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NEUROPSYCHOLOGICAL DISTURBANCE AMONG TRAMADOL USERS

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ABSTRACT

Background: Tramadol is a centrally acting analgesic that is used for the treatment of moderate to severe pain. The aim of this study: is to assess neuropsychological disturbance among tramadol users and to correlate these disturbances to the dose and duration of tramadol use. **Subjects & Methods:** This study was performed on 80 tramadol abusers admitted to the Neurology department and (NECTR), This study group was sub-divided into 4 groups depending on the dose (using <or= 600mg/day & using > 600mg/day and duration (<or=6 months & tramadol>6 months). The following data was collected from all subjects (Present History -Physical Examination-tramadol level in urine-EEG changes-psychological tests) **Results:** 46.2% of studied cases suffered from s, 81.2% of studied cases presented by convulsion, 72.5% of cases had psychological symptoms (52.5% had anxiety, 65.0% had mood disorder, 58.8% had aggression,28.9% had hallucination and 60.0% had insomnia). As regard EEG changes, 35 % of studied cases showed focal electrical activity. **Conclusion:** Tramadol abusers have neuropsychological effects eg.,(convulsion with focal electrical activity & increase incidence of depression , anxiety and aggressive behavior). Duration of tramadol intake and tramadol level in urine show significant relation to this neuropsychological disturbance.

Keywords: Neuropsychological Disturbance, Tramadol

INTRODUCTION

Tramadol is a synthetic 4-phenyl piperidine analogue of codeine. It is the most widely sold opioid analgesic in the world and is registered and marketed in more than 100 countries (Shipton, 2000). It has been approved for use in the United States since 1995 and in France since 1997 (Clarot *et al*., 2003).The Food and Drug Administration approved Tramadol in March 1995 and an extended-release (ER) formulation in September 2005 (McCarberg, 2007).

Seizures have been reported even with recommended dosages, due to the possibility of convulsions at high doses for some users, recreational use can be very dangerous, Tramadol can precipitate seizures in epileptic patients by lowering the seizure threshold. There have been several case reports of tramadol precipitating a seizure in non-epileptic patients. However, in this case the patient had a more complicated seizure presentation, which included generalized erythema, and profuse sustained diaphoresis (Labate *et al*., 2005)

It is apparent in community practice that psychological dependence to this agent may occur after as little as three months of use at the maximum dose generally depicted at 400 mg per day .the psychological deterioration signs of tramadol were angry, hostile, and aggressive. On the other hand, after treatment the main problem was the significant increase in comorbid anxiety, depressive, and obsessive-compulsive symptoms, (Rodriguez *et al*., 2007).

In Egypt, tramadol use has been markedly noticed since 2004 and it is now considered a major, serious health and public problems; as drug dependence mostly affects the youth with the highest working capacity especially with widespread of cheap Chinese tramadol. In Egyptian study, tramadol was found to be second most common substance abused after cannabis (Bango). As a result, tramadol abuser became commonly seen in the ER for acute intoxication as well as in outpatient clinics, Though the neuropsychatric deterioration of tramadol is not well addressed. (Abbas *et al*.., 2013).

There are suggestions that chronic opioid administration may induce a state of immune tolerance, although tramadol, in contrast to typical opioids may enhance immune function. Some have also stressed the negative effects of opioids on cognitive functioning and personality (Liu *et al*., 2006).

The aim of this study is to: Assess neuropsychological disturbance among tramadol users and to correlate these

disturbances to the dose and duration of tramadol use.

SUBJECTS AND METHOD

Subjects: This study was carried out on 100 subjects divided into two groups Group I (study group): consisted of 80 male patients with history of solitary tramadol use and age ranged from 18 to 60 years. They were admitted to the Neurology department and Clinical Toxicological Research Center (NECTR) during 2015 and 2016.This group was sub-divided into 4 subgroups depending on the dose and duration of abuse:

Group 1: using ≤ 600mg/day for ≤ 6 month.
Group 2: using> 600mg/day for ≤ 6 month.
Group 3: using ≤ 600mg/day for > 6month.
Group 4: using > 600mg/day for > 6month.

NB: We have chosen 600mg as it is double therapeutic dose (Ultram, 2006)

Group II (control group): consisted of 20 subjects with no previous history of drug abuse, this group was matched with the study group concerning the age, education and socioeconomic level.

Consent: Consent forms were signed and collected from all cases and control subjects included in the study and to do need investigation after given all the relevant study information, all relevant information's were given to all subjects before beginning of investigation.

