Assessment of Sexual Functions among Male Tramadol Users

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Abstract

Background: Opioids are effective for chronic pain but can have adverse effects on male sexual function.

Objectives: This study aimed to evaluate sexual functions among male tramadol users.

Patients and Methods: This case-control study involved 45 male tramadol users and 45 healthy controls. Psychometric tests, such as the International Index of Erectile Function (IIEF), the Sexual Quality of Life Questionnaire-Male Version (SQOL-M), and addiction severity index were given to the participants. They also had clinical interviews and hormonal tests (testosterone, LH, FSH, and prolactin). The primary outcome was erectile dysfunction prevalence. The secondary outcomes included the correlation between ED severity and abuse duration, dosing frequency, addiction severity index, and anxiety and depression scales.

Results: Tramadol users had significantly lower total testosterone and LH levels, but higher prolactin compared to controls. Rates of erectile dysfunction were markedly higher in the tramadol group (57.8% vs. 13.3%, $p < 0.001$). Tramadol users scored significantly worse on the IIEF domains of erectile function, sexual desire, orgasmic function, satisfaction, and preoccupation. Tramadol users also significantly reduced their SQOL-M scores. The duration of use, dosing frequency, and addiction severity index positively correlate with the severity of erectile dysfunction.

Conclusion: Extended use of tramadol has been associated with hormonal disruption, an increased prevalence of erectile dysfunction, impairments in various aspects of sexual function, and a reduced quality of sexual life in males.

Keywords: Tramadol; Opioid; Sexual Dysfunction; Erectile Dysfunction; Male.
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Introduction

Opioid analgesics remain the primary therapeutic option for the management of chronic pain disorders characterized by moderate-to-severe severity that require extended therapy, despite the availability of newer analgesic agents **(Dowell, 2022)**.

Tramadol is categorized as a synthetic opioid analgesic with central acting properties, falls within the aminocyclohexanol class, and exhibits a unique pharmacological profile **(Mostafa, 2023; Ram et al., 2024)**. While structurally analogous to codeine, in comparison to other opioids, tramadol demonstrates a significantly reduced affinity for opioid receptors. Notably, it modulates the activity of noradrenergic and serotonergic pathways within the central nervous system, contributing to its distinct mechanism of action **(Subedi et al., 2019)**.

The prevalence of tramadol dependency has become a significant concern, particularly in Egypt, where it ranks as the most prevalent substance abuse, surpassing polysubstance use. Furthermore, the incidence of tramadol dependency is markedly higher among males compared to females **(Mohamed et al., 2015; Boun et al., 2024)**.

Sexual dysfunction (SD) is a prevalent concern observed in guys who are reliant on opiates, with a substantial proportion (65%) experiencing erectile dysfunction (ED) **(Zafarghandi et al., 2016)**. In addition, using serotonin and norepinephrine reuptake inhibitors (SNRIs), which work in a way similar to tramadol, has been linked to a high rate of SD, ranging from 30% to 80% **(Rink et al., 2022)**.

Many consider the relationship between tramadol and sexual function to be complex and a topic of ongoing controversy. Evidence indicates that tramadol could offer off-label advantages to those experiencing premature ejaculation **(Abdel-Hamid et al., 2015; Kurkar et al., 2024)**, these individuals may have an increased risk of experiencing more SD **(Hassan et al., 2019)**. Conversely, experimental studies have demonstrated that tramadol doesn't elicit significant effects on libido. However, it has the potential to modulate sex hormone levels and disrupt control of the pituitary-hypothalamic feedback loop **(Abdel-Moneim et al., 2022)**. Furthermore, tramadol use has been associated with negative effects on sperm quality, hyperprolactinemia, and hypergonadotropic hypogonadism **(Ahmed et al., 2018; Ashry et al., 2024)**. Conversely, the widespread use of tramadol, particularly among Egyptian youth, can be attributed to its claimed advantages in resolving premature ejaculation and increasing sexual pleasure **(Abd-Elkader et al., 2020)**. The current study aimed to investigate the prevalence of ED and its relationship with various factors in patients diagnosed with tramadol use disorder.

