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Abuse and addiction in gabapentinoid drug users for neuropathic pain

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Abstract. – OBJECTIVE: Gabapentinoids are gamma-aminobutyric acid analogue agents used in the treatment of neuropathic pain. They are increasingly being abused to achieve euphoric and dissociative effects. This study aimed to determine drug misuse/abuse and related factors in patients who used gabapentinoids for neuropathic pain.

PATIENTS AND METHODS: This study included 140 patients over the age of 18. Patients were excluded from the study if they had aphasia, dementia, or diseases that led to aphasia or cooperative and cognitive dysfunction. They were also excluded if they lacked sufficient information about how long or at what dosage they had been using the drug.

The Beck Depression Inventory and Beck Anxiety Inventory were used to evaluate depression and anxiety states. The patients' levels of drug abuse were determined according to the definitions provided in the terminology for misuse, abuse, and related events.

RESULTS: The mean age of the patients was 56.78 ± 14.45 years, and 52.1% of them were females. While 57.9% of the patients used pregabalin, 42.1% of the patients used gabapentin. For the median (min-max) of the dataset, the pregabalin dose was 300 (50-600) mg/day, and the gabapentin dose was 900 (300-2,400) mg/day. Abuse was present in 17.9% of the patients. Risk factors for gabapentinoid abuse were smoking, alcohol, and antidepressant use, anxiety and depression, living alone, and drug dose and duration of use.

CONCLUSIONS: Before prescribing drugs and managing the treatment process in a controlled manner, questioning patients about their risk factors can reduce the rate of abuse.

Key Words:
Gabapentinoids, Pregabalin, Gabapentin, Abuse, Addiction.

Introduction

Neuropathic pain develops after neuron damage and/or undesirable changes to damaged neurons in the nociceptive and descending modulatory pathways of the central nervous system. Recommended pharmacotherapy for neuropathic pain includes the use of tricyclic antidepressants. Certain antidepressants, such as serotonin/noradrenaline reuptake inhibitors and anticonvulsants, such as gabapentinoids (e.g., gabapentin and pregabalin)[1].

Gabapentinoids are structurally similar to gamma-aminobutyric acid (GABA), but they have no effect on GABA receptors, GABA synthesis, or metabolism[2]. These drugs selectively bind to the α 2-δ subunit of voltage-gated calcium channels in the neuronal tissues of the central nervous system and inhibit the release of excitatory transmitters, such as glutamate and norepinephrine. In this way, they show antinociceptive, anticonvulsant, and anxiolytic effects[3].

Gabapentinoids (pregabalin and gabapentin), initially anticonvulsants, are now widely prescribed in physical medicine and rehabilitation clinics due to their proven efficacy in treating neuropathic pain caused by fibromyalgia, radiculopathy, and polyneuropathy. However, both drugs have recently been reported[4] to show potential for abuse. Gabapentinoids cause a dose-dependent increase in the level of extracellular GABA in the brain, resulting in weak GABAmimetic effects, such as relaxation and euphoria[2]. While gabapentinoids have low addictive potential at therapeutic doses, they can be abused for euphoric and dissociative effects, similar to those of recreational drugs[5].

We conducted this study for several reasons. Firstly, we wanted to raise awareness among prescribers and users about the potential harms associated with these drugs. Secondly, we aimed to identify patients who are at high risk of abusing these drugs. Thirdly, we intended to follow up on these patients and provide them with controlled drug use. Finally, we sought to collect data that can guide healthcare providers on how to reduce and discontinue the use of these drugs.

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Before the abuse potential of drugs becomes a public health problem, it is necessary to identify and take precautions[6]. As such, this study aimed to determine drug abuse and abuse-related factors in patients who applied to physical medicine and rehabilitation clinics and used gabapentinoids for neuropathic pain.

Patients and Methods

After participant consent was obtained, this study included 140 patients over the age of 18 who applied to physical medicine and outpatient rehabilitation clinics and used gabapentinoid drugs. Patient interviews were conducted by the physicians participating in the study. Patients were excluded from the study if they had aphasia, dementia, diseases that led to aphasia, cooperative and cognitive dysfunction, or insufficient information about how long and at what dose they had been using the drug. The demographic and clinical characteristics of the patients (diagnosis, duration of drug use, drug dose used, drug report, drug side effects, etc.) were recorded.

