Interdiscip Toxicol. 2019; **Vol. 12**(4): 157–162.
doi: 10.2478/intox-2019-0019

sciendo

interdisciplinary toxicology

ORIGINAL ARTICLE

Effect of tramadol dependence on male sexual dysfunction

Abdelmoty KABBASH, Rabab EL KELANY, Merfat OREBY, Dina EL GAMEEL

Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Tanta University, Tanta, Egypt

ITX120419A01 • Received: 16 June 2017 • Accepted: 17 March 2018

ABSTRACT

Tramadol dependence became an increasing and alarming problem in the Egyptian community. Wide availability of tramadol as a pain killer and its role in the treatment of premature ejaculation may be the most apparent causes of increased magnitude of the problem among youth who believe that tramadol has a positive impact on their sexual functions. This study aimed to explore the real impact of chronic tramadol administration on sexual functions in males dependent on tramadol. The study was carried on 80 subjects (50 subjects were tramadol dependent group and 30 subjects represented the control group). Personal, family and past histories were obtained from all the participants in addition to the toxicological history from tramadol dependent group. Urine screening for tramadol was done for all cases of history of tramadol dependence then confirmation by HPLC technique to measure tramadol blood level was done. Both groups were investigated for serum testosterone and prolactin level. Curiosity (22%) and treatment of premature ejaculation (20%) were the main motives for dependence. Erectile dysfunction and decreased libido occurred in 44% and 48% of tramadol dependent group respectively. Significant increase in erectile dysfunction and decreased libido was noted as the duration of dependence increased. Additionally, significant decrease in serum testosterone level and increase in serum prolactin level as tramadol daily dose and duration increased was found. In conclusion, men who take tramadol for premature ejaculation or any other purpose must know that they are very susceptible to many sexual dysfunctions.

KEY WORDS: tramadol; dependence; sexual dysfunction; testosterone; prolactin

Introduction

Opioids are the most potent and effective analgesics available and they are accepted as appropriate treatment for cancer and non-cancerous pain (Atici *et al.,* 2005). Tramadol is the most widely sold opioid analgesic in the world (Shipton, 2000). It was the second most frequent opioid reported for abuse among physicians (Adams *et al.,* 2006). Tramadol was considered as a controlled substance in some United States of America and Canada and requires a prescription. However, it is readily available by remote prescription including internet pharmacies with relative ease (Solarino *et al.,* 2010).

Tramadol dependence became an increasing and at the same time alarming problem in the Egyptian community. This could be noted through its popularity and massive use especially among Egyptian youth (Shipton, 2000; Eassa & El-Shazly, 2012). Easy and wide availability of tramadol as a pain killer for intermediate pain and many other forms of chronic pains could be basic factors of its wide spread and abuse (Marquardt *et al.* 2005; Tashakori & Afshari, 2010). Additionally, its role in treatment of premature ejaculation could be one of the most apparent causes of increased magnitude of the problem among youth who believe that tramadol has a positive impact on their sexual functions. (Vorsanger *et al.* 2008).

Disorders of sexual interest/desire, erectile dysfunction and ejaculation disorders are the most common sexual dysfunctions detected in men. It could be attributed to different factors – psychological, physical and iatrogenic (Hatzimouratidis, 2007; Kaminetsky, 2008). In 29 countries, 28% of men aged 40–80 years had one or more sexual dysfunctions (Nicolosi *et al.,* 2004). Worldwide, erectile dysfunction is the most prevalent dysfunction whereas limited information are available about other sexual dysfunctions (Hatzimouratidis, 2007).

The aim of this study was to explore the real impact of chronic tramadol administration on sexual functions in males dependent on tramadol.