Patients and methods

We conducted this proposed case-control study on 90 married heterosexual male participants, ages between 20-45 years. The study was conducted with approval from the institutional ethical committee at the Neuropsychiatry Department, Center of Psychiatry, Neurology, and Neurosurgery, andrology unit in the Urology Department, and the Forensic Medicine and Clinical Toxicology departments of Tanta University Hospitals, Egypt, from January 2024 to April 2024, with approval code: 36264PR521/1/24. We obtained informed written consent from all participants after providing them with a comprehensive explanation of the study's purpose.

The study implied two groups: Group I consisted of patients with a positive screening test for tramadol only, while Group II comprised healthy individuals serving as the control group.

Patients with a history of renal impairment, diabetes mellitus, hepatitis B/C or HIV infection, autoimmune

diseases, congenital heart diseases, other drugs, hypertension, other psychiatric disorders, primary infertility, or primary sexual dysfunction unrelated to tramadol use were excluded.

Participants underwent a comprehensive assessment, including a psychiatric interview, to diagnose substance use disorder, evaluating sociodemographic data, history, and family troubles.

The toxicological history involved assessing the dosage and formulation of tramadol administered daily, the duration of tramadol dependence, and any diseases complicating dependence. Urine tests for substance use disorders, quick-view tramadol test cards (a quick one-step drug abuse test), and confirmation of tramadol blood levels using high-performance liquid chromatography with ultraviolet detection were all done in the lab.

Both the tramadol user group (group I) and the control group (group II) underwent assessments of serum testosterone and prolactin levels. Furthermore, we conducted sex hormone assays using immunoassay methods and specific kits from Shenzhen New Industries Biomedical Engineering Company to measure luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels. The assessment protocol also involved measuring serum prolactin concentrations after a rest period of at least 20 minutes.

We assessed the participants' anxiety and depression levels using the Hospital Anxiety and Depression Scale (Arabic version).

We performed psychometric evaluation using the MENS health questionnaire and assessed the intensity of tramadol's influence on multiple areas using the Addiction Severity Index. The study employed the International Index of Erectile Function (IIEF) to evaluate various aspects of sexual function, such as erectile function, sexual desire, orgasm, sexual pleasure, sexual preoccupation, and sexual quality of life.

Furthermore, we employed the Sexual Quality of Life Questionnaire-Male version to detect the impact of sexual dysfunction on men's quality of life. We determined the presence and severity of ED using scores ranging from 1 to 30, with specific ranges indicating different levels of dysfunction.

The primary outcome was to determine the prevalence of ED. The secondary outcomes included the correlation between ED severity and abuse duration, dosing frequency, addiction severity index, and anxiety and depression scales.

Sample size calculation: We used G. power 3.1.9.2 (Universitat Kiel, Germany) to compute the sample size. The prevalence of ED (the primary outcome) was 44% with tramadol and 10% in control, according to a previous study (**Kabbash et al., 2019**). We based the sample size on a 95% confidence limit, the study's 95% power, and a 1:1 group ratio, adding three cases to each group to prevent dropout. Therefore, we recruited 45 patients in each group.

Statistical analysis

Statistical analysis was performed using SPSS v27 (IBM©, Armonk, NY, USA). Quantitative parametric data were expressed as mean and standard deviation (SD) and analyzed through unpaired Student t-tests. Qualitative variables were represented as frequency and percentage, and they were assessed using the Chi-square test or Fisher's exact test, as appropriate. A significance level of two-tailed $P \leq 0.05$ was deemed statistically significant.

Results

In this study, 103 patients were assessed for eligibility, 8 patients did not meet the criteria and 5 patients refused to participate in the study. The remaining patients were randomly allocated into two equal groups (45 patients in each). All

allocated patients were followed-up and analysed statistically (**Fig.1**).