The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were used to evaluate depression and anxiety states. Both scales have Turkish validity and reliability studies. The BDI is a self-administered questionnaire with a total score between 0 and 63, and it is the validated Turkish version of 21 items[7,8].

The BAI is a 21-item Likert-type scale that contains a total score range of 0-63. This scale assesses the anxiety symptoms experienced by an individua[19]. Scores from 10-18 indicate mild to moderate anxiety, scores from 19-29 indicate moderate to severe anxiety, and scores from 30-63 indicate severe anxiety. The Turkish version of the BAI was validated by Ulusoy et al[10].

The therapeutic use, misuse, abuse, and addiction status of the patients was determined according to the definitions in the misuse, abuse, and related events (MARE) terminology. The MARE terminology was established for medico-legal and regulatory practices, epidemiological research, patient care, research purposes, and the diagnosis of clinical diseases, such as substance use disorders. According to this terminology, misuse, abuse, addiction, and dependence definitions are created and used in studies to establish common terminology. Accordingly, misuse occurs when the use of a drug taken for therapeutic purposes does not comply with medical indications or prescribed dosing. Psychotropic or euphoric effects are not considered in the use of the drug. Abuse is defined as the use of a drug for non-therapeutic purposes to achieve psychotropic (i.e., euphoric, sedative, or anxiolytic) effects. Addiction is defined as compulsive drug use that occurs despite personal harm or negative consequences. Dependence is defined as a response to a drug associated with withdrawal symptoms or withdrawal syndrome, resulting in a rapid reduction in exposure to an antagonist[11].

Sample Size Calculation

According to the physical therapy outpatient clinic records of our hospital, the prevalence of patients using gabapentinoid drugs for more than six months due to neuropathic pain was found to be around 5.0%. The formula for the estimation of the appropriate sample size for the prevalence surveys was as follows:

$$n = \frac{(z^2)\ P\ (1-P)}{d^2}$$

This formula was proposed by Arya et al[12]. In the present work, at least 73 individuals had been tested for the null hypothesis, since z = 1.96, P (expected prevalence) = 5.0%, and d (allowable error) = 0.05 were considered to be sufficient parameters.

Statistical Analysis

The continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), and the categorical data were expressed as numbers and percentages. In the intergroup analysis of the continuous variables, normality analyses were performed using the Kolmogorov-Smirnov goodness-of-fit test. In the evaluation of the continuous variables between the two groups, a *t*-test was used if there was a normal distribution, and the Mann-Whitney U test was used if there was not. A Chi-square test (Fisher's exact test when necessary) was used to compare the categorical data. The risk factors for drug abuse and estimated relative risk (odds ratio) values were determined by binary logistic regression (LR) analysis (Enter and Backward: LR). Variables that were significant in univariate analyses were selected for multivariate analysis and evaluated with the multivariable logistic regression model. The Hosmer-Lemeshow test was used for model fit. Analyses were performed with SPSS (Statistics Package Program for Social Sciences) version 22.0

(IBM Corp., Armonk, NY, USA). The statistical significance level was accepted as $p < 0.05$.

Results

Of the patients, 52.1% were females, and the mean age was 56.8 ± 14.5 years; 57.9% were using pregabalin, and 42.1% were using gabapentin. In terms of median (min-max) neuropathic pain, the symptom duration was 60 (9-216) months, drug use was 24 (5-120) months, pregabalin dosage was 300 (50-600) mg/day, and gabapentin dosage was 900 (300-2400) mg/day. Of those included in the study, 45.0% underwent a dose-reduction trial, while 26.4% underwent a quit trial; 73.6% of the participants' usage was considered therapeutic, while 17.9% could be categorized as abuse, 5.7% as misuse, and 2.9% as addictive drug use. The sociodemographic and clinical parameters of the patients are presented in Table I.

When the characteristics of the gabapentin and pregabalin users were compared, the mean age of the gabapentin group (59.7 ± 13.7 years) was significantly higher than that of the pregabalin group (54.6 ± 14.7 years) ($p = 0.038$). In the pregabalin group, the use of antidepressants (44.4%), presence of fibromyalgia (32.1%), duration of drug use [24 (5-120)], Beck Anxiety Inventory scores [20 (0-47)], and Beck Depression Inventory scores [16 (0-40)] were found to be statistically significantly higher than those in the gabapentin group ($p < 0.05$) (Table II).

