



Original Article

The Possible Effects of Chronic Use of Tramadol and Nicotine on Male Fertility

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ABSTRACT

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Background: Tramadol abuse and tobacco smoking are global public health issues. Both are recognized for their deleterious effects on various aspects of health, including fertility. **Aim:** The present study aims to evaluate the combined effects of tramadol and nicotine on male fertility in humans and to compare this to the effects of nicotine. **Methods:** This prospective case-control study was conducted through collecting demographic, clinical data, blood and semen samples from patients attending the poison control center and andrology clinic - Ain Shams University Hospitals.

Participants were divided into three groups each comprising 20 males, where group 1 comprised patients with combined tramadol intake and smoking, group 2 comprised patients with smoking and group 3 comprised healthy males of matching age who do not smoke or abuse tramadol. Semen analysis as well as testosterone serum level were measured for each participant. **Results:** There was a high statistically significant decrease in serum testosterone level and all semen parameters in the smoking group and combined smoking and tramadol group when compared to controls. Aging and increased duration of smoking and tramadol abuse correlated negatively with most laboratory investigations in all groups. **Conclusions:** The findings of the current study highlight the detrimental effects of both tramadol abuse and nicotine smoking on semen parameters and testosterone serum level. The negative effects on male fertility are more profound with aging and longer duration of use of both substances. The study concluded that they exert synergistic effects that intensify harm to male fertility when used together compared to the effects of smoking alone. The study recommends educating patients,

particularly those of reproductive age, about the potential risks of smoking and tramadol abuse and their potential impacts on fertility.

Keywords: Combined use of tramadol and nicotine; Smoking; Male fertility; Testosterone; Semen analysis

I. INTRODUCTION:

Substance abuse is one of the common health problems in nearly every country around the world. According to the UN World Drug Report 2022, around 5.6% of people aged 15-64 worldwide used drugs in 2020, with young people under 35 years representing the majority in Africa and Latin America. Of those, opioid users for non-pharmaceutical purposes account for 61.3 million people worldwide (UNODC, 2022).

Tramadol is a centrally acting analgesic belonging to the opioid family. Its analgesic potency is claimed to be one tenth that of morphine. It is widely used to treat acute and chronic moderate to severe pain. It is also popular for its use to treat premature ejaculation and increase sexual pleasure. Although tramadol is considered as a medicinal drug with a low abuse potential compared to morphine, yet there is growing evidence of abuse of tramadol. This was reported by several Asian and African countries including Egypt. In Egypt, abuse of tramadol has become a serious problem with an increasing popularity among adolescents, that's why Egyptian authorities

have up-scheduled tramadol in 2009 (WHO, 2014; Bassiony et al., 2015; Abdel-Hamid et al., 2016).

Tobacco smoking is one of the most common habits in today's societies, with its maximum prevalence observed in young males. Nicotine (the addictive constituent) is distilled from tobacco during smoke inhalation and is carried to the lungs then to the blood stream. Tobacco smoking is a widely recognized health hazard, with numerous studies documenting its detrimental effects on various physiological systems. Nicotine chronic use is known to cause cardiac and respiratory diseases in addition to increased susceptibility to different types of cancer with the effects increasingly seen among males less than 35 years of age in low- and middle-income countries (Jha & Peto, 2014; Lingappa et al., 2015).

Fertility problems affect nearly 15% of couples with the male factor comprising 3%, with the percentage increasing in recent years (Jungwirth et al., 2012). Research studies on the effect of tramadol on male fertility in humans are scarce, and most

studies were done on experimental animals. Some of these studies revealed its effect on semen parameters showing decreased sperm count, concentration and motility (Azari et al., 2014), while others proved it to cause significant decrease in plasma levels of leutinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone (Ahmed & Kurkar, 2014).

On the other hand, there are numerous studies conducted on humans to evaluate the effects of nicotine smoking on male fertility. These studies reported a negative impact of nicotine smoking on all semen analysis parameters in addition to inducing oxidative stress, leading to DNA damage in spermatozoa, thus adding to the impairment of fertility (Hamad et al., 2014; Harlev et al., 2015; Cui et al., 2016).

Various research studies explored the effects of tramadol intake and tobacco smoking on men's reproductive health independently. Accordingly this study was designed to evaluate the combined effects of tramadol and nicotine on male fertility in humans and to compare this to the effects of nicotine, aiming to contribute to the understanding and the effective advice on male reproductive health issues among those patients.

II. PATIENTS & METHODS:

Study Design: Prospective case control study

Study population: Patients attending the andrology clinic - Ain Shams University Hospitals for premarital checkup or fertility consultation during the period from October 2022 till April 2023 and fitting the inclusion criteria till obtaining the designated patients' number according to sample size calculation.