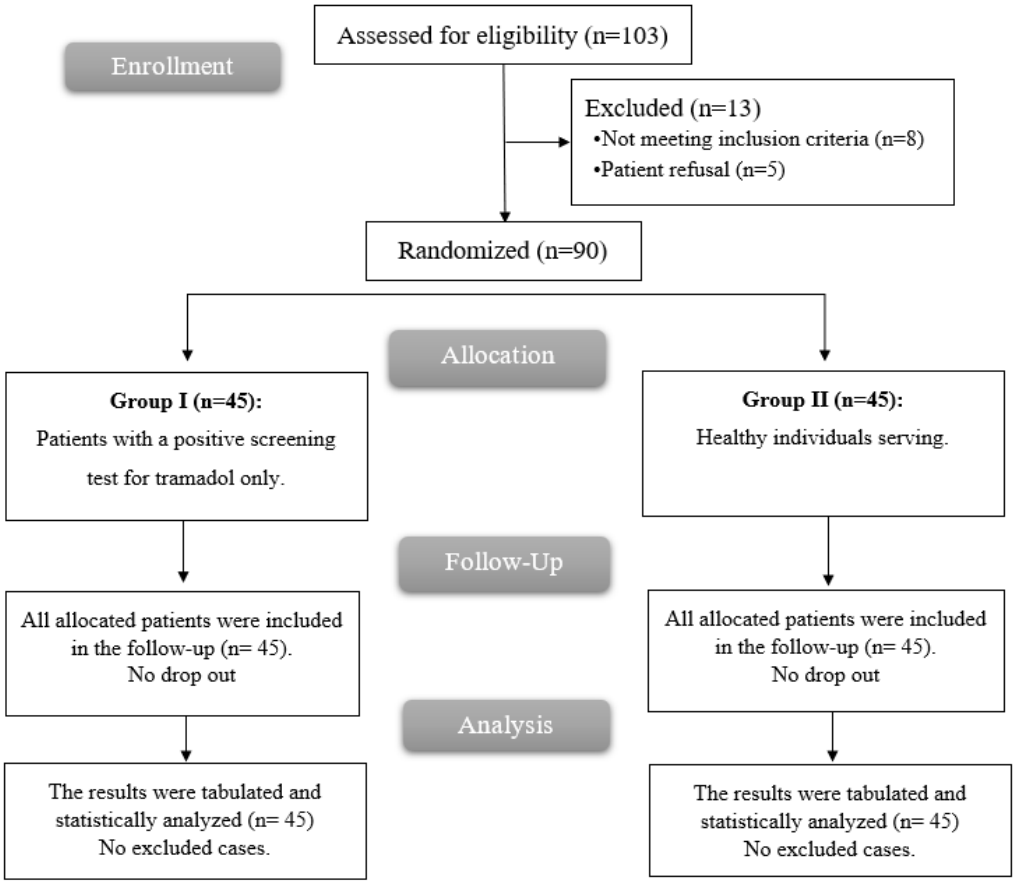

Fig. 1. CONSORT flowchart of the enrolled patients

Age, occupation, marital status, education, residence, and duration of marriage were insignificantly different between both groups. The smoking index, family history of substance use, and history of previous treatment trials were significantly higher in group I than in group II (P<0.05). In group I, the age of onset was 28.18 (± 6.73) years. Regarding tramadol dose frequency, 6 (13.33%) patients took ≤2 tablets, and 39 (86.67%) patients took >2 tablets in group I. In group I, the duration of tramadol dependence was 7.04 (± 3.57) years, (**Table .1**)

Table 1. Patient characteristics and tramadol duration and dose frequency of the studied groups

Variables		Group I (n=45)	Group II (n=45)	P
Age (years)		35.22 ± 5.94	33.69 ± 7.53	0.286
Occupation	**Manual worker**	13 (28.89%)	7 (15.56%)	0.396
	Employee	24 (53.33%)	26 (57.78%)	
	Teacher	3 (6.67%)	6 (13.33%)	
	Do not work	5 (11.11%)	6 (13.33%)	
Marital status	**Married**	28 (62.22%)	23 (51.11%)	0.690
	Single	13 (28.89%)	15 (33.33%)	
	Divorced	3 (6.67%)	5 (11.11%)	
	Separated	1 (2.22%)	2 (4.44%)	
Education	**Primary**	5 (11.11%)	7 (15.56%)	0.350