While smoking was significantly higher in males (45.5%), antidepressant use was significantly higher in females (44.4%). Fibromyalgia was the most common pathology in women (32.9%) and lumbar radiculopathy in men (34.3%) ($p = 0.035$). The duration of the quit attempt (34.2%) and the quit trial (14.4 ± 30.4) in women were found to be significantly higher than in men (17.9% and 7.6 ± 19.4, respectively) ($p = 0.035$ and $p = 0.041$, respectively). The Beck Anxiety Inventory scores [20 (3-44)] were statistically significantly higher in women [20 (3-4)] ($p < 0.05$) (Table III).

When the groups were compared according to therapeutic and drug abuse status, the mean age was statistically significantly lower in drug abusers (51.80 ± 15.98 years) than in those using drugs for therapeutic purposes (59.18 ± 12.60 years) ($p = 0.014$). Drug abuse was significantly higher in those who were single (24.0% *vs.* 2.9%) and widowed (24.0% *vs.* 11.7%) compared to therapeutic use ($p < 0.001$). Smoking (56.0%) and antidepressant use (56.0%) were significantly higher in drug abusers than in therapeutic drug users. The median values of pregabalin and gabapentin [375 (150-600) and 1,500)600-2,400), respectively] as well as the median values of the duration of drug use [54 (12-120)], Beck Anxiety Inventory scores [23 (4-27)], and Beck Depression Inventory scores [22 (3-40)] were significantly higher in the drug abuser group ($p < 0.05$) (Table IV).

The univariate logistic regression analysis identified several risk factors for drug abuse. The results showed that being single (compared to being married) significantly increased the risk of drug abuse by 13.6 times [OR = 13.65, 95% confidence interval (CI) = 3.011-60.875, $p = 0.001$], while being widowed (compared to being married) increased the risk by 3.3 times (OR = 3.38, 95% CI = 1.083-10.583, $p = 0.036$). Living alone (compared to living with others) raised the risk by 11.6 times (OR = 11.64, 95% CI = 1.083-10.583, $p < 0.001$), smoking (compared to not smoking) increased the risk by 3.5 times (OR = 3.58, 95% CI = 1.453-8.843, $p = 0.006$), alcohol use (compared to non-use) increased the risk by 6.9 times (OR = 6.88, 95% CI = 1.085-43.696, $p = 0.041$), and antidepressant drug use (compared to non-use) was also found to be a significant risk factor. It was determined that the use of pregabalin (compared to the use of gabapentin) increased 2.7 times (OR = 2.70, 95% CI = 1.107-6.585, $p = 0.029$), 2.8-fold (OR = 2.87, 95% CI = 1.061-7.779, $p = 0.038$). An increase of 1 mg/day in the pregabalin dose increased the risk for drug abuse 1.01-fold (OR = 1.012, 95% CI = 1.005-1.020, $p = 0.001$). A 1 mg/day increase in the gabapentin dose increased the risk for drug abuse 1.04-fold (OR = 1.004, 95% CI = 1.001-1.001, $p = 0.012$). A one-month increase in the duration of drug use increased the risk for drug abuse 1.05-fold (OR = 1.050, 95% CI = 1.028-1.073, $p < 0.001$). A one-unit increase in the Beck Anxiety Inventory score indicated a 1.06-fold increase in the risk for drug abuse (OR = 1.069, 95% CI = 1.026-1.125, $p = 0.001$), and a one-unit increase in the Beck Depression Inventory score posed a 1.12-fold increase in risk for drug abuse (OR = 1.125, 95% CI = 1.061-1.193, $p < 0.001$). Age and the presence of systemic disease were found to be protective factors for drug abuse. Furthermore, a one-year increase in age increased the risk for drug abuse by 0.9-fold (OR = 0.959, 95% CI = 0.926-0.993, $p = 0.017$) (Table V).

In the multivariate logistic regression model for drug abuse, variables of age, marital status, living alone, systemic disease, smoking, al-

Table I. Some socio-demographic and clinical parameters of the patients.

