

Attention and Memory in Tramadol Addiction

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Abstract

Background and Objective: Impairment in cognitive domains occurs commonly in substance use disorders. Tramadol abuse is a common problem in Egypt. The objective of this study was to study the effect of tramadol addiction on attention and memory.

Methods: This study included 30 patients with tramadol addiction and 30 control subjects (matched for age, sex, and education). The participants were interviewed using attention and memory subscales of Montreal Cognitive Assessment test (MoCA) and Trail making test A and B.

Results: The average score of memory in the tramadol addiction group was 2.46 ± 1.33 , while the average score in the control group was 4.47 ± 1.04 , there was significant difference between the two groups with **P value** < 0.0001 . There was no statistically significant impairment in Trail making tests A and B. There was no association between cognitive impairment and sociodemographic or clinical factors.

Conclusions: Tramadol addiction causes impairment in memory. There is no effect of tramadol dose or duration of abuse on cognitive impairment.

INTRODUCTION

Tramadol has a dual mechanism of action. Tramadol and its active metabolite, O-desmethyl tramadol, bind to μ opioid receptors, thus exerting their effect on GABAergic transmission. They also inhibit reuptake of 5-hydroxy tryptamine (serotonin) and noradrenaline (Shadnia, et al. 2008, and Taghaddosinejad, et al. 2011).

Few works studied the cognitive profile of tramadol dependence however, many studies were done regarding the cognitive profile of other substances of abuse particularly the opioids and cannabis. This can be explained by that tramadol is not a very common drug in the western world and does not represent a medical issue of importance regarding dependence to be a focus for the scientific research unlike in Egypt where it represents a major health issue (Abo-Elmagd, et al. 2013).

SUBJECTS AND METHODS

Subjects

This study compares between two groups regarding attention and

memory. The first group is composed of 30 patients with two years or more of regular tramadol abuse (Dependency). The second group is a control group of 30 persons from relatives of the first and second group who are matched with them regarding age, sex and educational level.

Inclusion criteria:

1. Patients fulfill criteria for the diagnosis of tramadol dependence based on DSM-5 criteria.
2. Age from 18:50 years.

Exclusion criteria:

1. Patients with other substance related or addictive disorders.
2. General medical condition that may affect cognition e.g. DM, HTN, Parkinson's disease, Huntington's disease, etc.

Methods

Each patient in the study was subjected to the following:

1. **Psychiatric interview:** Using semi structural interview with special emphasis on age, occupation, marital status, socioeconomic status and substance history including age of

onset, dose, duration, causes of intake and side effects (including any seizures during intake or withdrawal).

2. Physical examination Including temperature, blood pressure, pulse, heart, chest and abdominal examination to exclude general conditions that may affect cognition.

3. Routine neurological examination: Standardized neurological examination.

4. Liver and kidney functions and random blood sugar.

5. Urine toxicological screen for Tramadol, Cannabinoids, Benzodiazepines and Opioids to exclude effect of other substances on cognition.

7. To assess attention and memory:
A. Memory and Attention subscales of Montreal cognitive assessment (MoCA) (Nasreddine, et al. 2005). Arabic version (Rahman and El Gaafary, 2009). Short-term memory is assessed by recall task (5 points) which involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Attention is

evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each).

B. Trail making test (TMT) (Reitan, 1958): Part A requires the individual to draw lines to connect 25 encircled numbers distributed on a page. Part B is similar except the person must alternate between numbers and letters and is believed to be more difficult and takes longer to complete.

Statistical Analysis: Data was analyzed using SPSS program. Quantitative data was represented as mean, standard deviation, median and range. Data was analyzed using student t-test to compare means of two groups. When the data was not normally distributed Mann-Whitney test was used. Qualitative data was presented as number and percentage and compared using either Chi square test or fisher exact test. P value was considered significant if it was less than 0.05.

RESULTS

Sociodemographic characteristics

Table (1): Comparison between tramadol addicts and control group according to sociodemographic characteristics

Items	Active group	Control group	P1 value
Age/year			
Mean ± SD	32.33±7.54	30.37±6.20	0.27
Median (range)	31.5 (22-48)	28.5 (22-45)	
Education			
Diplom	22 (73.33%)	14 (46.67%)	0.10
Institute	3 (10.00%)	5 (16.67%)	
University	5 (16.67%)	11 (36.67%)	
Occupation			
Not working	5 (16.67%)	4 (13.33%)	0.95
Non-skillful	9 (30.00%)	11 (36.67%)	
Skillful	14 (46.67%)	13 (43.33%)	
Professional	2 (6.67%)	2 (6.67%)	
Marital status			
Single	12 (40.00%)	17 (56.67%)	0.20
Married	18 (60.00%)	13 (43.33%)	
Residence			
Rural	17 (56.67%)	19 (63.33%)	0.60
Urban	13 (43.33%)	11 (36.67%)	

Table (1) shows no statistically significant difference in age, education, occupation, marital status or residence between the two groups.