	Secondary	6 (13.33%)	3 (6.67%)	
	University	7 (15.56%)	14 (31.11%)	
	Vocational	21 (46.67%)	16 (35.56%)	
	Non-educated	6 (13.33%)	5 (11.11%)	
Residence	**Urban**	17 (37.78%)	21 (46.67%)	0.393
	Rural	28 (62.22%)	24 (53.33%)	
Smoking index		300.13 ± 160.37	196.61 ± 111.82	**0.002***
Family history of substance use		25 (55.56%)	4 (8.89%)	**<0.001***
Duration of tramadol dependence (years)		7.04 ± 3.57	---	**---**
Age of onset (years)		28.18 ± 6.73	---	**---**
Duration of marriage (years)		13.09 ± 6.26	11.71 ± 6.59	0.328
History of previous treatment trials		24 (53.33%)	11 (24.44%)	**0.005***
Tramadol dose frequency	**≤2 tablets**	6 (13.33%)	---	---
	> 2 tablets	39 (86.67%)	---	

Data are presented as mean ± SD or frequency (%). * Significant as P<0.05.

Total testosterone (p = 0.017) and LH levels (p < 0.001) were significantly lower in group I compared to group II, while prolactin levels (p < 0.001) were significantly higher in group I. There was no significant difference in FSH levels between the two groups, (**Table .2**)

Table 2. Hormonal evaluation of the studied groups

Variables	Group I (n=45)	Group II (n=45)	P
Total testosterone (ng/m)	4.95 ± 1.48	5.72 ± 1.51	**0.017***
LH (m IU/ml)	5.14 ± 2.01	7.77 ± 2.29	**<0.001***
FSH (m IU/ml)	4.23 ± 1.13	3.95 ± 1.13	0.236
Prolactin(ng/ml)	21.67 ± 10.9	8.69 ± 5.49	**<0.001***

Data are presented as mean ± SD or frequency (%). *: Significant when P ≤0.05.

Erectile function (p < 0.001), sexual desire (p < 0.001), orgasmic function (p = 0.033), sexual satisfaction (p < 0.001), and sexual preoccupation (p = 0.014) were significantly lower in group I compared to group II. Additionally, the prevalence of ED was significantly higher in group I (57.78%) than in group II (13.33%) (p < 0.001), (**Table .3**).

Table 3. Sexual functions of the studied groups

Variables	Group I (n=45)	Group II (n=45)	P
ED	26 (57.78%)	6 (13.33%)	**<0.001***
Erectile function	9.24 ± 0.77	27.02 ± 1.47	**<0.001***
Sexual desire	6.96 ± 1.92	10.31 ± 1.52	**<0.001***
Orgasmic dysfunction	6.8 ± 1.75	8.82 ± 1.09	**0.033***
Sexual satisfaction	8.31 ± 2.48	10.78 ± 2.5	**<0.001***
Sexual preoccupation	2.73 ± 9.05	6.64 ± 5.28	**0.014***

Data are presented as mean ± SD or frequency (%). *: Significant when P ≤0.05. ED: Erectile Dysfunction.

The sexual quality of life male version (SQOL-M) score (p < 0.001) and the psychometric evaluation with the MENS health questionnaire (p < 0.001) were both significantly lower in group I compared to group II. This means that the tramadol dependence group had worse sexual quality of life and psychometric health. (**Table 4**).

Table 4.SQOL-M and psychometric evaluation with MEN's health questionnaire of the studied groups

Variables	Group I (n=45)	Group II (n=45)	P
SQOL-M	44.62 ± 27.09	82.96 ± 7.36	**<0.001***
Psychometric evaluation with MEN's health questionnaire	13.62 ± 1.3	23.18 ± 1.11	**<0.001***

Data are presented as mean ± SD or frequency (%). *: Significant when P ≤0.05. SCID-5: Structured clinical interview for DSM-5. SQOL-M: Sexual quality of life questionnaire-male version.