Patients' Exclusion Criteria: Patients with negative tramadol, Patient with other drug dependence. Patient who have history of neurological disease (epilepsy, motor or sensory defect, mental retardation), Patients who have history of psychiatric disorder before tramadol use, and Patients who have medical history of chronic debilitating disease, (DM, liver disease, cancer).

Methods:

The following data was collected from all subjects:

A) Clinical Data:

I- Present History:

Age, age of beginning of tramadol abuse, occupation, residence, education, dose of tramadol, duration of exposure and mode of tramadol were recorded.

Methodology

II- Physical Examination:

Neurological Examination: for assessment of sensory & motor functions especially reflexes, to determine any impairment in the nervous system, and convulsions were recorded.

International Neuropsychiatric Interview: structured psychiatric interview for psychiatric evaluation; Anxiety disorder, Mood disorder, Psychotic disorder, Cognitive and dissociative disorder, Eating & sleep disorder, and Personality disorder:

B) Laboratory investigations:

Fresh urine specimen 10cc from each patient was collected and Semi-quantitative

analysis of tramadol was done by using VIVA-E analyzer, Siemens, USA.

C) Electroencephalogram (EEG): was done to detect epileptic focus or any electric activity changes among tramadol users.

D) Screening of specific psychiatric deterioration: using rating scales for anxiety (Hamlton rating scale), aggression (Overt aggression scale) and depression (Beck depression inventory scale).

Hamltonrating scale for anxiety0 not present 1 mild 2moderate 3 severe 4 very severe.

Overt aggression scale for aggression: Verbal aggression, Physical aggression against others, Physical aggression against self Physical aggression against objects Beck depression inventory scale for depression: +ve –ve.

Statistical Analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 23. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparing categorical data, Chi square (□2) test was performed. Exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 were considered as statistically significant.

RESULTS

Regarding the psychological manifestations among the studied cases, As shown Table (1):, 72.5% of cases had psychological symptoms (52.5% had anxiety & 65.0% had mood disorder&58.8% had aggression & 28.9% had hallucination and 60.0% had insomnia), As most patients had mixed psychological symptoms. A significant difference between studied group and control group (p value < 0.001).

Patients in G4 showed convulsion (96.8%) &psychological symptoms (100%) and (25.8%).Patients in G3 showed convulsion (96.4%) & psychological symptoms (96.4%) Patients in G2 showed convulsion (33.3%) & psychological symptoms (0%). Patients in G1 showed convulsion (40%) & psychological symptoms (0%). A significant difference between the 4 subgroups (p value < 0.001).(Table 2).

Results of psychological tests were shown in table (3); Hamlton scale for anxiety: 27.5% of cases presented by moderate anxiety; Overt aggression scale: 41.2% of cases presented by verbal aggression,13.8% of cases presented by physical aggression against others and 8.8% of cases presented

by physical aggression against self and Beck depression scale: 65.0% of cases had depression . A significant difference was found between the study group and control group concerning the results of these tests (p value < 0.001).According to this study, psychological tests (Hamlton scale & Overt aggression scale and Beckdepression scale) were common with G3 and G4 But these tests were negative with G1 and G2.Asignificant difference between the 4 subgroups (p value < 0.001)., (Table 4).

The mean tramadol level in G1 was 330.00 ±163.93 ng/ml, The mean tramadol level in G2 was 620.00 ± 126.33ng/ml, The mean tramadol level in G3 was 488.57 ± 192.94ng/ml, The mean tramadol level in G3 was 451.19 ± 192.74ng/ml. A significant difference between the 4 subgroups regarding tramadol level (p value < 0.001)., (Table 5).

Table (6): Show that the mean duration of exposure which presented by convulsion (3.41±2.85 years) & psychological symptoms (3.88±2.75 years), it Show that by comparing duration of exposure of different patients suffering convulsion and psychological symptoms from those who were not suffering, there was significant difference between duration of exposure and (convulsion & psychological symptoms).

Table (7): show that by comparing tramadol Level between patients suffering convulsions from those who were not suffering, there was significant difference between Tramadol level and convulsion (positive correlation)(P=0.040).It show that by comparing tramadol Level between patients suffering psychological symptoms from those who were not suffering, there was no significant difference.

Table 8 show Patients in G4 showed focal electrical activity in EEG (41.9%), Patients in G3 showed focal electrical activity in EEG (50%), Patients in G2 showed focal electrical activity in EEG (16.7%), Patients in G1 showed focal electrical activity in EEG (0%).