- Inclusion Criteria: Male patients aged 20-40 years, with positive history of chronic tobacco smoking (20 cigarettes/day for at least 6 months), or combined chronic tobacco and tramadol abuse (20 cigarettes/day + 500 mg tramadol/day for at least 6 months).
 - Exclusion Criteria: The presence of azoospermia or severe oligozoospermia, leucocytospermia, frank pyospermia, haemospermia, evident varicocele, congenital anomalies (eg: undescended testis), urinary tract infection, chronic diseases (renal, hepatic, diabetes), history of inguinal operations and history of sexually transmitted diseases.
- * Patients with tramadol abuse were originally treated in the poison control center, Ain Shams University Hospitals for tramadol overdose. Through history taking

they were found to be chronic tramadol users and chronic smokers, hence they were enrolled in the study after taking their consent, and sent to the andrology clinic for fertility consultation.

Sample Size: After reviewing previous study results (Farag et al., 2018) showing that the mean of sperm vitality (%) in patients with smoking and tramadol addiction was lower than healthy controls (47.0 + 29.0 versus 93.9 + 6.8 respectively); a sample size of at least **20 patients** with smoking and tramadol addiction and **20 healthy controls** will achieve 100% power, at alpha error 0.05, by using Power Analysis and Sample Size Software (PASS 15) (Version 15.0.10) for sample size calculation, with considering 20% dropout rate.

Study groups:

A- Patient groups: These were divided into two groups:

- Group (1): Patients with chronic tramadol abuse and chronic smoking (20 patients).
- Group (2): Patients with chronic smoking (20 patients).

B- Control group:

- Group (3): Healthy males of matching age who do not smoke or use tramadol (20 participants).

Data Collection tools:

- Data extraction sheet was used to import the required data from medical records. The data included patient demographics, medical history and local examination.
- Semen analysis:
 - Semen samples were collected in wide-mouthed sterile container by masturbation after 3-5 days of sexual abstinence.
 - Samples were kept at 37°C and examined after complete liquefaction for sperms number, concentration, motility, vitality and morphology.
 - Samples were examined by conventional methods (200x to 400x magnification light microscopy) and reference values of WHO laboratory manual for the examination and processing of human semen guidelines were used (**WHO, 2010**).
- Urine screening for tramadol:
 - Urine samples were collected in clean plastic containers. Samples were analyzed for the presence of tramadol by enzyme immunoassay.
- Total testosterone serum level:
 - A plastic disposable syringe was used to draw venous blood samples from each patient and each control subject under aseptic procedures.

- Blood was transferred to a clean dry centrifuge tube and left for 30 minutes to clot then centrifuged for 10 minutes at 4000 rpm.
- The serum was separated and kept at -20°C until runtime.
- Analysis of testosterone was done by enzyme immunoassay test kits according to manufacturer's recommendation.

Outcome Measures:

Male fertility was assessed in terms of total testosterone level (ng/dl) and semen parameters which included volume (ml), total sperm number (million/ejaculate), sperm concentration (million/ml), total motility (%), progressive motility (%), vitality (live spermatozoa, %), and sperm morphology (normal forms, %).

Data management and Statistical analysis:

Statistical analysis of the data was performed using SPSS, version 20 (SPSS Inc., Chicago, IL). Mean and standard deviation were used to describe quantitative data. Qualitative data were expressed by Frequency (n) and percentage (%). Chi square test was used to test the association between 2 qualitative variables. ANOVA test and Bonferroni test (as post hoc test) were used to compare quantitative variables between the three studied groups. Pearson

correlation coefficient test was used to assess the correlation between quantitative variables, where ($r = 0.0$ to 0.2 is considered negligible, $0.2 - 0.4$ is considered weak, $0.4 - 0.6$ is considered moderate, $0.6 - 0.8$ is considered strong, $0.8 - 0.99$ is considered very strong, and 1.0 is considered perfect). P-value ≤ 0.05 is considered statistically significant.

Ethical Considerations: The study was approved by the research ethics committee (REC) of Ain Shams University's Faculty of Medicine (Approval number: FMASU R192/2023). The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki (**WMA, 2013**). Informed consent was obtained after the provision of study-related information to each participant, including the study's purpose and any potential risks and benefits. Confidentiality of data was preserved.

III. RESULTS:

In terms of demographic data distribution, there was no statistically significant difference in marital status or age across the studied groups. There was also no statistically significant difference in smoking duration between patients who abuse tramadol alongside with a smoking habit and those who smoke without abuse of tramadol as stated in **Table 1**.

Table 1. Distribution of the patients' demographic data, and laboratory investigation results across the three groups under study.

