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Suicidal ideation and behavior among subjects with substance abuse disorder related to pregabalin

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Abstract

Background: Although pregabalin abuse is increasing worldwide and may be associated with increased suicidal ideation and behavior, few studies were done in Egypt searching for the effect of pregabalin on suicide. Eighty-three patients meeting DSM-IV criteria for substance abuse disorders related to pregabalin were identified from the addiction clinic of EL Khanka Psychiatric Hospital in Egypt for this observational cross-sectional study. We intended to assess suicidal ideation and behavior in patients with substance abuse disorder related to pregabalin and to identify the effects of other comorbid substances of abuse. All participants were subjected to semi-structured interview designed to collect and identify the socio-demographic data and patterns of substances 'use ,The Structured Clinical Interview for DSM-IV Axis I Disorders to diagnose patients with substance abuse disorder "related to pregabalin," Beck Scale for Suicidal Ideation for assessment of suicidal ideation and behavior and urine screening test for pregabalin and other substances of abuse.

Results: Most of participants used pregabalin continuously {86.7%}. More than seventy nine percent of the patients abused both pregabalin and other substances, tramadol 67.4%, heroin 66.3%, cannabis 65.1%, other drugs 44.6%, and benzodiazepines 27.7%. Screening urine test was positive in 62.7% of participants most frequently was heroin 41% and cannabis 34.9%. No suicidal ideation was found in 67.4%, 19.3% had low risk of suicide, and 13.3% had high risk of suicide so total participants who had suicidal ideation were 32.6%. There was statistical significant increase in risk of suicide among patients who were continuously abusing pregabalin and who had positive pregabalin urine test. There was significant positive correlation between Beck Suicidal Ideation score and duration of abusing pregabalin, maximum and daily dose of pregabalin. Also, there was a statistical significant relation between suicidal ideation and associated tramadol abuse and this was positively correlated with dose and duration of tramadol abuse.

Conclusions: About one third of patients abusing pregabalin had a risk of suicide and this risk increased with associated tramadol abuse so pregabalin abuse is dangerous like other substances of abuse and must be used with caution under strict medical supervision

Keywords: Pregabalin, Abuse, Suicide

Background

Substance use disorder is a set of behavioral, cognitive, and physiological symptoms resulting from using the substance continuously despite significant negative effects. It may result as a consequence of drug abuse and misuse [1]. Pregabalin is an analog of the

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gamma-aminobutyric acid (GABA) mammalian neurotransmitter, and its structurally related compound gabapentin known as α 2, δ ligands. They act as inhibitory modulators of neuronal excitability that reduce ectopic neuronal activation of hyperexcited neurons while normal activation remains unaffected [2]. Pregabalin was approved for the treatment of partial epilepsy, generalized anxiety disorder, peripheral and central neuropathic pain, and fibromyalgia with an accepted dosage range of 150 to 600 mg/day [2]. Pregabalin was classified as schedule V of the Controlled Substances Act in 2005 in the USA [3]. Pregabalin use as an addictive disorder is arising public health issue in the Middle East region, whether alone or with other substances. Use of pregabalin might warrant clinical attention during the health care of patients with substance use disorders or patients with risk factors for an addictive disorder [4]. Pregabalin misuse disorder is at the fourth rank between all substances misused in Egypt, with a percentage of 30%. The prevalence of pregabalin misuse disorder in males is more frequent than females. Pregabalin misuse is more prevalent among young people than in older age. Egyptian community needs more attention from family, educational, and health institutes for prevention and treatment of pregabalin abuse [5]. Recently in Egypt, ministry of health put pregabalin as schedule III of the controlled substance act. It was scheduled because the percentage of patients reporting euphoric effects was significantly greater than those receiving placebo [6]. There are published reports about the potential of novel antiepileptic drugs to induce suicidal behaviors and self-harm in epilepsy and of antiepileptic drugs generally when used in other disorders [7]. A recent study from Sweden indicates that gabapentinoid users have an increased risk of suicidal behavior, unintentional overdoses, road traffic incidents, offences, and head/body injuries [8]. Another recent study on pregabalin abuse in chronic pain patients found suicidal ideation in 39.2% as a clinical symptom of pregabalin abuse in Egypt [9]. Compared to the general population, subjects with alcohol use disorders are almost 10 times more likely to die by suicide and those who inject drugs are about 14 times more likely to commit suicide. Substance-dependent individuals entering into treatment are at elevated risk for suicide attempts for various reasons. They often enter with depressive symptoms and a number of severe stressors (relationship loss, job loss, health, and financial problems) that not only impel them to seek treatment but also put them at higher risk for suicidal behavior. Thus, suicidal behavior is a very significant problem in addiction treatment and should be assessed and treated along with the addiction. For this reason, suicide needs more clinical and research attention in the addictions field [10]. Addiction treatment providers should be prepared to

