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Pregabalin abuse among patients with opioid use disorders may increase the severity of withdrawal symptoms: a single-center, case-control study

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ABSTRACT

OBJECTIVE: Opioid addiction is a disease that is increasing in our country, Turkey, and around the world, which it is difficult to treat in medical, social, and economic terms. Pregabalin is a preparation used for the treatment of epilepsy, neuropathic pain, and anxiety disorders. In opioid users, pregabalin is increasingly being self-administered off-label due to its euphoria effect at high doses. We investigated the effects of pregabalin on addiction profile and opioid withdrawal severity by comparing patients with opioid addiction who were and were not using off-label pregabalin.

METHODS: Between July and August 2016, a total of 120 patients (60 patients were pregabalin users and 60 patients were non-users) who presented to Ankara Numune Training and Research Hospital Psychiatry Clinic Alcohol and Substance Addiction Treatment Center and were diagnosed with opioid use disorder according to the DSM-5, were included in the study. Patients who were using other substances were excluded from the study. A sociodemographic data form, the Clinical Opiate Withdrawal Scale, and Addiction Profile Index (API) were applied to the patients.

RESULTS: There was no statistically significant difference between pregabalin users and pregabalin non-users in terms of age, sex, age of onset, working status, and whether previous treatment had been received. In the pregabalin user group, the severity of opioid withdrawal, API substance use characteristics, diagnosis, effects on life, craving, motivation subscale scores, and API total score were found to be significantly higher than in the non-user group.

CONCLUSION: Off-label pregabalin use among patients with opioid addiction is becoming more common. Off-label, high-dose pregabalin use may worsen existing opioid addiction, create a new area of addiction, and an illegal market.

Highlights

- We aimed to investigate the effects of pregabalin on addiction profile and opioid withdrawal severity by comparing patients with opioid addiction who were and were not using off-label pregabalin.
- In the pregabalin user group, the severity of opioid withdrawal, and API total score were found to be significantly higher than in the non-user group.
- The use of off-label, high-dose pregabalin may worsen existing opioid addiction.

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1. Introduction

“Substance” in terms of “substance abuse” can be defined as any chemical substance that may lead to abuse and addiction, can be taken in different ways, and creates a change in mood, perception, cognition, and other brain functions [1]. Substance addiction can be defined as the loss of control of the individual on substance intake, the placement of the substance in a central position in the life of the individual, and physical and psychological problems related to substance use. The addictive substance affects the brain, causing the desire to take the substance regularly to

relieve restlessness that develops in its absence or to feel pleasure, and is often accompanied by behavioural disorders [2].

Thirty-nine out of every 100,000 deaths worldwide (35 alcohols, 4 illegal substances) are caused by alcohol and substance abuse-related incidents. The prevalence of opioid use among all substances varies between 0.3% and 0.5% worldwide. Many countries report problematic opioid users as “multi-substance users also using opioids” [3]. Opioid addiction is currently seen as a biopsychosocial disorder in which multiple factors interact in terms of initiation, maintenance, and recurrence after treatment phases of substance abuse [4].

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Pregabalin is a gamma-aminobutyric acid (GABA) analogue. Pregabalin reduces the release of numerous neurotransmitters including glutamate, noradrenaline, and substance P [5]. Pregabalin is approved in the United States for the treatment of NeP associated with post-herpetic neuralgia, painful diabetic peripheral neuropathy (pDPN), spinal cord injury, and fibromyalgia. It is also an adjunct therapy for partial onset seizures [6,7].

There are data and increasing numbers of case reports on the increased potential for abuse or addiction of pregabalin, a widely used drug with many indications, in patients with a history of opioid abuse or current opioid addiction [8–16].

Our aim was to investigate patients who presented to Ankara Numune Training and Research Hospital Alcohol and Substance Addiction Treatment and Training Center (AMATEM) Outpatient Clinic and were diagnosed as having opioid use disorder (OUD), and compare patients who used pregabalin despite having no prescription and those who did not use pregabalin, in terms of the severity of opioid withdrawal and addiction.