	Group (1) Tramadol and Smoking (Number=20)	Group (2) Smoking (Number=20)	Group (3) Control (Number=20)	P value	P (1 & 2)	P (1 & 3)	P (2 & 3)
	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)				
Married #	13 (65.0%)	15 (75.0%)	13 (65.0%)	.735			
Age (Years)	32.2 ± 4.5 (24 - 39)	31.2 ± 5.4 (22 - 39)	31.3 ± 4.5 (22 - 38)	.789	1.000	1.000	1.000
Duration of smoking (Years)	9.6 ± 2.9 (6 - 15)	8.6 ± 2.2 (6 - 13)	--	.274	.274	--	--
Duration of tramadol intake (Years)	4.4 ± 1.2 (3 - 7)	--	--	--	--	--	--
Testosterone serum level (ng/dL)	2.1 ± 0.1 (1.8 - 2.2)	4.3 ± 0.1 (4.1 - 4.4)	4.7 ± 0.1 (4.4 - 4.9)	.000*	.000*	.000*	.000*
Semen Volume (ml)	2.5 ± 0.5 (1.6 - 3.2)	2.6 ± 0.5 (1.8 - 3.5)	3.2 ± 0.6 (2.1 - 4.2)	.000*	1.000	.001*	.004*
Total sperm number (million/ejaculate)	84.4 ± 37.4 (18 - 120)	101.9 ± 34.2 (30 - 140)	321.2 ± 90.3 (140 - 446)	.000*	1.000	.000*	.000*
Sperm Concentration (million/ml)	32.4 ± 12.2 (10 - 53.5)	38.7 ± 10.9 (16.5 - 54.5)	100.5 ± 17.6 (64 - 131.8)	.000*	.474	.000*	.000*
Total motility (%)	30.2 ± 2.9 (25.3 - 35.8)	36.6 ± 2.8 (32.7 - 42.5)	50.3 ± 1.8 (47.2 - 54.3)	.000*	.000*	.000*	.000*
Progressive motility (%)	24.1 ± 2.5 (20.2 - 28.9)	29.2 ± 2.2 (26 - 34)	40 ± 1.5 (37.5 - 43.4)	.000*	.000*	.000*	.000*
Vitality (%)	46.7 ± 6.7 (38 - 59)	55.7 ± 4 (48 - 61)	78.8 ± 5.6 (69 - 90)	.000*	.000*	.000*	.000*
Normal sperm morphology (%)	2.4 ± 0.4 (1.8 - 3)	4.7 ± 0.2 (4.4 - 5.1)	6.1 ± 1 (5.1 - 8.2)	.000*	.000*	.000*	.000*

ANOVA test and Bonferroni as post hoc test were used for all except for (#) where chi square test was used. (SD) Standard deviation, (Min) Minimum, and (Max) Maximum. (*) P-value ≤ 0.05 is considered statistically significant.

The results of laboratory investigations

showed that there was statistically significant difference in all investigations between the studied patient groups (smokers group and combined smoking and tramadol group) with the control group having a higher testosterone serum level in smoking patients and patients who smoke and abuse

tramadol. Similar to the hormone level, patients who smoke (group 2) had higher values of semen parameters than patients who smoke and abuse tramadol (group 1). In addition, patients who smoke (group 2) were higher in testosterone serum level than patients who smoke and abuse tramadol (group 1). Controls (group 3) showed

higher values of semen parameters than smoking patients and patients who smoke and abuse tramadol as shown in (Table 1).

Regarding factors influencing male fertility in tramadol and smoking patients (group 1), age had a significant negative moderate to strong correlation with testosterone serum levels, sperm volume, total sperm number, and sperm concentration. The duration of

smoking revealed a significant negative moderate to strong correlation with all fertility laboratory investigations. While tramadol abuse duration revealed a significant negative moderate correlation with testosterone serum levels, total sperm quantity and sperm concentration as demonstrated in (Table 2).

Table 2. Correlation between patients' laboratory investigation results for assessing fertility and age and duration of use in group (1) tramadol and smoking group.

Group (1): Tramadol and Smoking group (Number = 20)				
		Age (Years)	Duration of smoking (Years)	Duration of tramadol intake (Years)
Testosterone serum level (ng/dL)	Pearson Correlation	-.476	-.764	-.628
	P-value	.034*	.000*	.003*
Semen Volume (ml)	Pearson Correlation	-.701	-.708	-.399
	P-value	.001*	.000*	.082
Total sperm number (million/ejaculate)	Pearson Correlation	-.590	-.837	-.512
	P-value	.006*	.000*	.021*
Sperm Concentration (million/ml)	Pearson Correlation	-.467	-.787	-.495
	P-value	.038*	.000*	.026*
Total motility (%)	Pearson Correlation	-.283	-.701	-.422
	P-value	.227	.001*	.064
Progressive motility (%)	Pearson Correlation	-.340	-.733	-.429
	P-value	.143	.000*	.059
Vitality (%)	Pearson Correlation	-.212	-.717	-.438
	P-value	.370	.000*	.054
Normal sperm morphology (%)	Pearson Correlation	-.305	-.724	-.375
	P-value	.191	.000*	.103

(*) P-value ≤ 0.05 is considered statistically significant.