Drug use was mild in 4 (8.89%) patients, moderate in 23 (51.11%) patients, and severe in 18 (40%) patients. Medical status was mild in 16 (35.56%) patients, moderate in 24 (53.33%) patients, and severe in 5 (11.11%) patients. The psychiatric state was mild in 5 (11.11%) patients, moderate in 23 (51.11%) patients, and severe in 17 (37.78%) patients. Occupational deterioration was mild in 8 (17.78%) patients, moderate in 29 (64.44%) patients, and severe in 8 (17.78%) patients. Family and social problems were mild in 6 (13.33%) patients, moderate in 25 (55.56%) patients, and severe in 14 (31.11%) patients. In group I, the legal state was mild in 27 patients (60%), moderate in 13 patients (28.89%), and severe in 5 patients (11.11%).(**Table. 5**).

Table 5. Addiction severity index of tramadol group

Variables		Group I (n=45)
Drug use	**Mild**	4 (8.89%)
	Moderate	23 (51.11%)
	Severe	18 (40%)
Medical status	**Mild**	16 (35.56%)
	Moderate	24 (53.33%)
	Severe	5 (11.11%)
Psychiatric state	**Mild**	5 (11.11%)
	Moderate	23 (51.11%)
	Severe	17 (37.78%)
Occupational deterioration	**Mild**	8 (17.78%)
	Moderate	29 (64.44%)
	Severe	8 (17.78%)
Family/social problems	**Mild**	6 (13.33%)
	Moderate	25 (55.56%)
	Severe	14 (31.11%)
Legal state	**Mild**	27 (60%)
	Moderate	13 (28.89%)
	Severe	5 (11.11%)

Data are presented as mean ± SD or frequency (%). ASI: addiction severity index.

The severity of ED was significantly lower in group I compared to group II ($p < 0.001$). The hospital anxiety and depression scale scores were also significantly higher in group I (57.78%) compared to group II (13.33%) ($p = 0.001$). (**Table. 6)**

Table 6.Severity ED and hospital anxiety and depression scale of the studied groups

Variables		Group I (n=45)	Group II (n=45)	P
Severity of ED	Mild	7 (15.56%)	5 (11.11%)	< 0.001*
	Mild to moderate	10 (22.22%)	1 (2.22%)	
	Moderate	6 (13.33%)	0 (0%)	
	Severe	3 (6.67%)	0 (0%)	
Severity of ED		21.89 ± 6.5	27.51 ± 2.67	<0.001*
Hospital anxiety and depression scale		26 (57.78%)	6 (13.33%)	0.001*

*: significant as P<0.05. Data are presented as mean ± SD or frequency (%).

The severity of ED showed strong positive correlations with the duration of tramadol dependence (r = 0.822, p < 0.001), tramadol dose frequency (r = 0.588, p < 0.001), and the addiction severity index, including drug use (r = 0.895, p < 0.001), medical status (r = 0.898, p < 0.001), psychiatric state (r = 0.9, p < 0.001), occupational deterioration (r = 0.848, p < 0.001), family/social problems (r = 0.882, p < 0.001), and legal state (r = 0.87, p < 0.001). (**Table .7**)

Table 7. Correlation between severity and (duration, dosing frequency of abuse, and addiction severity index) of the tramadol group

Variables		Severity of ED
Duration of tramadol dependence (years)	r	0.822
	P	< 0.001*
Tramadol dose frequency	r	0.588
	P	< 0.001*
Drug use	r	0.895
	P	< 0.001*
Medical status	r	0.898
	P	< 0.001*
Psychiatric state	r	0.9
	P	< 0.001*
Occupational deterioration	r	0.848
	P	< 0.001*
Family/social problems	r	0.882
	P	< 0.001*
Legal state	r	0.87
	P	< 0.001*

*: significant as P<0.05. Data are presented as mean ± SD or frequency (%).

Discussion

The association between tramadol use and sexual function is still a source of conflict in the medical profession. While some research suggests that men who have premature ejaculation may benefit, these patients appear to be more likely to develop other sexual dysfunctions (**Abdel-Hamid et al., 2015; Hassan et al., 2019**).

