Cognitive impairment and pregabalin dependence

Abouzed Mohamed[a], Emam M[b]

[a]Psychiatry Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt, [b]Neurlogy Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Correspondence to Mohamed Abouzed, MD, Lecturer of Psychiatry, Psychiatry Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Tel: +201009551109; fax: +20 2 22602687; e-mail: dr_m.abozeid@azhar.edu.eg

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Background
One of the major consequences of substance misuse is its effect on patient cognition. Pregabalin is a new-generation antiepileptic which is believed to have an addictive effect.
Objective
This cross-sectional study is aimed to estimate the prevalence of cognition impairment among patients with pregabalin misuse. This study includes 300 patients and 100 controls with matched age, sex, and education. The drug abuse patients were divided into two groups: the first group patients used pregabalin alone and the second was a polysubstance group; each group was formed of 150 patients matched in sex, age, and educational level to the pregabalin group. For the diagnosis we used urine screening for drugs. We used the Montreal cognitive assessment test in Arabic edition to evaluate the cognitive function of the patient.
Result
Cognitive impairment was more in pregabalin misuse patients (M=25.4, SD=3.3) than in the control group (M=27.5, SD=3.7) according to the Montreal cognitive assessment test, *P* value less than 0.001. The most affected domains were visuoconstruction, digit span, verbal fluency, and recall, with dose (M=625, SD=400). There was no association between cognitive impairment and dose of pregabalin or duration of substance abuse.
Conclusion
This study concluded that pregabalin misuse patients were likely to have cognitive impairment due to the drug effect and their cognitive impairment was less than the polysubstance misuse group.

Keywords:
cognitive impairment, polysubstance abuse, pregabalin

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Background

Pregabalin is one of the newest antiepileptic drugs that essentially acts as a gamma-aminobutyric acid analog. Pregabalin is used in neurology and psychiatry and, in 2011, it became the 30th most prescribed medication in the United States (Fornasari, 2017). It is used for the treatment of epilepsy, neuropathic pain, some anxiety disorders, fibromyalgia, and for alcohol withdrawal. Its off-label indications include hypnotic-dependent insomnia (Montgomery *et al.*, 2013), and its mechanism of action is similar to that of gabapentin. Pregabalin has inhibitory action on the brain and causes presynaptic inhibition of excitatory neurotransmitters. This antiglutamatergic effect resembles the effect of benzodiazepines and may be responsible for its addictive properties. It may also make alcohol-addicted or benzodiazepine-addicted patients more vulnerable to cross –tolerance (Bonnet and Scherbaum, 2017).

The prevalence of cognitive impairment in polysubstance abusers varies widely and may be as high as 80%(Hagen, 2016). Cognitive impairment includes deficits in cognitive flexibility and attention in cannabis users, deficits in cognitive flexibility in cocaine and opioid users, deficits in attention and impulse control in amphetamine users, and deficits in working memory and declarative learning in tobacco smokers. Alcoholics may develop permanent cognitive deficits, such as Wernicke–Korsakoff syndrome and impairment of psychomotor abilities reported in patients taking stable doses of opioids (Gould, 2010).

Cognitive deficits have an impact on treatment outcomes, including patient insight and judgment, compliance, and relapse prevention (Gupta *et al.*, 2018). Cognitive impairment may affect an individual's ability to benefit from counseling and/or abstinence-sustaining strategies (Fernandez-Serrano *et al.*, 2011). The cognition deficit may persist even

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after several months of abstinence. Even during opioid-substitution therapy, some patients have been reported to experience problems with cognitive function (Copersino *et al.*, 2012).

Few studies have examined the effects of pregabalin on cognition. Salinsky *et al.* (2010) reported that titration of pregabalin to 600 mg for 12 weeks induced mild cognitive deficits and complaints of neurotoxicity in healthy volunteers.

The objectives of the present study were to assess the prevalence and clinical correlates of cognitive impairment in patients with pregabalin abuse and to compare the levels of cognitive impairment among pregabalin and polysubstance abusers and healthy controls.

Patients and methods

Patients

A total of 150 patients from psychiatry, addiction, and neurology outpatient clinics, who asked for pregabalin prescription and diagnosed with pregabalin misuse disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria (American Psychiatric Association, 2013), and an equal number of age-matched, sex-matched, and education-matched polysubstance abusers were included in the present study. One hundred controls without a history of substance misuse were selected from the relatives of the patients and matched for age, sex, and education level.