Parameters	Patient group (n = 140)
Age (years) (Mean ± SD)	56.8 ± 14.5
BMI (kg/m^2) (Mean ± SD)	27.6 ± 4.3
Gender (n, %)	
Female	73 (52.1)
Male	67 (47.9)
Educational status (n, %)	
Primary school	70 (50.0)
Secondary education	50 (40.7)
University	13 (9.3)
Occupational status (n, %)	
Physical	38 (27.1)
Desk-job	35 (25.0)
Housewife	67 (47.9)
Marital status (n, %)	
Single	12 (8.6)
Married	109 (77.9)
Widow	19 (13.6)
Living alone (n, %)	
Yes	15 (10.7)
No	125 (89.3)
Systemic disease (n, %)	
Yes	92 (65.7)
No	48 (34.3)
Smoking (n, %)	
Yes	47 (33.6)
No	93 (66.4)
Alcohol use (n, %)	
Yes	10 (7.1)
No	130 (92.9)
Substance use (n, %)	
Yes	5 (3.6)
No	135 (96.4)
Diagnosis (n, %)	
Cervical radiculopathy	17 (12.1)
Lumbar radiculopathy	47 (33.6)
Fibromyalgia	32 (22.9)
Polyneuropathy	29 (20.7)
Neurological disease	15 (10.7)
Drug used (n, %)	
Pregabalin	81 (57.9)
Gabapentin	59 (42.1)
Pregabalin dose (mg/day) [median (min-max)]	300 (50-600)
Gabapentin dose (mg/day) [median (min-max)]	900 (300-2,400)
Symptom duration (months) [median (min-max)]	60 (9-216)
Medication duration (months) [median (min-max)]	24 (5-120)
Quit trial period (months) (Mean ± SD)	11.2 ± 25.9
Dose reduction trial time (months) (Mean ± SD)	29.6 ± 46.0
Attempt to quit (n, %)	
Yes	37 (26.4)
No	103 (73.6)
Dose reduction trial (n, %)	
Yes	63 (45.0)
No	77 (55.0)
Antidepressant use (n, %)	
Yes	50 (35.7)
No	90 (64.3)
Beck Anxiety Inventory Scores [median (min-max)]	15.5 (0-47)
Beck Depression Inventory Scores [median (min-max)]	15 (0-40)

Table continued

Table I *(Continued).* Some socio-demographic and clinical parameters of the patients.

Parameters	Patient group (n = 140)
MedDRA classification (n, %)	
Therapeutic	103 (73.6)
Misuse	8 (5.7)
Abuse	25 (17.9)
Addiction	4 (2.9)

Table II. Comparison of some sociodemographic and clinical parameters according to the drug group used.

Parameters	Pregabalin group (n = 81)	Gabapentin group (n = 59)	p
Age (years) (Mean ± SD)	54.6 ± 14.7	59.7 ± 13.7	0.038*
BMI (kg/m^2) (Mean ± SD)	27.9 ± 4.3	27.3 ± 4.4	0.485*
Gender (n, %)			
Female	46 (56.8)	27 (45.8)	0.197***
Male	35 (43.2)	32 (54.2)	
Educational status (n, %)			
Primary school	41 (50.6)	29 (49.2)	0.951***
Secondary education	33 (40.7)	24 (40.7)	
University	7 (8.6)	6 (10.2)	
Occupational status (n, %)			
Physical	24 (29.6)	14 (23.7)	0.116***
Desk-job	15 (18.5)	20 (33.9)	
Housewife	42 (51.9)	25 (42.4)	
Marital status (n, %)			
Single	9 (11.1)	3 (5.1)	0.230***
Married	59 (72.8)	50 (84.7)	
Widow	13 (16.0)	6 (10.2)	
Living alone (n, %)			
Yes	13 (16.0)	2 (3.4)	0.017***
No	68 (84.0)	57 (96.6)	
Systemic disease (n, %)			
Yes	50 (61.7)	42 (71.2)	0.244***
No	31 (38.3)	17 (28.8)	
Smoking (n, %)			
Yes	25 (30.9)	22 (37.3)	0.427***
No	56 (69.1)	37 (62.7)	
Alcohol use (n, %)			
Yes	7 (8.6)	3 (5.1)	0.420***
No	74 (91.4)	56 (94.9)	
Antidepressant use (n, %)			
Yes	36 (44.4)	14 (23.7)	0.012***
No	45 (55.6)	45 (76.3)	
Substance use (n, %)			
Yes	5 (6.2)	0 (0.0)	0.073***
No	76 (93.8)	59 (100.0)	
Diagnosis (n, %)			
Cervical radiculopathy	7 (8.6)	10 (16.9)	0.013***
Lumbar radiculopathy	21 (25.9)	26 (44.1)	
Fibromyalgia	26 (32.1)	6 (10.2)	
Polyneuropathy	18 (22.2)	11 (18.6)	
Neurological disease	9 (11.1)	6 (10.2)	
Attempt to quit (n, %)			
Yes	20 (24.7)	17 (28.8)	0.585***
No	61 (75.3)	42 (71.2)	
Dose reduction trial (n, %)			
Yes	38 (46.9)	25 (42.4)	0.594***
No	43 (53.1)	34 (57.6)	