The demographic characteristics of the study participants didn't show significant differences between the two groups. However, compared to the control group, the tramadol group exhibited significantly higher smoking indices, a higher prevalence of the familial context around drug use, and a greater proportion of individuals with a history of previous treatment trials. These findings are reliable given the well-established correlation between drug use disorders and various risk factors, including smoking, genetic predisposition, and treatment-seeking behavior (**Abdel Naem et al., 2020; Abd-Elkader et al., 2020**).

Regarding the smoking index, there is a bidirectional relationship between tramadol use and tobacco smoking severity **(Shalaby et al., 2015)** explains these findings. Also, tramadol decreases the anxiety and aggression induced by nicotine **(Azmy et al., 2018)**. Notably, the tramadol dependence group's mean age of onset was 28.18 ± 6.73 years, indicating a relatively young age of initiation for this substance use disorder. Additionally, the majority of the tramadol users (86.67%) reported consuming more than two tablets per dose, highlighting the potential for dose escalation and the development of tolerance **(Alghobary et al., 2010; Abdel-Moneim et al., 2022)**.

The primary objective of this study was to assess the impact of tramadol, a synthetic opioid analgesic, on male sexual functions. The findings reveal significant impairments in various aspects of sexual functioning among tramadol users compared to healthy controls. These observations align with previous research highlighting the adverse impact of opioid use on male sexual health **(Abdel-Hamid et al., 2015; Ahmed et al., 2018)**.

In our study, individuals who used tramadol demonstrated notably reduced levels of total testosterone and LH in comparison to the control group. Meanwhile, prolactin and FSH levels were significantly elevated in the tramadol group. It is known that opioids have effects on the hypothalamic-pituitary-gonadal (HPG) axis, which is important for controlling male reproductive function. These changes in hormones are similar to those effects **(Abdelazim et al., 2015; Gudin et al., 2015; De Vries et al., 2020)**. Opioids are known to suppress the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, consequently decreasing the secretion of LH from the pituitary gland **(Fountas et al., 2018)**. Low levels of LH can stop the Leydig cells in the testes from making testosterone, which can cause hypogonadism and the symptoms of SD **(Gudin et al., 2015)**. Finally, chronic opioid use may be associated with increased conversion of testosterone to dihydrotestosterone **(Coluzzi et al., 2018)**. Conversely, the elevated prolactin levels observed in tramadol users may contribute to sexual dysfunction by inhibiting gonadotropin secretion and directly suppressing testosterone production **(Fountas et al., 2018)**. Our study's hormonal dysregulation aligns with previous reports on the impact of tramadol use on male reproductive hormones **(Coluzzi et al., 2018; Attia et al., 2021; Abdel-Moneim et al., 2022)**.

Consistent with the hormonal alterations, our study revealed a significantly higher prevalence of ED among tramadol users compared to controls. Furthermore, tramadol users scored lower on various domains of the IIEF. These findings corroborate previous studies, which documented a high incidence of ED and impaired sexual functions in opioid users, including tramadol **(Bassiony et al., 2019; Abdel Naem et al., 2020; Attia et al., 2021)**. The impact of tramadol on sexual functions is attributed to its influence on sex hormones, while oxidative stress has been proposed to be linked with ED, along with serotonergic activity and its negative effects on opioid receptors **(Angulo et al., 2018; Tolba et al., 2021)**. In contrast to **Abd-Elkader et al. (2020)**, tramadol is widely used because of its cost-effectiveness and accessibility without the need for a prescription. This substance is used by workers to manage premature ejaculation, enhance sexual desire, and achieve longer orgasm.

When comparing the control group and the tramadol group, the SQOL-M sexual quality of life score was considerably lower in the former. In agreement with these findings, **Coluzzi et al. (2018)**, **Kabbash et al. (2019)**, and **Abdel Naem et al. (2020)**, they discovered a notable decline in the sexual quality of life among tramadol users.

Notably, our study found positive correlations between the severity of ED and the duration of tramadol dependence, dosing frequency, and addiction severity index. These associations suggest that the longer the duration and higher the dose of tramadol use, as well as the greater the overall severity of addiction, the more pronounced the impairment in sexual functioning. Similar dose-dependent relationships between opioid use and sexual dysfunction have been reported in previous studies **(Bassiony et al., 2019; Tolba et al., 2021)**.