In relation to factors influencing male fertility in smokers, age revealed a significant negative moderate to strong correlation with sperm volume, total sperm number, and concentration. The duration of

smoking demonstrated a significant negative moderate to strong correlation with semen volume, total sperm number, sperm concentration, total motility, and progressive motility as seen in (Table 3).

Table 3. Correlation between patients' laboratory investigation results for assessing fertility and age and duration of smoking in group (2) smoking group.

Group (1): Smoking group (Number = 20)			
		Age (Years)	Duration of smoking (years)
Testosterone serum level (ng/dL)	Pearson Correlation	-.264	-.342
	P-value	.262	.141
Semen Volume (ml)	Pearson Correlation	-.516	-.528
	P-value	.020*	.017*
Total sperm number (million/ejaculate)	Pearson Correlation	-.659	-.769
	P-value	.002*	.000*
Sperm Concentration (million/ml)	Pearson Correlation	-.559	-.689
	P-value	.010*	.001*
Total motility (%)	Pearson Correlation	-.273	-.490
	P-value	.244	.028*
Progressive motility (%)	Pearson Correlation	-.277	-.493
	P-value	.237	.027*
Vitality (%)	Pearson Correlation	-.204	-.410
	P-value	.389	.073
Normal sperm morphology (%)	Pearson Correlation	.055	-.372
	P-value	.819	.106

(*) P-value ≤ 0.05 is considered statistically significant.

Regarding the factors affecting male fertility in the control group (group 3), age showed a significant negative moderate to strong

correlation with testosterone serum levels, sperm volume, total sperm number, and sperm concentration (Table 4).

Table 4. Correlation between patients' laboratory investigation results for assessing fertility and age in group (3) control group.

Group (3): Control group (Number = 20)		
		Age (Years)
Testosterone serum level (ng/dL)	Pearson Correlation	-.451
	P-value	.046*
Semen Volume (ml)	Pearson Correlation	-.747
	P-value	.000*
Total sperm number (million/ejaculate)	Pearson Correlation	-.794
	P-value	.000*
Sperm Concentration (million/ml)	Pearson Correlation	-.563
	P-value	.010*
Total motility (%)	Pearson Correlation	-.184
	P-value	.437
Progressive motility (%)	Pearson Correlation	-.246
	P-value	.296
Vitality (%)	Pearson Correlation	-.407
	P-value	.075
Sperm morphology (%)	Pearson Correlation	-.178
	P-value	.452

(*) P-value ≤ 0.05 is considered statistically significant.

IV. DISCUSSION:

Tramadol abuse and smoking are global public health issues. Both are recognized for their deleterious effects on various aspects of health, including fertility (UNODC, 2020). Studies investigating the prevalence of both substances in Egypt recorded that tramadol is the most common abused drug and that tobacco smoking is seen in 22% of the population in 2010 and is increasing (Fouda et al., 2018; AbdelMoneim et al, 2020). Research suggests that tramadol misuse significantly impacts male reproductive health. Evidence points to a decrease in semen parameters and testosterone levels among habitual tramadol

users (Elghait et al., 2022). Similarly, smoking is reported to lead to a reduction in semen quality (Tang et al., 2019).

Given that both habits individually impact reproductive health, their combined use may potentially exacerbate these effects. This study presents a comparative analysis of the effects of chronic smoking, combined smoking and tramadol abuse on semen parameters and testosterone levels compared to healthy males who are non-smokers and non-users of tramadol. The study was conducted on patients attending the poison control center and andrology clinic - Ain Shams University Hospitals. Patients

attended the andrology clinic for premarital checkup or fertility consultation. Patients treated from acute tramadol toxicity in the poison control center were advised to be checked for the effects of tramadol on fertility in the andrology clinic. Participants were divided into three groups where group 1 comprised patients with combined chronic tramadol intake and chronic smoking, group 2 comprised patients with chronic smoking and group 3 comprised healthy males of matching age who do not smoke or abuse tramadol.

In the current study there was no statistically significant difference between the three groups regarding mean age or marital status. However, a slightly higher duration of smoking was seen in group 1 when compared to group 2 (9.6 years and 8.6 years respectively) but this difference was not statistically significant.