Patients aged less than 18 years and those aged more than 50 years; those with major physical problems (e.g. heart failure, hepatic failure, renal failure, brain insult, dementia); and those with comorbid mental illness (intellectual disability, acute psychosis, or dual diagnosis) were excluded.

Protocol

Sociodemographic and clinical data were collected from all patients, diagnoses of polysubstance misuse were based on the Structured Clinical Interview from *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Additionally, a routine urine test was performed to screen for substance and pregabalin abuse, which is not a routine investigation. The Montreal cognitive assessment (MoCA) test was used to assess cognitive function of the patients (Rahman and El Gaafary, 2009). The controls comprised relatives of the patients and they also underwent the MoCA and urine tests to exclude the possibility of any substance misuse.

Ethical considerations

The protocol is approved by Al-Azhar Faculty of Medicine Ethics Committee. Written informed consent was obtained from all participants, and the study was performed in accordance with the ethical standards of the Helsinki Declaration of 2004.

Statistical analysis

SPSS, version 11.0.1 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Quantitative data are expressed as mean and SD, and the Student's t test was used for comparisons. Fisher's exact test and the χ^2 test were used for qualitative data; P value less than or less than 0.05 was considered to be statistically significant. Comparisons between the polysubstance, pregabalin, and control groups were performed using analysis of variance adjusted for other variables (age and education).

Results

Sociodemographic information

Most of the patients diagnosed with a substance-use disorder (pregabalin or polysubstance) were men (94%). There were no significant differences between the controls and patients in terms of sex, age, education, and marital status. Fifty-four percent (n=81) of the patients took more than or equal to six tablets (900 mg) (M=1050, SD=122 per day). The initiation age of polysubstance misuse (M=16.27, SD=8.9 years) is less than the pregabalin misuse group (M=24.1, SD=6.94). The dose of pregabalin was M=625, SD=400.01 mg/day, and the duration of abuse was M=9.17, SD=7.72 years. The sociodemographic characteristics of the patients in the three groups (i.e. pregabalin alone, polysubstance, and control) were comparable.

Cognitive impairment

The total MoCA scores revealed that patients who abused polysubstance (M=24.9, SD=3.6) exhibited greater cognitive impairment than the controls (M=27.5, SD=3.7), t=5.53, P=0.0001. All cognitive function domains, except naming, t=0.019, P=0.98, were significantly impaired in polysubstance abusers (Table 1). On the contrary, patients who abused pregabalin exhibited impairment in all cognitive domains, but the impairment was significant in visuoconstruction t=3.22, P=0.0014, digit span t=2.65, P=0.0084, verbal fluency t=2.01, P=0.045, and recall domains t=3.15, P=0.0018. The total MoCA score was significantly impaired in pregabalin misuse group (M=25.4, SD=3.3) more than the control group (M=27.5, SD=3.7), t=4.69,

Table 1 Cognitive difference between the polysubstance abuse group and the control group

MoCA	Control	Polysubstance	*t* value	95% confidence interval	*P* value
Visuoexecutive/5	4.36±0.92	3.39±1.21	68.0941	0.94194 to 0.99806	<0.001*
Naming/3	2.87±0.34	2.77±0.52	0.0192	–10.15 to 10.35	0.9847
Digit span/2	1.97±0.17	1.83±0.45	2.9713	0.047 to 0.233	<0.001*
Attention/1	.95±0.21	0.73±0.45	4.5664	0.125 to 0.314	
Calculation/3	2.82±0.054	2.45±0.51	7.2232	0.269 to 0.471	<0.001*
Repetition/2	1.72±0.55	1.44±0.71	3.3323	0.115 to 0.445	<0.001*
Verbal fluency/1	0.82±0.18	0.38±0.20	17.7266	0.391 to 0.489	<0.001*
Abstraction/2	1.80±0.48	1.34±0.74	5.4917	0.295 to 0.625	<0.001*
Recall/5	3.39±1.85	2.45±1.57	4.3152	0.511 to 1.369	<0.001*
Orientation/6	6.72±0.67	5.66±0.58	13.2967	0.903 to 1.217	<0.001*
Total	27.5±3.7	24.9±3.6	5.5325	1.674 to 3.526	0.0001*

MoCA, Montreal cognitive assessment. *By conventional criteria, this difference is considered to be statistically significant.