Correspondence address:
Dr. Merfat Oreby
Department of Forensic Medicine and Clinical Toxicology,
Faculty of Medicine, Tanta University,
Tanta, Egypt
TEL.: 01152047794 • E-MAIL: oreby.a@gmail.com

Subjects and methods

Patients

This study was carried out on 80 male subjects who were divided into 50 patients (tramadol dependent group (TDG) who fulfilled the DSM V criteria of dependence (American Psychiatric Association, 2013) and 30 healthy volunteers (control group). The protocol of this work was approved by the ethical committee of faculty of medicine, Tanta University. A written informed consent was obtained from each participant prior to participation. Subjects coding was done to maintain records confidentiality.

Inclusion criteria

Tramadol dependent group: adult male aged below 40 years dependent on tramadol only, with fulfillment of DSM V criteria of dependence. Control group: apparently healthy adult male of the same age range.

Exclusion criteria

Patients with chronic disease such as diabetes, bronchial asthma, hepatic, renal, cardiovascular diseases, cancer and those under radio or chemotherapy. Dependents on mixed drugs were also excluded.

Methods

For all subjects the followings were done:

History

Personal history: name, age, occupation, marital status and residence. Past history: chronic diseases and long term medications. The motive for tramadol dependence; initiation and urge by friends, curiosity, financial and/or social troubles, pain killer or for premature ejaculation. Smoking: (Mild: <10 cigarette/day – Moderate smokers: 10–19 cigarette/day – Heavy smokers: ≥20 cigarette/day) (Rebecca et al., 2010). Toxicological history: amount and form of tramadol received per day and duration of tramadol dependence (lifetime use of tramadol) and diseases complicating dependence. Family history: smoking, substance or drug abuse by parents or other siblings, family troubles (broken or united family).

Laboratory investigations:

Quick view tramadol test card: (rapid one step drug of abuse test): it is an *in vitro* immunochromatographic assay for the rapid visual qualitative detection of tramadol in human urine (Marquardt *et al.,* 2005).

Positive cases were investigated for tramadol blood level: a high-performance liquid chromatographic method using UV detection was used for confirmation of diagnosis and for determination of tramadol concentration in human plasma according to Geng-Chang *et al.* (1999).

Both positive cases and the control group were investigated for: Serum testosterone level: Normal level: 270–1070 ng/dl)(Travison *et al.,* 2007) and serum prolactin level: Normal level: 2–18 ng/ml (Frantz *et al.,* 1997).

Statistics

Statistical presentation and analysis of the present study was conducted using the mean standard deviation, Student (T) test (for estimation of the difference between two means), chi-square (χ^2) (for comparison between two groups as regards qualitative data), Analysis of variance [ANOVA] tests (F) (for comparison among different times in the same group in quantitative data) and Linear Correlation Coefficient [r] test by SPSS Version 20. *Post-hoc* test (Tukey test) was used when F is significant. A *p*-value <0.05 was considered significant.

Results

The age of control group was 31.07±5.79 and that of tramadol dependent group was 30.90±5.06 with no significant difference between both groups (t=0.018 and *p*=0.893). It was found that 45% of TDG were skilled workers, 32% were non skilled workers, 14% were employees, and 8% had no job. Regarding the control group, 53.3% were non skilled workers, 23.3% were skilled workers, 16.7% were employees, whereas only 6.7% has no work. Concerning education, about 56% and 86.7% of the patients were educated, in TDG and control group respectively. More than half of the patients in TDG (56%) and control group (56.7%) were from rural residence.

All cases were married with no history of chronic diseases, long term medications or abuse of any psychotropic substances (other than tramadol) and received tramadol in tablet forms.

The present study showed significant difference between tramadol dependent group and control group regarding the family history of drug dependence which was positive in 38% of tramadol dependent group and in 10% of the control group. It also revealed non-significant difference between tramadol dependent group and control group regarding smoking, non-smokers represented 38% of cases in tramadol dependent group, 18% of cases were mild smokers, 12% were moderate smokers while, 32% of cases were heavy smokers.

Table 1 shows the different motives that pushed the cases for dependence, curiosity was the most common motive (22%) followed by tramadol taken as a treatment of premature ejaculation (20%) and the least found motive was the social and/or financial troubles (10%).