On the other hand, a highly significant decrease in testosterone serum level was observed in both patient groups (groups 1&2) when compared to the control group (group 3) as well as a statistically significant low testosterone serum level in group 1 when compared to group 2. This aligns with previous researches which suggested that tramadol exerts its effects through the central suppression of the hypothalamic-

pituitary-gonadal axis, which is critical in maintaining normal testosterone levels and sperm production (Osadolor & Omo-Erabor, 2016). Tramadol was also reported to cause oxidative stress leading to an increase in secondary toxic compounds that exert a negative effect on testosterone level by decreasing the antioxidant capacity (Hindawy et al., 2019). In addition, smoking was reported to lead to hormonal imbalances that might lead to reduced testosterone levels (Harlev et al., 2015).

Regarding the analysis of semen parameters in the three groups, there was a highly significant decrease in all parameters in both patient groups when compared to the control group ($p \leq 0.01$). Whereas, no statistical difference was recorded between the two patient groups regarding semen volume, sperm number or concentration. Contrarily, there was a highly significant statistical decrease in total motility, progressive motility, vitality, and normal sperm morphology in group 1 when compared to group 2.

Ahmed and Kurkar, (2014) and Koohsari et al., (2020) reported that tramadol affects testicular functions through overproduction of nitric oxide and oxidative stress which leads to apoptosis in the spermatocytes. Meri et al., (2013) reported that smoking

causes increased concentration of reactive oxygen species (ROS) leading to a decrease in sperm quality. Caserta et al., (2013) and Hamad et al., (2014) concluded that smoking can induce oxidative stress, leading to DNA damage in spermatozoa, further impairing fertility.

The results of the current study shows that there is a significant reduction in semen quality and testosterone levels in the smokers who abuse tramadol compared to healthy males not using both substances. Similar but less pronounced deterioration is seen in the smoking-only group when compared to healthy non-smoking males.

Similar results suggesting that smoking may lead to a reduction in semen quality were recorded by other studies. Lotti et al., (2015) suggested that chronic nicotine exposure negatively affects seminal vesicles secretion and contraction yielding less volume per ejaculate. In addition, Sharma et al., 2016 and Rehman et al., 2019 reported that smoking affects sperm count, motility, and morphology, all of which are crucial indicators of male fertility.

The peak of male fertility is seen in their early thirties then semen parameters start to decline after the age of 35 years (Stone et al., 2013). Age also affects male hormones. Leydig cells, the ones responsible for

testosterone production decrease in number with increasing age. In addition, Hypothalamic-Pituitary-Testicular axis alterations occur with ageing leading to disturbance in the functions of various reproductive hormones as well as testicular atrophy (Sharma et al., 2015).

The effect of age was also investigated in the current study. In the combined smoking and tramadol group, a significant negative correlation was observed between the increase in age and testosterone serum levels, semen volume, total sperm number, and sperm concentration. Similar findings were observed in the control group. This implies that as age increases in these groups, these fertility parameters decrease. Interestingly, in the smokers group a significant negative correlation was observed with semen volume, total sperm number, and sperm concentration but not with testosterone serum levels which remained relatively stable with increase in age. Wang et al., (2013) reported that smokers had a significantly higher total testosterone serum level than non-smokers. They attributed this to the ability of nicotine to stimulate the release of gonadotropin-releasing hormone and luteinizing hormone. Moreover, their study suggested that smoking can increase testosterone levels by reducing

the conversion of testosterone to estradiol. In addition, a meta-analysis performed by Zhao et al, (2016) concluded the same finding of an increase in the level of testosterone in smokers when compared to non-smokers. This explains the findings in our study where only the smokers group showed stable levels of testosterone with progressing age.

No significant correlation was observed between age and total motility, progressive motility, vitality, and normal sperm morphology in the three groups despite their decrease with aging but the differences were not statistically significant. This underscores the complex nature of fertility and the multiple factors that influence it.

The analysis of chronic smokers revealed a clear trend of deteriorating semen parameters with increasing years of smoking. Semen volume, total sperm number, sperm concentration, and vitality decrease with increasing smoking duration, suggesting that prolonged exposure to smoking contributes to impairment of spermatogenesis and reduced fertility potential. This is in line with previous studies showing that prolonged smoking can lead to impairment in sperm count and function decreasing the overall fertility

potential (Bundhun et al., 2019; Omolaoye et al., 2022).

Regarding the combined smoking and tramadol abuse group, the data of the current study suggests even more pronounced harmful effects on semen parameters compared to the smoking-only group. The longer the duration of exposure to both substances, the greater the deterioration of semen parameters as well as testosterone serum level. All semen parameters decreased with the increase in the duration of use of both substances. Tramadol prolonged intake has been shown in several studies to negatively affect semen parameters and testosterone levels (Azari et al., 2014; Salah et al., 2019; Soliman et al., 2021). In combination with smoking, they both exert synergistic effects that intensify harm to male fertility (Shalaby et al., 2015). When comparing the group of chronic smokers and the group that combined smoking with tramadol use, the detrimental effect on semen parameters and testosterone levels were found to be more pronounced in the group combining smoking with tramadol use. This finding suggests a potential synergistic impact of smoking and tramadol abuse on male reproductive health, which aligns with other studies reporting an increase in accumulation of tramadol in the

body and decrease in its clearance when it is used with tobacco smoking (Farag et al., 2018).