Table 2 Cognitive difference between the pregabalin abuse group and the control group

MoCA	Control	Pregabalin	*t* value	95% confidence interval	*P* value
Visuoexecutive/5	4.36±0.92	3.39±1.10	3.2277	0.1676 to 0.6924	0.0014*
Naming/3	2.87±0.34	2.77±0.48	1.8030	–0.0092 to 0.2092	0.0726
Digit span/2	1.97±0.17	1.86±0.39	2.6559	0.0284 to 0.1916	0.0084*
Attention/1	0.95±0.21	0.90±0.30	1.4466	–0.0181 to 0.1181	0.1493
Calculation/3	2.82±0.054	2.68±0.71	0.1067	–0.1947 to 0.1747	0.9151
Repetition/2	1.72±0.55	1.59±0.66	1.6283	–0.0273 to 0.2873	0.1047
Verbal fluency/1	0.82±0.18	0.71±0.45	2.0122	0.0023 to 0.2177	0.0453*
Abstraction/2	1.80±0.48	1.73±0.59	0.9881	–0.0695 to 0.2095	0.3241
Recall/5	3.39±1.85	2.72±1.49	3.1584	0.2522 to 1.0878	0.0018*
Orientation/6	6.72±0.67	6.51±0.98	1.8706	–0.0111 to 0.4311	0.0626
Total	27.5±3.7	25.4±3.3	4.6942	1.219 to 2.981	<0.001*

MoCA, Montreal cognitive assessment. *By conventional criteria, this difference is considered to be statistically significant.

Table 3 Cognitive difference between the polysubstance abuse group and the pregabalin group

MoCA	Pregabalin	Polysubstance	*t* value	95% confidence interval	*P* value
Visuoexecutive/5	3.39±1.10	3.39±1.21	0	–0.262 to 0.262	1.0
Naming/3	2.77±0.48	2.77±0.52	0.	–0.1137 to 0.1137	1.0
Digit span/2	1.86±0.39	1.83±0.45	0.61	–0.1257 to 0.0657	0.53
Attention/1	0.90±0.30	0.73±0.45	3.84	0.083 to 0.256	<0.001*
Calculation/3	2.45±0.51	2.45±0.51	0	–0.115 to 0.115	1.0000
Repetition/2	1.59±0.66	1.44±0.71	1.89	–0.005 to 0.305	0.05
Verbal fluency/1	0.71±0.45	0.38±0.20	8.20	0.25 to 0.40	<0.001*
Abstraction/2	1.73±0.59	1.34±0.74	5.04	0.23 to 0.54	<0.001*
Recall/5	2.72±1.49	2.45±1.57	1.52	–0.07 to 0.61	0.12
Orientation/6	6.51±0.98	5.66±0.58	9.14	–1.03 to –0.66	<0.001*
Total	25.4±3.3	24.9±3.6	1.25	–0.28 to 1.28	0.21

MoCA, Montreal cognitive assessment. *By conventional criteria, this difference is considered to be statistically significant.

P=0.0001 (Table 2). Sociodemographic data including age, sex, education level, occupation, and marital status demonstrated no association with cognitive impairment. Polysubstance abusers were more likely to experience cognitive impairment (M=24.9, SD=3.6) than those who abused pregabalin alone (M=25.4, SD=3.3) but not significant *t*=1.25, *P*=0.21. All cognitive domains were more impaired in the polysubstance abuse group than in the pregabalin abuse group. Differences were significant in verbal fluency and *t*=3.84, *P*=0.0001, abstraction *t*=5.04, *P*=0.0001, and orientation *t*=9.14, *P*=0.0001 (Tables 3–5).