Table (1): Comparison between study group & Control group regarding psychological manifestations

		Groups				
		Study group		Control group		P value
		Count	%	Count	%	
psychological symptoms	-ve	22	27.5%	20	100.0%	< 0.001
	+ve	58	72.5%	0	.0%	
anxiety disorder	Not present	38	47.5%	20	100.0%	< 0.001
	Present	42	52.5%	0	.0%	
mood disorder	Not present	28	35.0%	20	100.0%	< 0.001
	Present	52	65.0%	0	.0%	
psychotic disorder	No	53	69.7%	20	100.0%	0.007
	Delusions	1	1.3%	0	.0%	
	Hallucination	22	28.9%	0	.0%	
	Schizopherenic	0	.0%	0	.0%	
eating &sleep disorder	No	29	36.2%	20	100.0%	< 0.001
	Insomnia	48	60.0%	0	.0%	
	Hypersomnia	3	3.8%	0	.0%	
	anorexia nervosa	0	.0%	0	.0%	
	bulimia nervosa	0	.0%	0	.0%	
personality disorder	No	30	37.5%	20	100.0%	< 0.001
	Paranoid	2	2.5%	0	.0%	
	Avoidant	1	1.2%	0	.0%	
	Dependant	0	.0%	0	.0%	
	Schizoid	0	.0%	0	.0%	
	Aggressive	47	58.8%	0	.0%	

Table (2): Comparison between the 4 groups (G1 & G2& G3 and G4) regarding Neurological manifestation and psychological symptoms: Chi square ($\chi 2$) test

		Dose of tramadol									
		G1		G2		G3		G4		X^2	P value
		Count	%	Count	%	Count	%	Count	%		
Convulsion	+v	6	40.0%	2	33.3%	27	96.4%	30	96.8%	34.935	<0.001
	-ve	9	60.0%	4	66.7%	1	3.6%	1	3.2%		
psychological symptoms	+v	0	.0%	0	.0%	27	96.4%	31	100.0%	75.163	<0.001
	-ve	15	100.0%	6	100.0%	1	3.6%	0	.0%		
	-ve	0	.0%	0	.0%	20	71.4%	23	74.2%		

Group 1: using ≤ 600mg/day for ≤ 6 month, Group 2:using > 600mg/day for ≤ 6 month, Group 3:using ≤ 600mg/day for > 6month, Group 4 using > 600mg/day for > 6month.

Table (3): Comparison between studied group & Control group regarding psychological tests

		Groups				
		Study group		Control group		P value
		Count	%	Count	%	
Hamlton scale (anxiety)	No	38	47.5%	20	100.0%	< 0.001
	Mild	2	2.5%	0	.0%	
	Moderate	22	27.5%	0	.0%	
	Severe	17	21.2%	0	.0%	
	very severe	1	1.2%	0	.0%	
Overt aggression scale	No	29	36.2%	20	100.0%	< 0.001
	Verbal	33	41.2%	0	.0%	
	physical against others	11	13.8%	0	.0%	
	physical against self	7	8.8%	0	.0%	
	physical against objects	0	.0%	0	.0%	
Bpeck depression scale	-ve	28	35.0%	20	100.0%	< 0.001
	+v	52	65.0%	0	.0%	

Table (4): Comparison between the 4 groups (G1 & G2 & G3 and G4) regarding psychological tests

		Dose of tramadol									
		G1		G2		G3		G4		X^2	P value
		Count	%	Count	%	Count	%	Count	%		
hamlton scale (anxiety)	No	15	100.0%	6	100.0%	10	35.7%	7	22.6%	34.683	<0.001
	Mild	0	.0%	0	.0%	1	3.6%	1	3.2%		
	moderate	0	.0%	0	.0%	11	39.3%	11	35.5%		
	Severe	0	.0%	0	.0%	6	21.4%	11	35.5%		
	very severe	0	.0%	0	.0%	0	.0%	1	3.2%		
overt aggression scale	No	15	100.0%	6	100.0%	8	28.6%	0	.0%	55.702	<0.001
	Verbal	0	.0%	0	.0%	12	42.9%	21	67.7%		
	physical against others	0	.0%	0	.0%	5	17.9%	6	19.4%		
	physical against self	0	.0%	0	.0%	3	10.7%	4	12.9%		
	physical against objects	0	.0%	0	.0%	0	.0%	0	.0%		
beck depression scale	-ve	15	100.0%	6	100.0%	4	14.3%	3	9.7%	53.019	<0.001
	+v	0	.0%	0	.0%	24	85.7%	28	90.3%		