In general, the results of the current study suggest that increased age, prolonged smoking, and prolonged tramadol abuse are associated with detrimental effects on several key fertility parameters in males. In addition, the control group of healthy individuals shows better semen parameters and serum testosterone level, emphasizing the detrimental effects of smoking and tramadol abuse on male fertility.

The current study has some limitations. The sample size is relatively small, and we did not consider other potential influential factors like diet, lifestyle, or underlying health conditions. Further research with larger samples and more control for potential confounders is needed to confirm these findings.

V. CONCLUSION & RECOMMENDATIONS:

The findings of the current study highlight the detrimental effects of both tramadol abuse and nicotine smoking on semen parameters and testosterone serum level. The negative effects on male fertility are more profound with aging and longer duration of use of both substances. The study concluded that they exert synergistic

effects that intensify harm to male fertility when used together compared to the effects of smoking alone. The outcomes of this study underscore the importance of educating patients, particularly those of reproductive age, about the potential risks of smoking and tramadol abuse and their potential impacts on fertility. The study underlines the need for public health awareness and interventions aimed at combating the misuse of these substances given their considerable implications on male fertility and overall health.

VI. REFERENCES:

- AbdelMoneim WM, Abdellah NZ, Fawzy M, Mohammed SA. (2020): Assessment of Addicted Cases Admitted to Addiction Management Unit of Neurology and Psychiatry Hospital at Assiut University. *Zagazig J. Forensic Med. & Toxicology*. 18(1): 108-125.
- Abdel-Hamid IA, Andersson KE, Waldinger MD, Anis TH. (2016): Tramadol Abuse and Sexual Function. *Sexual Medicine Reviews*. 4:235-246.
- Ahmed MA, Kurkar A. (2014): Effects of Opioid (Tramadol) Treatment on Testicular Functions in Adult Male Rats: The Role of Nitric Oxide and Oxidative Stress. *Clin Exp Pharmacol Physiol*. 41:317-23.

- Azari O, Emadi L, Kheirandish R, Shafiei Bafti H, Esmaili Nejad MR, Faroghi F. (2014): The Effects of Long-term Administration of Tramadol on Epididymal Sperm Quality and Testicular Tissue in Mice. *Iranian Journal of Veterinary Surgery*. 9:23-30.
- Bassiony MM, Salah El-Deen GM, Yousef U, Raya Y, Abdel-Ghani MM, El-Gohari H, Atwa SA. (2015): Adolescent tramadol use and abuse in Egypt, *The American Journal of Drug and Alcohol Abuse*, 41:3, 206-211, DOI: 10.3109/00952990.2015.1014959
- Bundhun PK, Janoo G, Bhurtu A, Teeluck AR, Soogund MZS, Pursun M, Huang F. (2019): Tobacco smoking and semen quality in infertile males: a systematic review and meta-analysis. *BMC Public Health*. 19(1):36. doi: 10.1186/s12889-018-6319-3.
- Caserta D, Bordi G, Di Segni N, D'Ambrosio A, Mallozzi M, Moscarini M. (2013): The influence of cigarette smoking on a population of infertile men and women. *Arch Gynecol Obstet*. 287(4):813-8. doi: 10.1007/s00404-012-2643-5.
- Cui X, Jing X, Wu X, Wang Z, Li Q. (2016): Potential effect of smoking on semen quality through DNA damage and the downregulation of Chk1 in sperm. *Mol Med Rep*. 14(1):753-61. doi: 10.3892/mmr.2016.5318.
- Elghait ATA, Mostafa TM, Gameaa FK, Mohammed GK, Meligy FY, Sayed MM. (2022): Comparative Histological Study on the Effect of Tramadol Abuse on the Testis of Juvenile and Adult Male Albino Mice. *Anat Cell Biol*. 55(3):341-355. doi: 10.5115/acb.22.013.
- Farag AGA, Basha MA, Amin SA, Elnaidany NF, Elhelbawy NG, Mostafa MMT, Khodier SA, Ibrahem RA, Mahfouz RZ. (2018): Tramadol (opioid) abuse is associated with a dose- and time-dependent poor sperm quality and hyperprolactinaemia in young men. *Andrologia*. 50(6):e13026. doi: 10.1111/and.13026.
- Fouda S, Kelany M, Moustafa N, Abushouk AI, Hassane A, Sleem A, Mokhtar O, Negida A, Bassiony M. (2018): Tobacco smoking in Egypt: a scoping literature review of its epidemiology and control measures. *Eastern Mediterranean Health Journal* 24(2): 198-215.