Table 1. Types of motives for dependence in tramadol dependent group (TDG)

	Tramadol dependent group (n =50)		
		N	%
Motives for dependence	Social/financial troubles	5	10
	Friends	7	14
	Pain killer	8	16
	Combined motives	9	18
	Premature ejaculation	10	20
	Curiosity	11	22

The majority of cases (62%) received tramadol in a dosage ranged from 400 to 1000 mg/d, 24% in a dosage more than 1000 mg/d and 14% in a dosage less than 400 mg/d (the maximum therapeutic dose = 400 mg/d). Furthermore, 52% of the cases took tramadol for more than 5 years, 38% of them took it for 2–5 years and 10% took it for less than 2 years.

As shown in Table 2 significant difference was detected regarding erectile dysfunction and decreased libido when comparing cases in tramadol dependent group and control group. Erectile dysfunction and decreased libido occurred in 44% and 48% of tramadol dependent group respectively.

A statistically significant decrease in serum testosterone and significant increase in serum prolactin level was noticed in cases of tramadol dependent group compared to control group (Table 3).

Table 2. Prevalence of erectile dysfunction and decreased libido among tramadol dependent group (TDG) and control group

			TDG n=50	Control group n=30	χ^2	*p*-value
Erectile dysfunction	Present	N	22	3	10.089	0.001*
		%	44%	10%		
	Absent	N	28	27		
		%	56%	90%		
Decreased libido	Present	N	24	5	7.966	0.005*
		%	48%	16.7%		
	Absent	N	26	25		
		%	52%	83.3%		

χ^2: Chi-square test.* Significant at *p*-value <0.05. TDG: Tramadol dependent group.

Table 3. Serum testosterone and prolactin hormonal levels in tramadol dependent group (TDG) and control group

Hormonal levels (Mean±SD)	TDG n=50	Control group n=30	T-test	*p*-value
Serum testosterone (ng/dl)	400.66±163.48	674.20±221.97	22.654	0.001*
Serum prolactin (ng/ml)	22.79±8.37	9.45±4.04	21.907	0.001*

T-test: Student t-test.* Significant at *p*-value <0.05. TDG: Tramadol dependent group.

Table 4 showed a significant relation between tramadol daily dose and both testosterone and prolactin serum levels. Significant decrease in serum testosterone level and significant increase in serum prolactin level occurred as tramadol dose increased. On the other hand, increasing the dose from 400–1000 to >1000 mg/d resulted in statistically non-significant decrease in the level of serum testosterone.

There was no significant relation between tramadol dose and both erectile dysfunction and decreased libido as shown in Table 5.

Table 6 illustrates significant decrease in testosterone and significant increase in prolactin serum levels as the duration of tramadol dependence prolonged till 5 years, while the change in hormonal levels became non-significant as the duration of dependence increased from 2–5 years to >5 years.

As the duration of dependence prolonged, significant increase in erectile dysfunction and decreased libido was noticed (Table 7).

Figures 1 and 2 show that there was a significant negative correlation between tramadol blood level and serum testosterone where r=–0.450 and *p* value=0.0010. However, a significant positive correlation was evident between tramadol blood level and serum prolactin (r=0.553 and *p*-value=0.001).

Discussion

The choice of tramadol in this study was based on its wide prevalence among drug dependent patients in Egypt. This was in agreement with International Narcotics Board Report International Narcotics Control Board Report (2013) which found that in the first six months in 2013 tramadol was at the top of narcotic substances in Egypt followed by poly drugs abuse and then by cannabis and other materials. On the other hand, Abou Eleinen *et al.* (2014) studied the prevalence of drug dependence among toxicology unit patients in Mansoura Emergency Hospital and Hamdi *et al.* (2013), whose study included eight different governorates in Egypt, found that cannabis (marijuana) was the most common substance of abuse.