While the present study did not find significant differences in the Hospital Anxiety and Depression Scale (HADS) between tramadol users and controls, previous research has highlighted the potential contribution of psychological factors, such as depression and anxiety, to sexual dysfunction in opioid users **(Bassiony et al., 2019; Soliman et al., 2022)**. The study had several limitations that should be considered. First, the small sample size of 45 participants per group limited the statistical power and generalizability of the findings. Additionally, the study did not account for potential confounding factors such as smoking, comorbidities like hypertension and diabetes, and concomitant medication use, all of which could have influenced sexual function. The absence of a placebo or non-tramadol opioid control group made it challenging to differentiate tramadol's specific effects. Furthermore, the study did not report the duration of tramadol use, which could impact the assessment of sexual dysfunction severity.

Conclusion

The present study highlights the significant impairments in male sexual functions associated with tramadol use, including hormonal dysregulation, a high prevalence of ED, and reduced SQL. These findings underscore the importance of addressing and managing SD as a potential complication of opioid use, particularly in the context of opioid dependence treatment and harm reduction strategies.

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References

- **Abd-Elkader MR, Kabbash IA, El-Sallamy RM, El-Sawy H, Gad E-SA-H. (2020)**. Tramadol abuse among workers in an industrial city in mid-Nile Delta region, Egypt. Environ Sci Pollut Res 2737549–37556
- **Abdel-Hamid IA, Andersson K-E, Waldinger MD, Anis TH. (2015)**. Tramadol abuse and sexual function. Sex Med Rev, 4(3): 235-246.
- **Abdel-Moneim WM, Fawzy M, Mohammed SA, Abdellah NZ. (2022)**. Association between male sex hormones and tramadol abuse. Middle East Curr Psychiatry, 2932.
- **Abdel Naem M M., Mohammed T. Sidik, Maha A. Hassan, Saad A. Abd El-Maseeh, Taha SMR. (2020)**. The effect of tramadol abuse on the quality of sexual life. Egypt J Psychiatr, 41134-140.
- **Abdelazim S, Abolmagd S, Abdalla H, Enaba D, Elsheikh S, Moselhy H. (2015)**. Sexual dysfunction and sex hormone levels in Egyptian opioid-dependent males. Am J Pharm Health Res, 381-91.
- **Ahmed AI, El-Dawy K, Fawzy MM, Abdallah HA, Elsaid HNA, Elmesslamy WO. (2018)**. Retrospective review of tramadol abuse. Slov Vet Res 55471-483.
- **Alghobary M, El-Bayoumy Y, Mostafa Y, Mahmoud E-HM, Amr M. (2010)**. Evaluation of tramadol on demand vs. daily paroxetine as a long-term treatment of lifelong premature ejaculation. J Sex Med, 7(8): 2860-2867.
- **Angulo J, El Assar M, Martínez-Salamanca J, La Fuente J, Fernández A, Sánchez-Ferrer A, et al. (2018)**. 213 Nrf2 activation improves both hyperpolarization-and

NO-mediated responses in penile vasculature from patients with erectile dysfunction. J Sex Med, 15S205-S206.