- Hamad MF, Shelko N, Kartarius S, Montenarh M, Hammadeh ME. (2014): Impact of cigarette smoking on histone (H2B) to protamine ratio in human spermatozoa and its relation to sperm parameters. *Andrology*. 2(5):666-77. doi: 10.1111/j.2047-2927.2014.00245.x.
- Harlev A, Agarwal A, Gunes SO, Shetty A, du Plessis SS. (2015): Smoking and Male Infertility: An Evidence-Based Review. *World J Mens Health*. 33(3):143-60. doi: 10.5534/wjmh.2015.33.3.143.
- Hindawy RF, Ali NEM, Hendawy FF. (2019): Ameliorative Effect Of Aloe Vera Gel On Tramadol Reproductive Toxicity In Adult Albino Rats. *Zagazig J. Forensic Med. & Toxicology*. 17(2): 71-83.
- Jha P, Peto R. (2014): Global Effects of Smoking, of Quitting, and of Taxing Tobacco. *N Engl J Med* 370:60-68. DOI: 10.1056/NEJMra1308383
- Jungwirth A, Giwercman A, Tournaye H, Diemer T, Kopa Z, Dohle G, Krausz C. (2012): European Association of Urology Working Group on Male: the 2012 update. *Eur Urol*. 62:324-32.
- Koohsari M, Ahangar N, Mohammadi E, Shaki F. (2020): Ameliorative Effect of Melatonin Against Reproductive Toxicity of Tramadol in Rats via the Regulation of Oxidative Stress, Mitochondrial Dysfunction, and Apoptosis-related Gene Expression Signaling Pathway. *Addict Health*. 12(2):118-129. doi: 10.22122/ahj.v12i2.265.
- Lingappa HA, Govindashetty AM, Puttaveerachary AK, Manchaiah S, Krishnamurthy A, Bashir S, Doodaiah N. (2015): Evaluation of Effect of Cigarette Smoking on Vital Seminal Parameters which Influence Fertility. *J Clin Diagn Res*. 9:EC13-5.
- Lotti F, Corona G, Vitale P, Maseroli E, Rossi M, Fino M, Maggi M. (2015): Current smoking is associated with lower seminal vesicles and ejaculate volume, despite higher testosterone levels, in male subjects of infertile couples. *Human Reproduction*. 30 (3): 590-602.
- Meri ZB, Irshid IB, Migdadi M, Irshid AB, Mhanna SA. (2013): Does cigarette smoking affect seminal fluid parameters? A comparative study. *Oman Med J*. 28(1):12-5. doi: 10.5001/omj.2013.03.
- Omolaoye TS, El Shahawy O, Skosana BT, Boillat T, Loney T, du Plessis SS. (2022): The mutagenic effect of tobacco

- smoke on male fertility. *Environ Sci Pollut Res Int.* 29(41):62055-62066. doi: 10.1007/s11356-021-16331-x.
- Osadolor, H., & Omo-Erhabor, J. (2016): Effects of tramadol on fertility hormones (follicle stimulating hormone, luteinizing hormone, prolactin, testosterone, estrogen and β -HCG) in laboratory rabbits. *British Journal of Medicine & Medical Research*, 14, 1–11.
 - Rehman R, Zahid N, Amjad S, Baig M, Gazzaz ZJ. (2019): Relationship Between Smoking Habit and Sperm Parameters Among Patients Attending an Infertility Clinic. *Front Physiol.* 10:1356. doi: 10.3389/fphys.2019.01356.
 - Salah S, Wagih M, Zaki A, Fathy W, Eid A. (2019): Long-term effects of tramadol on the reproductive function of male albino rats: an experimental biochemical and histopathological study. *Middle East Fertility Society Journal.* 24:3. <https://doi.org/10.1186/s43043-019-0003-0>
 - Shalaby AS, El-Hady Sweilum OA, Ads MK. (2015): Does Tramadol Increase the Severity of Nicotine Dependence? A Study in an Egyptian Sample. *J Psychoactive Drugs.* 47(3):197-202. doi: 10.1080/02791072.2015.1050534.
 - Sharma, R., Agarwal, A., Rohra, V.K. Assidi M, Abu-Elmagd M, Turki RF. (2015): Effects of increased paternal age on sperm quality, reproductive outcome and associated epigenetic risks to offspring. *Reprod Biol Endocrinol* 13, 35. <https://doi.org/10.1186/s12958-015-0028-x>
 - Sharma R, Harlev A, Agarwal A, Esteves SC. (2016): Cigarette Smoking and Semen Quality: A New Meta-analysis Examining the Effect of the 2010 World Health Organization Laboratory Methods for the Examination of Human Semen. *Eur Urol.* 70(4):635-645. doi: 10.1016/j.eururo.2016.04.010.
 - Soliman T, Shafer H, Mohey A, El-Shaer W, Sebaey A. (2021): Gonadotoxic effect of tramadol administration: A prospective controlled study. *Arab J Urol.* 20(1):54-60. doi: 10.1080/2090598X.2021.2002634.
 - Stone BA, Alex A, Werlin LB, Marrs RP. (2013): Age thresholds for changes in semen parameters in men. *Fertil Steril.* 100:952–8.
 - Tang Q, Pan F, Wu X, Nichols CE, Wang X, Xia Y, London SJ, Wu W. (2019): Semen quality and cigarette smoking in a cohort of healthy fertile