Table 4. Comparison between tramadol daily dose and both testosterone and prolactin serum levels

Hormonal Levels (Mean ±SD)	Tramadol dose (mg/d)			F-test	*p*-value	Tukey test	
	≤400	400–1000	>1000				
Serum testosterone (ng/dl)	706.29±273.40	374.13±246.16	290.92±169.27	7.467	0.002*	P1	0.001*
						P2	0.001*
						P3	0.302
Serum prolactin (ng/ml)	18.84±4.71	22.38±11.35	26.05±11.36	6.997	0.012*	P1	0.043*
						P2	0.008*
						P3	0.032*

F. test: Analysis of variance [ANOVA]. * Significant at *p* value <0.05. *Post hoc* test (tukey test): P1: comparison between cases received tramadol doses ≤400 mg/d and cases received tramadol doses 400–1000 mg/d, P2: comparison between cases received tramadol doses ≤400 mg/d and cases received tramadol doses >1000 mg/d, P3: comparison between cases received tramadol doses 400–1000 mg/d and cases received tramadol doses >1000 mg/d.

The age of participants in this study was selected to be below 40 years to exclude the effect of aging on sexual dysfunction. The prevalence of erectile dysfunction increases as the age increase. It increases from 40% to 70% as the age increase from 40 to 70 years (Feldman *et al.,* 1994).

Curiosity was the most prevailed motive of dependence among cases of tramadol dependent group in this study (22% of cases). This is similar to De Micheli *et al.* (2002) who found that curiosity and pleasure seeking were the most prominent reasons for initiation of drug abuse, and he suggested that drug use prevention should not simply focus on reducing drug availability but also on helping young people to develop good family/peer relationships and find healthy ways to enjoy themselves. Administering tramadol as a pain killer is another motive for its dependence that was found in 16% of tramadol dependent cases in this study. Similarly, Deering *et al.* (2008) clarified that prolonged self-administration of tramadol for the purpose of pain relief was one of the most important motives for its dependence among the studied cases.

Peer influence play a crucial role in the involvement in drug dependence; this motive was found in 14% of the studied cases in the present study. A study done in Saudi Arabia by Bassiony (2013) reported that peer pressure was a risk factor for initiation as well as relapse of drug and substance abuse. Being accepted by peers is of critical importance to youth. Many of them are worried about how well they are liked and accepted by their peers and accordingly they adjust their behaviors, attitudes and beliefs (McElhaney *et al.,* 2008; Monahan *et al.,* 2011). Social and financial troubles represent 10% of the motives for tramadol dependence in the present study and this goes with Oshodi *et al.* (2010) in Nigeria who stated that social troubles are among the main causes of substance dependence.

Twenty percent of tramadol dependent cases in the current study received tramadol as a treatment for premature ejaculation and then prolonged self-administration that led them to become tramadol dependent. In accordance with that, Goda (2013) in Cairo University found that

Table 5. Association between tramadol dose and presence of erectile dysfunction and decreased libido in tramadol dependent group.

			Tramadol Dose (mg/d)			χ^2	*p*-value
			≤400	400–1000	>1000		
Erectile dysfunction	Present	N	1	15	6	2.926	0.232
		%	14.3%	48.4%	50%		
	Absent	N	6	16	6		
		%	85.7%	51.6%	50%		
Decreased libido	Present	N	1	15	8	4.865	0.088
		%	14.3%	48.4%	66.7%		
	Absent	N	6	16	4		
		%	85.7%	51.6%	33.3%		

χ^2: Chi-square test.

Table 6. Comparison between the duration of tramadol dependence and both testosterone and prolactin serum levels.