Group 1: using ≤ 600mg/day for ≤ 6 month, Group 2:using > 600mg/day for ≤ 6 month, Group 3:using ≤ 600mg/day for > 6month, Group 4 using > 600mg/day for > 6month

Table (5): Comparison between the 4 groups (G1 & G2 & G3 and G4) regarding tramadol level

		Dose of tramadol				
		G1	G2	G3	G4	P value
tramadol level	Mean	330.00	620.00	488.57	451.19	0.008
	Standard Deviation	163.93	126.33	192.94	192.74	
	Median	300.00	635.00	460.00	400.00	
	Minimum	120.00	420.00	230.00	190.00	
	Maximum	770.00	780.00	800.00	930.00	

Group 1: using ≤ 600mg/day for ≤ 6 month, Group 2:using > 600mg/day for ≤ 6 month, Group 3:using ≤ 600mg/day for > 6month, Group 4 using > 600mg/day for > 6month

Table (6): Relation between Duration of exposure (year) with convulsion &psychological symptoms

		duration of exposure(year)					
		Mean	Standard Deviation	Median	Minimum	Maximum	P value
Convulsion	+v	3.41	2.85	3.00	.25	15.00	<0.001
	-ve	.76	1.25	.33	.15	5.00	
psychological symptoms	+v	3.88	2.75	3.00	1.00	15.00	<0.001
	-ve	.38	.18	.33	.15	1.00	
	-ve	2.78	3.15	2.00	.00	15.00	

Table (7): Relation between tramadol level with convulsion & Psychological symptoms

		tramadol level					
		Mean	Standard Deviation	Median	Minimum	Maximum	P value
Convulsion	+v	476.26	193.98	450.00	190.00	930.00	0.040
	-ve	358.67	174.96	320.00	120.00	780.00	
psychological symptoms	+v	466.67	192.98	440.00	190.00	930.00	0.400
	-ve	421.36	201.17	365.00	120.00	780.00	
	-ve	471.09	183.02	450.00	230.00	800.00	

Table 8: Comparison between the 4 subgroups (G1 & G2 & G3 and G4) regarding EEG changes

		Dose of tramadol								X^2	P value
		G1:using <or= 600mg/day for <or= 6 month		G2:using > 600mg/day for <or= 6 month		G3:using <or= 600mg/day for > 6 month		G4:using >600mg/day for >6 month			
		Count	%	Count	%	Count	%	Count	%		
EEG changes	Normal	15	100.0%	5	83.3%	13	46.4%	17	54.8%	14.011	0.004
	focal electrical activity	0	.0%	1	16.7%	14	50.0%	13	41.9%		
	generalized electrical activity	0	.0%	0	.0%	1	3.6%	1	3.3%		

DISCUSSION

Tramadol is a centrally acting analgesic which is extensively used in the management of moderate to severe pain. It slightly affects opioid receptors and inhibits the reuptake of norepinephrine and serotonin in the CNS (Shadina *et al*., 2012). In Egypt, tramadol use has been markedly noticed since 2004 and it is now considered a major, serious health and public problems; as drug dependence mostly affects the youth with the highest working capacity especially with widespread of cheap Chinese tramadol (Abbas *et al*., 2013).

The psychological deterioration signs of tramadol manifested in patient being angry, hostile, and aggressive. On the other hand, after treatment the main problem was the significant increase in anxiety, depressive, and obsessive-compulsive symptoms (Rodriguez *et al*., 2007).

Regarding the neurological manifestations among the studied cases, the total percent of cases presented with seizures was 81.2%, while 40% of the cases presented with seizures at dose <600mg/day for <6 months use.

The exact mechanism of tramadol in induction of seizure is yet to be elucidated. Research indicates that in high concentrations tramadol exerts an inhibitory effect on gamma-aminobutyric acid (GABA) receptors. Inhibition of GABA receptors has been found to potentiate the severity of seizures in animal models. In addition, GABA receptor inhibition induced by tramadol can be secondary to its opioid receptor agonist activity (Rehni *et al*., 2008), and continuing this agonist activity on opioid receptor has been proven to precipitate seizure due to inhibition of GABA pathways (Miura *et al*., 2007).

Approximately similar results were obtained by Ahmadi *et al*. (2012) who noticed that 41.8% of cases had seizure. Also Talaie *et al*. (2009) study stated that seizure occurred in 46.2% of patients, it occurred within 24 hours post-tramadol intake.