Cognitive tests

Table (2): Comparison between the two groups according to MoCAsubscores

Items	Tramadol group	Control group	P value
Attention Mean ± SD Median (range)	5.3±0.88 6 (3-6)	5.57±0.50 6 (5-6)	0.15
Delayed recall Mean ± SD Median (range)	2.46±1.33 2 (1-5)	4.47±1.04 5 (1-5)	<0.0001

Table (2) shows significant difference between the two groups in subscore delayed recall.

Table (3): Comparison between "active group" and "control group" according to Trail making A and B scores.

Items	Tramadol group	Control group	P value
Trail A Mean ± SD Median (range)	44.43±13.31 45 (27-96)	43.23±12.99 40 (27-94)	0.56
Trail B Mean ± SD Median (range)	98.87±46.39 83 (57-210)	91.63±36.82 82 (57-198)	0.71

Table (3) shows no significant difference between the two groups **Trail making A and B scores**.

Correlates of cognitive impairment

Table (4): Correlation between cognitive impairment and different items in "Tramadol group"

Items	Impaired N=16	Normal N=14	P value
Age Mean ± SD Median (range)	31.06±8.27 28.5 (22-48)	33.79±6.61 33.5 (22-44)	0.33
Occupation Not working Non-skillful Skillful Professional	4 (25.00%) 3 (18.75%) 8 (50.00%) 1 (6.25%)	1 (7.14%) 6 (42.86%) 6 (42.86%) 1 (7.14%)	0.40
Education Diplom Institute University	10 (62.50%) 3 (18.75%) 3 (18.75%)	12 (85.71%) 0 2 (14.29%)	0.20
Dose of tramadol Mean ± SD Median (range)	1301.56±987.94 1100 (450-4250)	787.5±285.35 787.5 (450-1350)	0.19
Duration of tramadol use Mean ± SD Median (range)	6.93±1.77 5.5 (4-11)	7.86±1.83 7.5 (5-11)	0.17
Age of onset at tramadol use Mean ± SD Median (range)	25.31±8.24 22.5 (16-44)	26.0±6.78 24 (15-39)	0.52
Fits No Yes	13 (81.25%) 3 (18.75%)	14 (100%) 0	0.23
Nicotine use No Yes	4 (25.00%) 12 (75.00%)	0 14 (100%)	0.10

Table (4) shows no statistically significant correlation between cognitive impairment and age of the patient, occupation, education, dose of tramadol, duration of tramadol use, seizures or nicotine use.

DISCUSSION

Sociodemographic data

Age: The mean age in tramadol group was 32.33 years with an average range 22-48 years. The mean age in control group was 30 years with an average

range 22-45 years. There was no statistically significant difference in age between the two groups. This indicates cross-matching between the two groups regarding age.

Other sociodemographic factors : There was no difference between the two groups in education, marital status, or occupation.

Regarding cognitive tests: Tramadol addiction group showed significant impairment in memory subscale of MoCA test in relation to control group.

Regarding **Trail-A and Trail-B tests** scores, we did not find any significant difference between the two groups.

There are few studies that assessed the cognitive effects of tramadol and their results were controversial. Some studies found that tramadol caused cognitive impairment, other studies found that tramadol did not impair cognition.

Our results were similar to results of **Bassiony and his colleagues (2017)**. Bassiony and his colleagues used MoCA to evaluate cognitive effects of long term tramadol use. Tramadol abuse patients had significant impairment in all cognitive domains except attention, visuoconstructional (cube), and trail-making test. The most affected cognitive domains were memory, visuospatial skills, and verbal fluency. There was no association between cognitive impairment and dose of tramadol, duration of tramadol abuse, or age at onset of tramadol abuse.

Also, our results were in agreement with the results of **Zakaryae, et al. (2012)**, who assessed cognitive functions in 26 tramadol dependent patients (who were abstinent for 30-90 days) with 26 non-users control group matched for age, education and male gender. They found significant impairment in neuropsychological performance in the tramadol use group. We found two studies that assessed cognitive effects of tramadol used as preoperative medication. The first study done by **Ng, et al. (2006)** and the second study done by **Ulusoy, et al.**

(2016). Both studies found that tramadol did not cause cognitive impairment. These two studies are different from our study because they assessed cognitive effects of single therapeutic dose of tramadol, while our study assessed the cognitive effects of long-term suprathreshold doses of tramadol.

Against our results, a study done by **Zacny, et al. (2005)** reported that neither tramadol (50, 100 mg orally) nor morphine (25 mg orally) impaired psychomotor performance relative to placebo in sporadic drug users. But this study assessed the cognitive effects of low doses for short duration and the patients were recreational drug users.

CONCLUSION

Tramadol addiction causes impairment in memory. No effect of daily dose of tramadol on cognitive performance. No effect of duration of dependence on tramadol on cognitive performance.

Recommendations

We recommend future studies to: Include larger sample size, use of more detailed assessment tools for more accurate assessment of certain cognitive domains.

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