Hormonal levels (Mean ±SD)	Duration of dependence			F-test	*p*-value	Tukey test	
	1-2 years	2-5 years	>5 years				
Serum testosterone (ng/dl)	583.60±172.71	404.00±198.70	360.35±113.75	4.695	0.021*	P1	0.035*
						P2	0.018*
						P3	0.052
Serum prolactin (ng/ml)	17.08±3.43	23.33±3.56	26.03±4.70	5.589	0.017*	P1	0.021*
						P2	0.008*
						P3	0.687

F test: Analysis of variance [ANOVA]. * Significant at *p* value <0.05. *Post hoc* test (tukey test): P1: comparison between cases with 1–2 years duration and cases with 2–5 years duration. P2: comparison between cases with 1–2 years duration and cases with >5 years duration. P3: comparison between cases with 2–5 years duration and cases with >5 years duration.

Table 7. Association between the duration of tramadol dependence and presence of erectile dysfunction and decreased libido.

			Duration of dependence			χ^2	*p*-value
			1–2 years	2–5 years	>5 years		
Erectile dysfunction	Present	N	1	7	14	6.327	0.042*
		%	20%	30.4%	63.6%		
	Absent	N	4	16	8		
		%	80%	69.6%	36.4%		
Decreased libido	Present	N	1	6	17	10.859	0.004*
		%	20%	26.1%	77.2%		
	Absent	N	4	17	5		
		%	80%	73.9%	22.8%		

χ^2: Chi-square test. * Significant at *p*-value <0.05

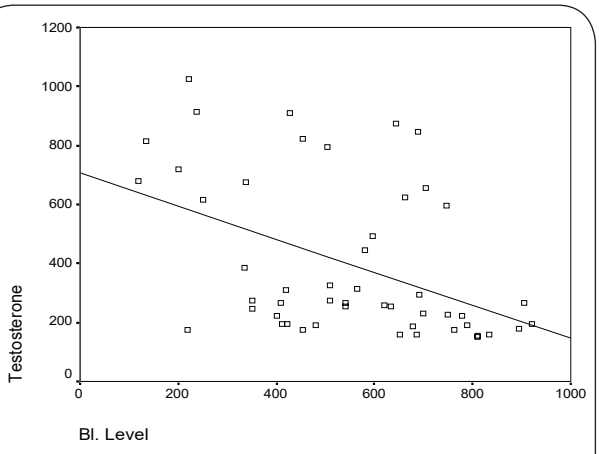

Figure 1. Correlation between tramadol blood level and serum testosterone level.

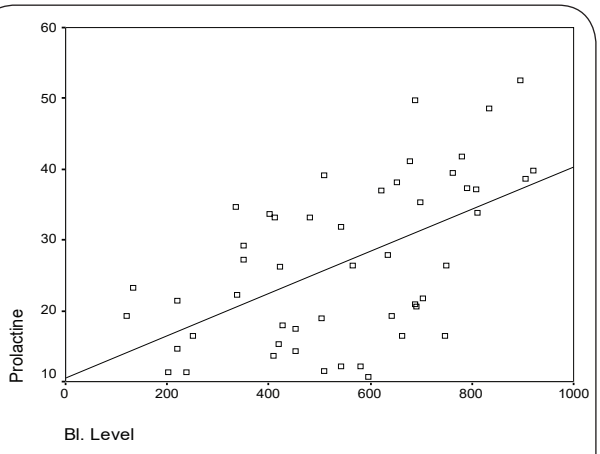

Figure 2. Correlation between tramadol blood level and serum prolactin level.

30% of his tramadol dependent cases, who sought medical advice at National Egyptian Center for Toxicological Research (NECTR), used tramadol with the same motive. Salem *et al.* (2008) used treatment with tramadol on demand (2 hours before sexual intercourse) for cases of premature ejaculation. They stated that tramadol showed good results in improving the condition and increased the intravaginal ejaculation latency time but they also reported that a potential risk of tramadol dependence should be kept in mind during long term therapy.