routinely gather information about client's suicidal histories, thoughts, and plans and determine if important risk factors are present in order to assess suicidality at various points in treatment. In general, the greater the burden of risk factors, the more likely suicidal behavior will manifest. However, there are also protective factors that mitigate suicide risk and it is important to identify those factors [11]. Suicide does not just occur in high-income countries, but is a global phenomenon in all regions of the world. In fact, over 79% of global suicides occurred in low- and middle-income countries in 2016 [12]. In this study, we intended to assess suicidal ideation and behavior in patients with substance abuse disorder related to pregabalin and to identify the effects of other associated substances of abuse and their clinical correlates.

Methods

Study site, design, and participants

This descriptive cross-sectional study was done at the addiction outpatient clinic of El Khanka Psychiatric Hospital in Egypt from March 2020 to February 2021. The sample size was 83 consecutively recruited subjects with substance abuse disorder related to pregabalin. This number was calculated by the OPEN EPI software package [13]. Assuming that the total number of patients with substance abuse disorder related to pregabalin was 120 patients and prevalence of suicidal ideation and behavior is 22% so sample size was 83, at confidence level 95% and power 80%. Inclusion criteria were as follows: participants had to fulfill the DSM IV criteria for substance abuse disorders "related to pregabalin" or within 1 month of abstinence and asked for treatment at the addiction clinic, the age was ranged from 18 to 60 years and both sexes were included. Exclusion criteria were as follows: intellectual disability, dementia, delirium, epileptic disorders, other neurological disorders, severe withdrawal or intoxication symptoms [e.g., delirious state, unstable vital signs, agitation or positive psychotic features], psychiatric disorders (except for major depression disorder, generalized anxiety disorder borderline personality disorder and antisocial personality disorder), and chronic debilitating medical diseases. We determined subjects who were eligible for the study and explained our study's aims and procedures to them and an informed consent was obtained before enrolling in the study.

Study tools

Participants were evaluated using the following measures:

- (1) The semi-structured interview designed to collect and identify the following: (a) sociodemographic data including age, sex, occupation, education, soci-

oeconomic level, marital status, residence, and cigarette smoking (number per day and duration); (b) clinical assessment of patients, history of pregabalin abuse including daily dose, maximum dose, duration, causes of abuse, last dose, presence of pain, monosubstance or polysubstance, and continuous or intermittent course; (c) history of other substances' abuse as type, dose per day, duration, and route. These substances including alcohol, cannabis, tramadol, heroin, benzodiazepine, and others; (d) past history of any suicidal attempts.