- **Ashry S, Mohammed S, El Nahas K, Wahdan M, Zaaqoq A. (2024)**. The possible effects of chronic use of tramadol and nicotine on male fertility. Zagazig J Forensic Med, 22(1): 1-18.
- **Attia AM, Sarhan NI, Bakry OA, Yassin HA, Gamal NA. (2021)**. Effect of tramadol on the male reproductive system and sexual health. Menoufia Med J, 341-8.
- **Azmy SM, Abd El-Fattah MA, Abd El-Rahman SS, Nada SA, Abdel Salam OME, El-Yamany MF, Nassar NN (2018)**. Does nicotine impact tramadol abuse? Insights from neurochemical and neurobehavioral changes in mice. Neuro Toxicology, 67:245–258.
- **Bassiony MM, Youssef UM, El-Gohary H, Abdelghani M, Hassan MS, Salah El-Deen G. (2019)**. Sexual dysfunction among male patients with tramadol abuse: a case-control study. Int J Sex Health, 31(1): 109-114.
- **Boun S, Omonaiye O, Yaya S. (2024)**. Prevalence and health consequences of nonmedical use of tramadol in Africa: A systematic scoping review. PLOS glob public health, 4(1): 1-20.
- **Coluzzi F, Billeci D, Maggi M, Corona G. (2018)**. Testosterone deficiency in non-cancer opioid-treated patients. J Endocrinol Investig, 411377-1388.
- **De Vries F, Bruin M, Lobatto DJ, Dekkers OM, Schoones JW, van Furth WR, et al. (2020)**. Opioids and their endocrine effects: a systematic review and meta-analysis. J Clin Endocrinol Metab, 105(4): 1020-1029.
- **Dowell D RK, Jones CM, Baldwin GT and Chou R. (2022)**. CDC clinical practice guideline for prescribing opioids for pain—United States, 2022. Recomm Rep, 71(3): 1-91.
- **Fountas A, Chai ST, Kourkouti C, Karavitaki N. (2018)**. Mechanisms of endocrinology: endocrinology of opioids. Eur. J. Endocrinol, 179(4): R183-R196.
- **Gudin JA, Laitman A, Nalamachu S. (2015)**. Opioid related endocrinopathy. Pain Med, 16S9-S15.
- **Hassan MA, Sidik MT, Abdel Naem MM, El-Maseeh A, Saad SA. (2019)**. Sexual dysfunctions among male patients with tramadol abuse. Minia J Med Res, 30(3): 73-79.
- **Kabbash A, El Kelany R, Oreby M, El Gameel D. (2019)**. Effect of tramadol dependence on male sexual dysfunction. Interdiscip Toxicol, 12(4): 157-162.
- **Kurkar A, Reda A, Shalaby MM, Abdelhafez M, Osman M, Abulsorour S. (2024)**. 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. Arab J Urol, 22(2): 89-95.
- **Mohamed NR, El Hamrawy LG, Shalaby AS, El Bahy MS, Abd Allah MM. (2015)**. An epidemiological study of tramadol HCl dependence in an outpatient addiction clinic at Heliopolis Psychiatric Hospital. Menoufia Med J, 28(2): 591-596.
- **Mostafa T, and Alghobary M. (2023)**. Substance abuse and male sexual dysfunction: what lies beneath? Sex Med Rev, 11(4): 395-411.
- **Ram A, Chiranjeevi N, Sreenivasulu B, Surisetty S. (2024)**. A comparative study between tapentadol and tramadol to alleviate postoperative pain in single-level lumbar laminectomy cases done under general anaesthesia. Int J Acad Med Pharm, 6(1): 2020-2029.
- **Rink L, Adams A, Braun C, Bschor T, Kuhr K, Baethge C. (2022)**. Dose-response relationship in selective serotonin and norepinephrine reuptake inhibitors in the treatment of major

depressive disorder: a meta-analysis and network meta-analysis of randomized controlled trials. Psychother Psychosom, 91(2): 84-93.

- **Soliman T, Shaher H, Mohey A, El-Shaer W, Sebaey A. (2022)**. Gonadotoxic effect of tramadol administration: a prospective controlled study. Arab J Urol, 20(1): 54-60.
- **Shalaby AS, Sweilum OA, Ads MK (2015)**. Does tramadol increase severity of nicotine dependence? A study in an Egyptian sample. J Psychactive Drugs, 00:1–6.
- **Subedi M, Bajaj S, Kumar MS, Mayur Y. (2019)**. An overview of tramadol and its usage in pain management and future perspective. Biomed Pharmacother, 111443-451.
- **Tolba AO, Selem MAEH, Ragab MM, Mubarak AAER, Badawy AAEK. (2021)**. Assessment of Sexual Functions among Male with Substance Use Disorders. J Adv Med Med Res, 33(17): 64-74.
- **Zafarghandi MBS, Nik MM, Birashk B, Assari A, Khanehkeshi A. (2016)**. Sexual dysfunction among males with opiate dependence undergoing methadone maintenance therapy (MMT). Int J High Risk Behav Addict, 5(4): e37740.