Significant differences in the serum testosterone and prolactin levels were found between tramadol cases and controls in this study. This is compatible with the study done by Daniell (2002) who measured the hormonal profile of 54 outpatient men consuming oral form of opioids several times daily and he reported significantly decreased levels of serum testosterone with increased prolactin levels referring this to the disturbance of hypothalamic pituitary gonadal axis. Auernhammer *et al.* (1993) stated that opioids bind to specific receptors in the hypothalamus and pituitary gland, disrupt the pulsatile release of corticotrophin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), and interfere with the production of cortisol and androgen precursors. Testosterone is also reduced due to direct inhibition of testicular testosterone synthesis (Daniell, 2002). Chan *et al.* (2011) also explain the lowering of serum testosterone level by that tramadol might lead to adrenal insufficiency secondary to chronic use.

In the present study significant difference was detected regarding erectile dysfunction and decreased libido when comparing tramadol dependent group and control group. This is in accordance with other studies that reported hypogonadism as serious sequelae of long-term tramadol administration. Symptoms of tramadol-induced hypogonadism include loss of libido, infertility, fatigue, depression, anxiety, loss of muscle strength and impotence in men (Daniell, 2002; Katz *et al.*, 2009). Daniell (2002) contributed the erectile dysfunction and decreased libido to the subnormal sex hormone levels induced by chronic tramadol administration that predisposed his studied cases to a diminished quality of sexual life.

Das (2014) had implicated that chronic use of tramadol, fentanyl, and hydromorphone can lead to adrenocortical insufficiency. Patients with dependence usually have chronically low levels of ACTH, cortisol and testosterone concentrations which impair an individual's ability to respond to physical, emotional and metabolic stresses. This impaired ability leads to abnormal mental health, metabolic alterations and sexual troubles in the form of diminished sexual motivation, experiences and sexual preference.

In the present study, it was observed that the effect of tramadol on hormonal levels (testosterone and prolactin) was dose and duration dependent. This goes with the result of Mckim (2003) who reported that changes in sex hormones levels are dependent on the administered dose of tramadol. Additionally, Gowing *et al.* (2000); Herzog *et al.* (2004) found that the influence of tramadol on testosterone and prolactin serum levels was significantly related to its dose. Large doses of tramadol administration lead to more pronounced effects. Moreover, Mckim (2003) stated that tramadol is known to decrease the levels of sex hormones and this lowered hormonal level is thought to be a chronic outcome. Furthermore, an animal study done by El-Gaafarawi (2006) revealed a slight influence on testosterone and prolactin levels in rats receiving 40 mg/kg of tramadol after 30 days but 80 mg/kg tramadol exerted moderate effects at 20 and 30 days.

There was no significant relation between tramadol dose and both erectile dysfunction and decreased libido in this study. On contrary Daniell (2002) revealed that erectile dysfunction and decreased libido had a dose-related pattern in his study. Besides that, Goodyear-Smith *et al.* (2008) stated that reduced libido and erectile dysfunction were dose dependent effects and both were improved by lowering the administered dose.

In the present study, increased duration of dependence led to significant increase in both erectile dysfunction

and decreased libido. This is in agreement with Daniell (2002) who declared that tramadol induced sexual dysfunction should be kept in mind during long term therapy especially in large doses. Additionally El-Ghawet (2015) concluded that chronic tramadol administration led to reproductive dysfunction and increased average of infertility. Also, Katz *et al.* (2009) reported that long-term tramadol administration for either dependence or chronic pain treatment often induces hypogonadism.

Significant negative correlation between tramadol blood level and serum testosterone level and significant positive correlation between tramadol and serum prolactin was noted among tramadol dependents in this study. Deer & Gunn (2015) reported low testosterone level and high prolactin level with increasing tramadol blood level among cases of chronic tramadol administration. They also recommended measuring serum testosterone level in patient on long-term therapy by tramadol to avoid hypogonadism.

Conclusion

From this work we can conclude that the majority of studied cases were smokers and curiosity played a crucial role as a strong motive in tramadol dependence. Men who take tramadol for premature ejaculation or any other purpose must know that they are very susceptible to many sexual dysfunctions.

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