- (2) The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [14] used to diagnose patients with substance abuse disorder "related to pregabalin." The basic procedure involves the interviewer reading the SCID-1 questions to the subject in sequence, the goal being to elicit the necessary information to allow the interviewer to decide whether the individual DSM-IV criterion was met or not. The Arabic version of the SCID I used in this study was converted and validated by prior studies undertaken at the Institute of Psychiatry, Ain Shams University [15].
- (3) Beck Suicidal Ideation Scale is a 19-item clinical research instrument designed to quantify and assess suicidal intention. Each statement group consists of three sentences that describe different intensities of suicidal ideation, representing three point scale (0 to 2) the total score can range from 0 to 38 with higher values indicating a greater risk of suicide. No specific cut-off scores exist to classify severity or guide patient management. Increasing scores reflect greater suicide risk, and any positive response merits investigation. The scale was found to have high internal consistency and moderately high correlations with clinical ratings of suicidal risk and self-administered measures of self-harm. Its construct validity was supported by two studies by different investigators [16].
- (4) Urine screening test: urine samples were collected after the session of assessment. Urine specimens in clean and dry plastic containers at room temperature were screened using a rapid, one-step screen test for the simultaneous, qualitative detection of multiple drugs and metabolites in human urine in vitro. The Multi Drug One Step Screen Test Panel (urine) is a lateral flow chromatographic immunoassay for the qualitative detection of the following seven drugs without the need for instruments: (amphetamines, barbiturates, benzodiazepines, cocaine, heroin, tetrahydrocannabinol (THC), and tramadol). We also used Right Sign screen test to search for pregabalin in urine samples

Statistical analysis

SPSS program version 27 was used for statistical analysis [17]. Tables were used to display the information. The mean, median, standard deviation, and range were used to present quantitative results. Frequencies and proportions were used to present qualitative results. The Shapiro-Wilk test was used to assess the variance homogeneity and distribution properties of variables. To evaluate qualitative variables, Pearson's chi-squared test, Fisher's exact test, and chi-square for linear trend were used as required. The Mann-Whitney *U* (MW) test and the Student *t* test were used to compare quantitative variables between two classes, as indicated. A *P* value of < 0.05 was considered statistically significant [18]

Results

The age of the studied group ranged from 20 to 56 years with mean 32.61 years. Regarding sex, almost all of them were male (96.4%). About 72% of them were resident in urban area and 53% of them were married. Regarding education and occupation, 37.5% had moderate education and 69.9% of them were skilled workers. Low and moderate social classes were founded among 54.2% and 45.8% respectively. Finally, almost all of them were smoker (98.8%) with median duration 16.5 years and median 20 cig./day (Table 1).

The median duration of pregabalin abuse was 24 months. The median daily dose and maximum daily dose was 1500 mg. Median of days since last dose were taken was 15 day. About 86.7% of them used pregabalin continuously and 79.5% had it with other substances. Most frequent cause for addiction was as a replacement of heroin (59%). Pain was reported in 51.8% of them and +ve urine test in 27.7% (Table 2).

About 65% of participants used cannabis with median dose 5 cig/day for median 9.5 years duration, 67.4% used tramadol with median dose 950 mg/day for median 7 years duration, 66.3% used heroin with median dose 3 gm/day for median 4 years duration, 27.7% used benzodiazepine with median dose 8 mg/day for median 3 years duration, and 44.6% used other substances (most frequent was conventin) for median 6 months duration. Urine test was +ve in 62.7% of the studied group (most frequent was heroin and cannabis 41% and 34.9% respectively) (Table 3).

About 67% had no risk of suicide ideation, 19.3% had low risk and 13.3% had high risk according to Beck Suicidal Ideation Score (Table 4).

There was significant increase of suicidal ideation among subjects with continuous course of pregabalin abuse comparable to those with intermitting course. Also there was increase of suicidal ideation among subjects

Table 1 Demographic characteristics of the studied group

Variable	(n = 83)	
Age	Mean ± SD	32.61 ± 7.07
	Range	20–56
Variable	No	%
Sex	Male	80 96.4
	Female	3 3.6
Residence	Urban	60 72.3
	Rural	23 27.7
Marital status	Single	34 41
	Married	44 53
	Widow	1 1.2
	Divorced	4 4.8
Education	Illiterate	22 26.5
	Read and write	22 26.5
	Moderate	31 37.3
	High	8 9.6
Occupation	Not working	8 9.6
	Skilled	58 69.9
	Employee	14 16.9
	Student	1 1.2
	Professional	1 1.2
	Other	1 1.2
Social class	Low	45 54.2
	Middle	38 45.8
Smoking	No	1 1.2
	Yes	82 98.8
Duration of smoking (years)	Median (IQR)	16.5 (11.75–22.25)
No. of cig/day	Median (IQR)	20 (20–40)

SD stander deviation, IQR interquartile range

with positive urine test comparable to those negative urine test (Table 5).