2. Material and methods

The study comprised 130 patients from the AMATEM Department of Psychiatry clinic of Ankara Numune Training and Research Hospital between July and August 2016. Patients diagnosed with opioid use dependence syndrome according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), who were literate, had no mental retardation, and had no history of head trauma and neurologic disease were included in the study. Sixty-five patients with only opioid abuse were considered as group 1, and 65 patients with opioid and pregabalin abuse were considered as group 2. From group 1, two patients with additional substance use other than nicotine (one had cocaine abuse and the other had alcohol abuse) and three patients with additional psychiatric disorders were excluded. From group 2, three patients with additional substance use other than nicotine (two had alcohol abuse and the other had cannabis abuse) and two patients with additional psychiatric disorders were excluded.

Approval for the study was received from the ethics committee of Ankara Numune Training and Research Hospital (Approval date: 2016, Ethic committee number: E-16-1002). Patients were informed about the study and informed consent was obtained.

A sociodemographic data form and the Addiction Profile Index (API) scale were provided for the patients included in the study, and the scales were completed under the supervision of the responsible researcher. The Clinical Opiate Withdrawal Scale (COWS) was completed by the responsible researcher.

2.1. Addiction profile index (API)

The API is a valid and reliable scale that assesses the extent of problems related to alcohol and substance use, motivation to quit, craving, and severity of addiction [17]. It is a self-report scale consisting of 37 questions and 5 subscales. The subscales measure substance use characteristics, addiction diagnostic criteria, the effect of substance use on a person's life, craving for substance use, and motivation to quit. The substance use characteristics category consists of 12 questions investigating the types of substances and frequencies of use. There are 8 questions in the addiction diagnostic criteria category, 10 in the effect of substance use on the person's life category, four in the craving category, and three in the motivation to quit category [17].

2.2. Clinical opiate withdrawal scale (COWS)

COWS was developed in 2003 to measure the severity of opioid withdrawal in patients with opioid addiction [18]. The scale provides for very rapid evaluation and is sensitive to changes that occur in withdrawal treatment. Therefore, its use has rapidly become widespread. Altıntoprak et al. conducted a study on the validity and reliability of the Turkish version in 2015 [19]. COWS provides a total score by evaluating all symptoms of opioid deprivation and enables physicians to monitor the severity of the person's physical deprivation and the effectiveness of treatment from the beginning. The total score ranges from 0 to 47, with higher scores indicating more severe deprivation. A score of 5–12 indicates mild withdrawal, 13–24 indicates moderate, 25–36 indicates moderate-severe, and more than 36 indicates severe withdrawal [19].

2.3. Statistical analysis

The research data were uploaded to a computer and evaluated using the SPSS for Windows 22.0 software package (SPSS Inc., Chicago, IL). Descriptive statistics are presented as mean \pm standard deviation (minimum-maximum), frequency distribution, and percentage. Pearson's Chi-square test and Fisher's exact tests were used to evaluate categorical variables. The normality of distribution of the variables was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) and it was determined that not all measurement variables were normally distributed. The Mann-Whitney U test was used to compare variables with statistical differences. Statistical significance level was accepted as $p < 0.05$. Effect Size Cohen's d was also calculated [20].

Table 1. Distribution of sociodemographic and clinical characteristics between Pregabalin using and non-using patients with OUD.

	Total (n = 120)	Pregabalin users (n = 60)	Pregabalin non-users (n = 60)	p
Age (years), $\bar{X} \pm S$	24.13 \pm 4.57	24.18 \pm 4.49	24.08 \pm 4.68	0.833**
Marital Status#, n (%)				
Married	24 (20.0)	13 (21.7)	11 (18.3)	0.648
Single/Divorced/Widow(er)	96 (80.0)	47 (78.3)	49 (81.7)	
Years of Education, $\bar{X} \pm S$	8.91 \pm 1.60	8.92 \pm 1.72	8.90 \pm 1.48	0.653**
Occupational Status, n (%)	55 (45.8)	23 (38.3)	32 (53.3)	0.099
Occupational Functionality (n = 118), n (%)				
Never worked because of addiction	8 (6.8)	3 (5.0)	5 (8.6)	0.151
Could not get a job, worked for a while, then did not work	21 (36.2)	33 (55.0)	21 (36.2)	
Has acquired a profession, works from time to time due to addiction, but continues to work	17 (29.3)	16 (26.7)	17 (29.3)	
Has acquired a profession and always worked	15 (25.9)	8 (13.3)	15 (15.9)	
Applying to hospital, n (%)	108 (90.0)	54 (90.0)	54 (90.0)	0.999
Number of hospitalizations $\bar{X} \pm S$	1.58 \pm 0.79	1.57 \pm 0.66	1.60 \pm 0.91	0.735**

n: Patient number; %: Column percentage; \bar{X} : Mean; S: Standard deviation; #Single, divorced and widow(ers) were combined and included in the analysis; *Chi-Square test; **Mann-Whitney U test; OUD: Opioid use disorder.