A one-way analysis of variance was conducted to compare the effect of addiction on cognition (MoCA test) in polysubstance, pregabalin, and control groups. There was significant difference at *F* (2, 397)=29.72, *P* value less than 0.001 between the three groups. Post-hoc analyses using Tukey's honestly significant difference indicated a significant difference between the polysubstance group (M=24.9, SD=3.6)

Table 4 Analysis of variance test to compare between polysubstance, pregabalin, and control groups

Source of variation	ss	df	ms	*f*	*P*
Between groups	735.000	2	367.500	29.721	<0.001*
Within groups	4908.960	397	12.365		
Total	5643.960	399			

*By conventional criteria, this difference is considered to be statistically significant.

Table 5 Tukey honestly significant difference post-hoc test

	Difference	95% confidence interval	*P*
Control vs. polysubstance	2.6	−3.66 to −1.53	<0.001
Control vs. pregabalin	2.1	−3.16 to −1.03	<0.001
Polysubstance vs. pregabalin	0.5	−0.45 to 1.45	0.435

and the control group (M=27.5, SD=3.7) *P* value less than 0.001. Also there was significant difference between the control group (M=27.5, SD=3.7) and the pregabalin group (M=25.4, SD=3.3) *P* value less than 0.001. However, the polysubstance group (*M*=24.9, *SD*=3.6) did not significantly differ *P*=0.453 from the pregabalin group (M=25.4, SD=3.3). Taken together, these results suggest that both polysubstance misuse and pregabalin misuse have a bad effect on cognition.

Discussion

Only a few studies have addressed cognitive impairment with regard to pregabalin; however, these studies involved patients with epilepsy or medically ill patients. Moreover, even in investigations that included healthy volunteers, the study period was short (a few weeks), and doses of pregabalin were limited and did not exceed 500 mg (Salinsky et al., 2010). However, in the present study, the sample used a large amount of pregabalin [mean, 625 mg (range, 200–1200 mg)] over a long period [mean, 9.17±7.72 years (range, 1–18 years)].

Cognitive impairment is important to study patients taking pregabalin due to its nature of use in epilepsy and polyneuropathy, which tend to be chronic and high dose in patients already prone to cognitive impairment because of other physiological and pathological causes. Secondary causes of impairment include novel misuse as an addictive substance, which can also involve large doses over long durations (Landi *et al.*, 2019).

In the present study, four of 10 cognitive domains (visuoconstructional, digit span, verbal fluency, and recall) demonstrated significantly worse scores in patients who abused pregabalin compared with healthy controls. These negative effects were, however, less severe than the cognitive impairment exhibited by polysubstance abusers, in whom nine of 10 cognitive domains were significantly impaired (all except for naming). A previous study that evaluated the cognitive side effects of pregabalin in healthy volunteers after 3 days of treatment (450 mg/day) reported no cognitive side effects (Zacny *et al.*, 2012). In contrast, a double-blinded study involving healthy volunteers who underwent 12 weeks of treatment at 600 mg/day reported more negative effects on cognitive measures (digit symbol, stroop, controlled oral word association task) (Salinsky *et al.*, 2010). In a study comparing the cognitive effects of pregabalin (75 mg dose) versus duloxetine in postoperative pain management, there was a significant decrease in mean MoCA scores in the pregabalin group (1.83±1.31 points) (Myhre *et al.*, 2019). Gabapentin, which has many properties similar to pregabalin, induces mild cognitive side effects; however, this difference may be due selective binding of pregabalin to the alpha-2 delta subunits of voltage-gated calcium channels (Altiparmak *et al.*, 2018). Long-term potentiation in N-type Ca^{2+} channel deficiency was associated with chronic memory impairment (Nagase *et al.*, 2003). N-type Ca^{2+} channels are present in the hippocampus and are responsible for hippocampus-dependent memory and learning (Hagen *et al.*, 2007). Pregabalin inhibits depolarization-dependent calcium influx, resulting in decreased neurotransmitter release, mainly in the hippocampus and the cerebellum, thus leading to cognitive impairment (Verma *et al.*, 2014).Cognitive deficits in substance abusers reflect drug-induced impairment, which depend on the type of drug, its mechanism of action, drug–drug interactions, onset of use, duration, and dose (Fowler *et al.*, 2007; Mackey and Paulus, 2013; Battistella *et al.*, 2014).

Conclusion

Patients who abused pregabalin are more likely to exhibit cognitive impairment, although cognitive impairment in this group is less severe than in those with polysubstance abuse.

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Conflicts of interest

There are no conflicts of interest.

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