinded, placebo-controlled randomized trial	Level I or level A	604	62, 89 mg on demand	12	2.4-2.5-fold increase in IELT
Eid *et al.* [20]	Prospective, cross-over, single-blind trial	Level I or level A	44	50 mg on demand; paroxitine on demand	3	12.4-fold increase in IELT with tramadol versus 4.4-fold increase with paroxitine
Kaynar *et al.* [21]	Prospective, single-blind trial	Level I or level A	60	25 mg on demand	8	3.9-fold increase in IELT, ability of ejaculation control, and sexual satisfaction score (SSS)
Kahn and Rasaily [22]	Prospective randomized control trial	Level I or level A	60	100 mg daily and on demand	8 (4 weeks for each regimen)	3.4-fold (daily use) and 4-fold (on-demand use) increase in IELT1.7-fold (daily use) and 2.3-fold (on-demand use) increase in coital frequency
Eassa and El-Shazly [23]	Randomized control trial	Level I or level A)	300	25 mg, 50 mg, and 100 mg on demand	24	4.5-fold (25 mg), 8-fold (50 mg), and 12.6-fold (100 mg) increase in IELT
Gameel *et al.* [24]	Randomized, placebo-controlled clinical trial	Level I or level A	150 (30 in each group)	50 mg on demand vs. on-demand 20 mg paroxetine, 50 mg sildenafil, and lidocaine gel 2.5%	4	5.2-fold (tramadol), 3.9-fold (sildenafil), 2.6-fold (paroxetine), and 5.1-fold (topical lidocaine) increase in IELT3.44-fold (tramadol), 3.5-fold (sildenafil), 3.1-fold (paroxetine), and 2.7-fold (topical lidocaine) increase in sexual satisfaction score
Nima *et al.* [25]	Single-blind placebo-controlled clinical trial.	Level I or level A	28	50 mg on demand	8	6-fold increase in IEL67. 9% high sexual satisfaction
Kurkar *et al.* [26]	Prospective double-blinded placebo-controlled, crossover study	Level I or level A	125	50 mg and 100 mg tramadol on demand	16	2.1-fold (50 mg) and 3.8-fold (100 mg) increase in IELT
Yang *et al.* [27]	Systematic review	Comes in the second level with regard to the pyramid of EBM	-	-	-	Yes, tramadol is an effective treatment for PE
Martyn-St James *et al.* [28]	Systematic review	Comes in the second level with regard to the pyramid of EBM	-	-	-	Yes, tramadol appears effective for treating PE
Kirby *et al.* [29]	Systematic review	Comes in the second level with regard to the pyramid of EBM	-	-	-	Yes, tramadol is effective for treating PE

EBM, evidence-based medicine; IELT, intravaginal ejaculation latency time; PE, premature ejaculation.

Table 3 Studies investigating the effects of tramadol administration on sexual satisfaction

References	Type	Level of EBM	Effects
El-Hadidy and El-Gilany [30]	Quasiexperimental study	Level II-d	Tramadol negatively affects the overall sexual satisfaction
Giuliano and Droupy [31]	Review of the literature	Comes in the second level as regards the pyramid of EBM	Tramadol is potentially deleterious to sexual satisfaction.

EBM, evidence-based medicine.

eNOS is found in the testis, and is involved in spermatogenesis, sperm maturation, and programmed cell death of Sertoli and germ cells, which might explain the deleterious effects of tramadol on spermatogenesis and testicular function [33].

The abnormalities observed in the testicular structures, including germ and Leydig cells, might be attributed to the peroxidation of polyunsaturated fatty acids in their plasma membranes by tramadol [34].

Noteworthy, two studies showed that the structural damage caused by chronic tramadol administration was potentially reversible after cessation of drug, both on light and electron microscopic examination [12,13].

On studying the effect of tramadol on the reproductive hormones, five studies demonstrated a significant increase in estradiol and prolactin and a significant decrease in LH, FSH, and testosterone. This may be the cause of arrested spermatogenesis and derangements in the testicular histology noticed after tramadol administration.

These hormonal changes may be attributed to the fact that tramadol interferes with the normal pulsatility of gonadotropin-releasing hormone release at the level of the hypothalamus, and this leads to a decrease in LH and FSH release from the pituitary and consequently of testosterone from the testis [35].

On studying the effect of tramadol on the sexual function, nearly all studies concerned with this regard were human studies: case–control, quasiexperimental, or systematic review articles.

Despite the conflicting results in this domain with most studies recommending tramadol as an option for the treatment of premature ejaculation, this must be taken with great caution, especially due to addictive and abusive properties of tramadol and in the light of the hazardous effects of tramadol on the testicular structure and spermatogenesis previously mentioned. Indeed, some studies demonstrated no superior efficacy of tramadol compared with paroxetine in the treatment of premature ejaculation.

On reviewing studies on tramadol and erectile dysfunction, it was suggested that tramadol may be involved in erectile dysfunction [18,36].

Although there is evidence that tramadol increases dopamine release (which has facilitative effects on penile erection), it inhibits reuptake of noradrenaline and serotonin, which have inhibitory effects on penile erection [36].

Conclusion

This review demonstrates a significant damage to testicular tissue with chronic tramadol administration. This damage was proved to affect different components of the spermatogenic process from primary spermatogonia until sperm concentration and vitality. The damage also affects Sertoli and Leydig cells.

Tramadol was demonstrated to affect male reproductive hormones by decreasing serum testosterone and gonadotrophins and increasing estradiol and prolactin.

As regards its effect on sexual function, it was demonstrated that it is neither more effective nor safer compared with other drugs used in the treatment of premature ejaculation. Moreover, it may be associated with erectile dysfunction.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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