There was a statistical significant positive correlation between Beck Suicidal Ideation score and duration of pregabalin abuse, maximum and daily dose of pregabalin (Table 6).

There was a statistical significant relation between suicidal ideation and tramadol addiction among the studied group (Table 7).

There was a statistical significant positive correlation between Beck Suicidal Ideation score and both dose and duration of tramadol abuse (Table 8).

Discussion

In our study, we found that most of participants used pregabalin in a continuous course (86.7%). This may be due to its cheap price and its euphoric effect. Also, our results revealed that 79.5% of the patients abused pregabalin with other substances. Close to our results, Lancia et al. who found that pregabalin was frequently combined with other substances mostly opiates [19]. This result agree with Al-Husseini et al. 2017 who reported that pregabalin abuse is common among cigarette smokers and poly-drug users [20]. This can be explained some pregabalin abusers mix it with other drugs like tramadol and synthetic cannabinoid to potentiate its effect [9].

In our study, we found that our participants took other substances, 67.4% of them received tramadol, heroin 66.3%, cannabis 65.1%, other drugs (most frequent was conventin) 44.6%, and benzodiazepines 27.7%. Screening urine test was positive in 62.7% of

Table 2 Characteristics of pregabalin abuse among the studied group

Variable	(n = 83)	
Duration (months)	Median (IQR)	24 (12–36)
Maximum dose (mg)	Median (IQR)	1500(750–1500)
Daily dose (mg)	Median (IQR)	1500(750–1500)
Last dose since (day)	Median (IQR)	15(4–30)
Variable	No	%
Course	Continuous	72 86.7
	Intermittent	11 13.3
Type of addiction	Mono	17 20.5
	Poly	66 79.5
Cause of abuse	Replacement of heroin	49 59
	Replacement of tramadol	26 31.3
	For its euphoric and analgesic effect	8 9.6
Pain	No	43 51.8
	Yes	40 48.2
Urine test	–ve	60 72.3
	+ve	23 27.7

IQR interquartile range

Table 3 Characteristics of other substances of abuse among the studied group

Variable	(n = 83)		
		No	%
Cannabis (smoking)	Yes	54	65.1
Dose (cig)	Median (IQR)	5(4–10)	
Duration (years)	Median (IQR)	9.5(5–14)	
Tramadol (oral)	Yes	56	67.4
Dose (mg)	Median (IQR)	950(232.25–2250)	
Duration (years)	Median (IQR)	7(4–11)	
Heroin	Yes	55	66.3
Route	Sniff	23	41.8
Dose (gm.)	IV	32	58.2
Duration (years)	Median (IQR)	3(2–5)	
	Median (IQR)	4(2–9)	
Benzo (oral)	Yes	23	27.7
Dose (mg)	Median (IQR)	8(4–20)	
Duration (years)	Median (IQR)	5(3–10)	
Other	Yes	37	44.6
Type	Conventin (oral)	18	21.7
	Gabamash (oral)	4	4.8
	Gabtin (oral)	1	1.2
	Gak 300 mg (oral)	1	1.2
	Parkinol (oral)	1	1.2
	Powder (Sniff)	1	1.2
	Rometril (IV)	1	1.2
	Shadow (Sniff)	1	1.2
	Snappgab (oral)	1	1.2
	Strox (Sniff)	4	4.8
	Tusskan (oral)	4	4.8
Duration (duration)	Median (IQR)	6 months (5 months–1 year)	
Urine test	–ve	31	37.3
	+ve	52	62.7
	Opioid	34	41
	Benzo	7	8.4
	Cannabis	29	34.9
	Tramadol	12	14.5

IQR interquartile range

Table 4 Suicidal ideation among the studied group

Variable	(n = 83)	
Beck Suicidal Ideation	Mean ± SD	5.46 ± 8.86
	Median (IQR)	0(0–12)
	Range	0–32
	No risk, N (%)	56 (67.6%)
	Score = 0	
	Low risk, N (%)	16 (19.3%)
	Score(7–19)	
	High risk, N (%)	11 (13.3%)
	Score (20–32)	

SD stander deviation, IQR interquartile range

participants most frequently was heroin 41% and cannabis 34.9%. In line with our results, numerous studies found that pregabalin was frequently combined with other drugs but mostly opiates [21, 22]. In contrast to our result Gabr found that heroin was not commonly abused with pregabalin 6.5% [5], and these differences may be due to different targeted population.