- men. *Environ Epidemiol.* 3(4):e055. doi: 10.1097/EE9.0000000000000055.
- United Nations Office on Drugs and Crime UNODC: World Drug Report 2022, Vienna, June 2022.
 - United Nations Office on Drugs and Crime UNODC: World Drug Report 2020, Vienna, June 2020.
 - Wang W, Yang X, Liang J, Liao M, Zhang H, Qin X, Mo L, Lv W, Mo Z. (2013): Cigarette smoking has a positive and independent effect on testosterone levels. *Hormones (Athens).* 12(4):567-77. doi: 10.14310/horm.2002.1445.
 - WMA World medical association 18th General Assembly (2013): Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 310: 2191–2194.
 - World Health Organization (WHO): WHO laboratory manual for the examination and processing of human semen. Fourth edition. WHO, Geneva. 2010. p. 224.
 - World Health Organization WHO: Tramadol, Update Review Report, Geneva, 2014.
 - Zhao J, Leung JYY, Lin SL, Schooling CM. (2016): Cigarette smoking and testosterone in men and women: A systematic review and meta-analysis of observational studies. *Preventive Medicine.* 85:1-10. <https://doi.org/10.1016/j.ypmed.2015.12.021>.

الآثار المحتملة للاستخدام المزمن للترامادول والنيكوتين على الخصوبة لدى الرجال

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الملخص العربي

الخلفية: تعاطى الترامادول وتدخين التبغ من قضايا الصحة العامة العالمية. كلاهما معروف بآثاره الضارة على الصحة، بما في ذلك الخصوبة.

الهدف: تهدف الدراسة إلى تقييم التأثير المجمع لتعاطى الترامادول والنيكوتين على خصوبة الرجال ومقارنة ذلك بآثار النيكوتين.

الطريقة: أجريت هذه الدراسة المستقبلية من خلال جمع البيانات الديموغرافية والسرييرية وعينات الدم والسائل المنوي من المرضى الذين يترددون على مركز علاج التسمم وعيادة أمراض الذكورة - مستشفيات جامعة عين شمس. تم تقسيم المشاركين إلى ثلاث مجموعات تضم كل منها 20 ذكراً، حيث تتألف المجموعة الأولى من المرضى المدخنين الذين يتعاطون الترامادول، أما المجموعة الثانية فتتألف من المرضى المدخنين والمجموعة الثالثة تضمنت ذكوراً أصحاء من أعمار مماثلة لا يدخنون أو يتعاطون الترامادول. تم تحليل السائل المنوي وكذلك قياس مستوى التستوستيرون في الدم لكل مشارك.

النتائج: كان هناك انخفاض ذو دلالة إحصائية عالية في مستوى هرمون التستوستيرون في الدم وجميع نتائج تحاليل السائل المنوي في مجموعتي المدخنين وأيضاً المدخنين الذين يتعاطون الترامادول بالمقارنة مع مجموعة المقارنة. ارتبط تقدم السن وزيادة مدة التدخين وتعاطى الترامادول سلباً مع نتائج معظم الفحوصات المعملية في جميع المجموعات.

الخلاصة: تسلط نتائج الدراسة الحالية الضوء على الآثار الضارة لكل من تعاطى الترامادول وتدخين النيكوتين على جودة السائل المنوي ومستوى هرمون التستوستيرون فى الدم. تزداد الآثار السلبية على خصوبة الذكور أكثر مع تقدم السن وطول مدة استخدام كلتا المادتين. وخلصت الدراسة إلى أن استخدام المادتين معاً يحدث تأثيرات تآزرية تزيد من الضرر على خصوبة الرجال مقارنة بآثار التدخين وحده. توصى الدراسة بتوعية المرضى خاصة من هم فى سن الإنجاب عن مخاطر التدخين وتعاطى الترامادول على الخصوبة.