Table 2. Distribution of addiction profile index and clinical opioid withdrawal scale scores and levels between pregabalin users and non-users with OUS.

	Total (N = 120)	Pregabalin users (n = 60)	Pregabalin non-users (n = 60)	p**	Effect Size Cohen d
COWS , $\bar{X} \pm S$	23.84 \pm 4.52	25.00 \pm 5.00	22.68 \pm 3.68	0.002	0.528
Poverty Severity According to COWS , n (%)					
Moderate withdrawal	63 (52.5)	21 (35.0)	42 (70.0)	<0.001*	
Moderate-severe withdrawal	57 (47.5)	39 (65.0)	18 (30.0)		
API , $\bar{X} \pm S$					
Substance use property	3.34 \pm 0.53	3.47 \pm 0.56	3.20 \pm 0.46	<0.001	0.527
Diagnosis	18.23 \pm 2.20	19.45 \pm 1.40	17.02 \pm 2.19	<0.001	1.224
Effects on life	29.75 \pm 4.51	32.38 \pm 3.09	27.12 \pm 4.17	<0.001	1.433
Craving	14.60 \pm 1.37	15.20 \pm 0.78	14.00 \pm 1.56	<0.001	0.973
Motivation	11.67 \pm 0.94	11.95 \pm 0.39	11.38 \pm 1.21	0.001	0.634
TOTAL	15.22 \pm 1.23	16.00 \pm 0.65	14.44 \pm 1.17	<0.001	1.654

n: Patient number; %: Column percentage; \bar{X} : Mean; S: Standard deviation; COWS: Clinical opioid withdrawal scale; API: Addiction profile index *Chi-Square test; **Mann-Whitney U test; OUD: Opioid use disorder, Effect size: Cohen d.

3. Results

One hundred twenty male patients with OUD were enrolled in the study. All participants in this study used cigarettes. No statistical differences were found in terms of age, marital status, years of education, occupational status, occupational functionality, previous presentation to any AMATEM clinic, and number of hospitalizations to any AMATEM clinic between the pregabalin user and non-user groups ($p > 0.05$) (Table 1).

There was a statistically significant difference between pregabalin users and non-users in terms of API subscale scores and API total scores, and COWS score and severity of withdrawal ($p < 0.05$). The COWS score and API substance use characteristics, diagnosis, effects on life, craving, motivation subscale scores, and API total score were significantly higher in pregabalin users than in non-users. Effect sizes were above the recommended level (≥ 0.5) for the clinical studies (Table 2).

4. Discussion

Although it is widely used, there are clinical observations that pregabalin is used outside the current indications without the recommendations of physician. Pregabalin

was reported as having very low abuse potential in pre-marketing studies and had a very limited potential for developing addiction even when abused [21]. Pregabalin is also classified as Class V (i.e. with low potential for developing addiction) in the United States according to Controlled Substance Act Scheduling [22]. Despite this early knowledge, in recent years, there are data on the potential for abuse or addiction in patients with a history of opioid abuse or those with current opioid addiction, and there have been increasing numbers of case reports showing examples of pregabalin abuse and addiction [8–16].

The COWS scores of the patients using pregabalin were significantly higher than those who are not using pregabalin. These scores indicate that opioid abusers with addicts who use pregabalin experience more severe withdrawal symptoms. The dose range of pregabalin for use in indications such as neuropathic pain, epilepsy, and anxiety disorders is recommended to be a maximum of 600 mg, and studies on its effects have been conducted according to this dose range [23]. The use of the preparation between 3 and 10 times the maximum dose recommended for opioid users may cause the expected effects and adverse effects to vary.