According to Beck Suicidal Ideation Scale, our finding showed that 67.6%of participants had no suicidal ideations but 19.3% of them had low risk of suicide and 13.3 had high risk of suicide so total participants who had suicidal ideation were 32.6%. Close to our result, Hashish and Awad found that suicidal ideation in pregabalin

Table 5 Relation between suicidal ideation and pregabalin abuse among the studied group

Variable	N	No risk (n = 56)		Low risk (n = 16)		High risk (n = 11)		χ^2	P	
		No	%	No	%	No	%			
		Continuity	Continuous	72	45	62.3	16			22.2
	Intermittent	11	11	100	0	0	0	0		
Type of addiction	Mono	17	13	76.5	2	11.8	2	11.8	0.92	0.63
	Poly	66	43	65.2	14	21.2	9	13.6		
Cause of abuse	Replac. of heroin	49	35	71.4	9	18.4	5	10.2	2	0.74
	Replac. of tramadol	26	15	57.7	6	23.1	5	19.2		
	For its euphoric and analgesic effect	8	6	75	1	12.5	1	12.5		
Pain	No	43	30	69.8	9	20.9	4	9.3	1.25	0.54
	Yes	40	26	65	7	17.5	7	17.5		
Urine test	-ve	60	46	76.7	10	16.7	4	6.7	10.57	0.005
	+ve	23	10	43.5	6	26.1	7	30.4		

χ^2 chi-square test, NS non-significant ($P > 0.05$)

*Significant ($P < 0.05$)

Table 6 Correlation between Beck Suicidal Ideation and different parameters of pregabalin abuse among studied group

Variable	Beck Suicidal Ideation (n = 83)	
	R	P
Age (years)	- 0.06	0.57 NS
Duration of smoking (years)	0.02	0.88 NS
No of cig/day	0.04	0.74 NS
Duration of pregabalin (months)	0.31	0.03 *
Maximum dose (mg)	0.22	0.04*
Continuous daily dose (mg)	0.21	0.05*
Last dose since (day)	- 0.02	0.84 NS

r Spearman's correlation coefficient. NS non-significant ($P > 0.05$)

*Significant ($P < 0.05$)

**Highly significant

abuse group was 39.2% [9]. Pregabalin decreases the serotonin level and this may be responsible for suicidal ideation and self-harm [23]. Acute and chronic drug abuse may impair judgment, decline impulse control, and interrupt neurotransmitter pathways, leading to suicidal tendencies through disinhibition [24].

Our result revealed that there was statistical significant increase in risk of suicide among patients who were continuously abusing pregabalin and who had positive pregabalin urine test. In line with our result, Tandon et al. reported a case of pregabalin-induced suicidal ideation and behaviors after continuous use of pregabalin. The probable mechanism explained for the self-harm behavior is the reduction of serotonin by pregabalin [23].

In our study, there was significant positive correlation between Beck suicidal ideation score and duration of pregabalin abuse, maximum and daily dose. In line with this result, Andersohn et al. (2010) present a case of dose-dependent pregabalin-induced suicidal ideations. They found that increasing the treatment with pregabalin at a dosage of 600 mg lead to suicidal ideation experienced by the patient. After reducing the dosage to 300 mg/day, the suicidal thoughts disappeared completely. They propose a dose-dependent effect of pregabalin to induce suicidal ideation. They report that pregabalin may have a potential for inducing suicidal ideations, which was a dose-dependent effect in their case [25]. Another study confirmed our result, revealed that after the beginning of pregabalin, the patients reported changes in mood, and development of depression and/or suicidal ideation, which improved with decreasing the dose of pregabalin [26]. Our results revealed that there was significant positive relation between suicidal ideation and tramadol addiction and there was a positive statistical significant correlation between beck suicidal ideation score and both the dose and the duration of tramadol abuse. In line with our result, Artenie et al. (2014) revealed that the main risk factor for suicide attempt among addict was increase duration of substance use [27]. Another study confirmed our result, revealed that the duration of tramadol use could be considered a strong risk factor for suicide, as increasing the duration of tramadol results in increasing suicide risk [28]. The effects of comorbid psychiatric disorders including major depression disorder, generalized anxiety disorder