This result agrees with Shadnia *et al*. (2012) noticed seizures in 35.1% who related this finding to the high doses of tramadol, except in one case, who ingested 300 mg of tramadol.

Mazor *et al*. (2008) reported unusual neurological presentation in a case of 8-week-old boy who exhibited an altered mental status and dystonia while the other case of a 10-month-old girl exhibited seizures that was not related with tramadol level .

Petramfar and Haghighi (2010) study showed that tramadol provoked seizures not only in supratherapeutic doses, but also in the recommended herapeutic doses even as low as 50 mg. As a matter of fact, in that study more than 80% of patients had seizure(s) after ingesting recommended doses of tramadol.

Marquardt *et al*. (2005) study showed that seizures could occur with doses not much greater than the therapeutic dose. The lowest reported dose causing seizures of 190 patients was 200 mg taken by a 26-year-old male. Koussa et al. (2003) a case report described 2 generalized seizures in a non-epileptic 17-year-old patient following oral intake of 200–250 mg of tramadol.

On contrary, Persson and Sjöberg (2008), showed that few cases have symptoms of seizure, this is because the studied cases were acutely intoxicated with tramadol.

In the present study, the total percent of cases presented with tonic colonic convulsion was 61.2%. Approximately similar results were obtained by Petramfar and Haghighi (2010) who noticed that 80% of cases had tonic colonic convulsion.

On contrary, Persson and Sjöberg (2008), Shadnia *et al*. (2012) showed that few cases have symptoms of seizure.

In the present study, EEG changes revealed that 35 % of studied cases showed focal electrical activity, 2.5% of cases showed generalized electrical activity and 62.5% of cases were normal. This agrees with **(**Petramfar & Haghighi, 2010) who noticed that 106 patients, postictal electroencephalogram, which was conducted 1-3 days after the seizure event, was normal in 50 patients out of 106 cases (47.2%). It also showed non-specific findings, including diffused slowing in 49 patients out of 106 cases (46.1%) and epileptiform discharges in seven patients out of 106 cases. On contrary, Afshari (2010)showed that no EEG changes among tramadol users.

Regarding the psychological manifestations among the studied cases, 72.5% of cases had psychological symptoms (52.5% had anxiety, 65.0% had mood disorder also 58.8% had aggression, 28.9% had hallucination and 60.0% had insomnia), As

most patients had mixed psychological symptoms.

This agrees with El-Hadidy *et al*., 2015 who noticed 90% of patients expressed mild anxiety and the remaining group demonstrated moderate anxiety. All patients expressed mild depression, As regards to obsessive-compulsive disorders; no case was detected in that study to be associated with tramadol dependence before treatment. Patients during tramadol dependence period were angry, hostile, and aggressive. Tramadol dependence on high dose could be physically safe to some limit, but psychiatrically it has many side effects.

Rajabizadeh *et al*. (2009) study showed that the incidence of psychosis increased after long-term abuse of tramadol in spite of successful detoxification, most common psychological symptoms among tramadol users are anxiety, depression and aggression.

This shows agreement with results obtained by Marquardt *et al*. (2005) who noticed ; coma 70%, seizures 60%, agitation 40%, hallucination 30%, aggression 45% and depression 30% due to multiple actions of tramadol on the CNS.

On the contrary, Ahmad and Reza (2010) reported that 87% of cases were comatosed and minor psychological symptoms (3% agitation, 8% hallucination and 6% depression) in a study about tramadol abuse.

According to this study, the mean Tramadol level was 454.21±195.04 (ng/ml). Moreover, Tramadol levels were 330 ng/ml in G1, 620 ng/ml in G2, 448.5 ng/ml in G3 and 451 ng/ml in G4; this finding agrees with Petramfar and Haghighi (2010) stated that in their study the mean Tramadol level was 363.2 ± 30. (ng/ml).

In this study 3 tests were made: Hamlton scale for anxiety: 27.5% of cases presented by moderate anxiety, Overt aggression scale: 41.2% of cases presented by verbal aggression, 13.8% of cases presented by physical aggression against others and 8.8% of cases presented by physical aggression against self, Beck depression scale: 65.0% of cases had depression .This agrees with El-Hadidy *et al*., 2015 who made the same psychological tests and reports.

In Conclusion, Tramadol abusers have neuropsychological effects eg., (convulsion with focal electrical activity & increase incidence of depression , anxiety and aggressive behavior). Duration of tramadol intake and tramadol level in urine show significant relation to this neuropsychological disturbance.

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