The reason for this may be distressed or restless mood in the pregabalin group due to not using pregabalin in the last 24 h. From a different perspective, the increase in the severity of addiction as a result of the euphoric and anxiety-relieving effects that may reinforce pregabalin addiction may be the reason for the higher COWS scores in pregabalin users.

Similarly, in this study, API total scores and all subscale scores were significantly higher in pregabalin using patients than in non-users. API is a valid and reliable scale for the assessment of the extent of addiction-related problems, motivation to quit, craving, and addiction severity in alcohol and drug addicts; therefore, the significantly higher API total scores and all subscale scores in pregabalin users than in non-users suggest that patients with opioid dependence using pregabalin had more severe addiction than those not using pregabalin [17].

There are studies in the literature showing that pregabalin abuse is present in patients with opioid dependence [24]. In addition to these data, there is a case report showing that pregabalin reduces opioid withdrawal symptoms, and findings reported that pregabalin is an effective, safe, and tolerable molecule for use in the treatment of opioid withdrawal symptoms [25,26]. In addition, the dose-dependent (100 and 200 mg doses) use of pregabalin in rats has been shown to reduce tolerance to the analgesic effect of morphine and opioid withdrawal symptoms induced by naloxone, and prevent morphine addiction [27]. There are also studies reporting that using high doses of pregabalin may cause withdrawal symptoms. Accompanied by these findings, although pregabalin is used as a self-medication to alleviate symptoms such as pain, restlessness, and anxiety by opioid users, it may negatively affect the existing opioid dependence. Related to that point, pregabalin itself might even have a distinct addictive potential [11].

The development of tolerance to opioids and opioid addiction is complex and has many different aspects, and the causative mechanisms are not well understood. However, neurotransmitters such as glutamate and GABA may be potential candidates for explaining these mechanisms through direct or indirect effects [28–31]. Pregabalin is a new molecule that does not directly affect GABA-a or GABA-b receptors, increases GABA synthesis by acting on the glutamate-GABA cycle, and it has been shown in many studies that the GABA agonist effect reduces the tolerance and addiction of opioid analgesics [29,32–36]. It has been suggested that regulation of dopamine in the mesolimbic region might affect morphine addiction and tolerance.

One of the rare adverse effects of pregabalin is dose-dependent mild euphoria [37]. Indeed, the most pronounced effect indicated by users in case reports about abuse is the euphoric effect of the drug, which is thought to increase the risk of pregabalin abuse [11,12,15,38].

This effect of pregabalin (1–10%) is expressed by more patients compared with placebo (0.5%).

Although the drug product information indicates that the potential for the euphoric effect of pregabalin at the recommended dose is low, the mean pregabalin use of the subjects included in this study was 860 mg/day, and increased up to 1500 mg/day. It can be predicted that this high dose of pregabalin, which is well above the recommended dose, increases the euphoric effect.

In light of the findings identified in this study and the available literature data mentioned above, patients with opioid addiction who use pregabalin without a recommendation/prescription by a physician were found to have more severe addiction and more intense withdrawal symptoms than patients who were not using pregabalin.

Although there is evidence that pregabalin reduces opioid withdrawal symptoms, it can be said that the illegal use/abuse of pregabalin in this patient group without physician's advice, as evidenced by increasing data in recent years, may lead to more severe symptoms of addiction and withdrawal.

4.1. Limitations

Although the sample number was sufficient in terms of statistical concerns, increasing the sample size would increase the power of the study. The non-inclusion of female patients is also a limitation. The dose-dependent effects of using off-label, high-dose pregabalin could also have been examined in our study.

5. Conclusion

This study is the first to investigate the effect of pregabalin use with opioids on addiction severity in patients with OUD. According to the findings of this study, patients with opioid dependence who use pregabalin without the recommendation/prescription by a physician, have more severe dependence than patients who do not use pregabalin and experience more intense withdrawal symptoms when pregabalin is discontinued. Therefore, physicians should be alert to pregabalin use and advise patients that concurrent use/abuse of pregabalin will exacerbate/worsen withdrawal symptoms. There is also a need for prospective studies to examine the effects of high-dose pregabalin on opioid users.

Disclosure statement

No potential conflict of interest was reported by the authors.

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