Table 7 Relation between suicidal ideation and abuse of other substances among the studied groups

Variable	N	No risk (n = 56)		Low risk (n = 16)		High risk (n = 11)		χ^2	P	
		No	%	No	%	No	%			
		<i>Cannabis:</i>	No	29	17	58.6	8			27.6
	Yes	54	39	72.2	8	14.8	7	13		NS
<i>Tramadol</i>	No	27	23	85.1	2	7.4	2	7.4	4.32	0.03*
	Yes	56	33	58.8	14	25	9	16		
<i>Heroin</i>	No	28	18	64.3	6	21.4	4	14.3	0.20	0.91
	Yes	55	38	69.1	10	18.2	7	12.7		NS
<i>Benzo</i>	No	60	41	68.3	11	18.3	8	13.3	0.13	0.94
	Yes	23	15	65.2	5	21.7	3	13		NS
<i>Other</i>	No	46	29	63	12	26.1	5	10.9	3.22	0.20
	Yes	37	27	73	4	10.8	6	16.2		NS
<i>Urine test</i>	-ve	31	21	67.7	5	16.1	5	16.1	0.56	0.75
	+ve	52	35	67.3	11	21.2	6	11.5		NS

χ^2 chi-square test, NS non-significant ($P > 0.05$)

Table 8 Correlation between Beck Suicidal Ideation and different parameters of other substances of abuse among the studied group

Variable	Beck Suicidal Ideation (n = 83)	
	R	P
Cannabis dose (cig)	- 0.03	0.83 NS
Cannabis duration (years)	0.12	0.40 NS
Tramadol dose (mg)	0.26	0.04*
Tramadol duration (years)	0.24	0.04*
Heroin dose (gm)	0.20	0.07 NS
Heroin duration (years)	0.19	0.08 NS
Benzo dose (mg)	- 0.06	0.78 NS
Benzo duration (years)	-0.05	0.84 NS
Other duration (years)	-0.13	0.45 NS

r Spearman's correlation coefficient. NS non-significant ($P > 0.05$)

*Significant ($P < 0.05$)

**Highly significant

borderline personality disorder and antisocial personality disorder were studied in another paper under revision of Middle east Current Psychiatry Journal .

Limitations of the study

1. With increased number of our sample size, the association between suicide and pregabalin abuse will be more obvious.

2. We did not assess the bidirectional link between pregabalin abuse and suicide; so, longitudinal studies are recommended to clarify the relation and causality between pregabalin abuse and suicide.

3. Most of our subjects were abusing other substances with pregabalin; future studies with monosubstance abuse of pregabalin were recommended to clarify with more certainty the relation between pregabalin and suicide.

The conclusions

There is a comorbidity between pregabalin abuse and risk of suicidal ideations. This risk is increased with associated tramadol abuse. So, pregabalin abuse is dangerous like other substances of abuse and must be used with caution under strict medical supervision.

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Authors' contributions

AY put the study's design, shared in revising the records to choose the eligible sample, shared in collecting the data, made the final revision of the manuscript, and submitted it. AE and MS shared in revising the records to choose the eligible sample, helped collect and analyze the data, and the drafted the article. All authors agreed with the results and conclusions of this research and approved the final manuscript.

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Availability of data and materials

Upon request.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the Faculty of Medicine, Zagazig University, accepted this study with official permission (ZU-IRB#5952).

We explained the aim of our study, its procedures, and an obligatory "Yes" or "No" inquiry representing the participants' acceptance or refusal to participate

in our research. Only the study researchers could access the participants' personal data, hidden as data were analyzed.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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