Table continued

Table II *(Continued)*. Comparison of some sociodemographic and clinical parameters according to the drug group used.

Parameters	Pregabalin group (n=81)	Gabapentin group (n=59)	p
Quit trial period (months) (Mean ± SD)	8.6±20.5	14.6 ± 31.7	0.398**
Dose reduction trial time (months) (Mean ± SD)	28.6±43.5	31.0 ± 49.6	0.944**
Symptom duration (months) [median (min-max)]	60 (9-192)	48 (12-216)	0.073**
Medication duration (months) [median (min-max)]	24 (5-120)	18 (6-96)	0.030**
Beck Anxiety Inventory Scores [median (min-max)]	20 (0-47)	13 (4-47)	0.012**
Beck Depression Inventory Scores [median (min-max)]	16 (0-40)	14 (2-39)	0.042**
MedDRA classification (n, %)			
Therapeutic	54 (66.7)	49 (83.1)	0.052***
Misuse	4 (4.9)	4 (6.8)	
Abuse	19 (23.5)	6 (10.2)	
Addiction	4 (4.9)	0 (0.0)	

*t-test in Independent Groups. **Mann-Whitney U-Test. ***Chi-square Test (Fisher's Exact Test).

Table III. Comparison of some sociodemographic and clinical parameters by gender.

Parameters	Female (n = 73)	Male (n = 67)	p
Age (years) (Mean ± SD)	55.7 ± 13.2	58.0 ± 15.7	0.337*
BMI (kg/m^2) (Mean ± SD)	28.8 ± 4.9	26.4 ± 3.2	0.001*
Educational status (n, %)			
Primary school	44 (60.3)	26 (38.8)	0.014***
Secondary education	26 (35.6)	31 (46.3)	
University	3 (4.1)	10 (14.9)	
Occupational status (n, %)			
Physical	9 (12.3)	29 (43.3)	<0.001***
Desk-job	5 (6.8)	30 (44.8)	
Housewife	59 (80.8)	8 (11.9)	
Marital status (n, %)			
Single	4 (5.5)	8 (11.9)	0.367***
Married	59 (79.5)	51 (76.1)	
Widow	11 (15.1)	8 (11.9)	
Living alone (n, %)			
Yes	9 (12.3)	6 (9.0)	0.592***
No	64 (87.7)	61 (91.0)	
Systemic disease (n, %)			
Yes	50 (68.5)	42 (62.7)	0.470**
No	23 (31.5)	25 (37.3)	
Smoking (n, %)			
Yes	12 (16.4)	35 (52.2)	<0.001***
No	61 (83.6)	32 (47.8)	
Alcohol use (n, %)			
Yes	3 (4.1)	7 (10.4)	0.194***
No	70 (95.9)	60 (89.6)	
Antidepressant use (n, %)			
Yes	33 (45.2)	17 (25.4)	0.014***
No	40 (54.8)	50 (74.6)	
Substance use (n, %)			
Yes	3 (4.1)	2 (3.0)	1.000***
No	70 (95.9)	65 (97.0)	
Diagnosis (n, %)			
Cervical radiculopathy	8 (11.0)	9 (13.4)	0.035***
Lumbar radiculopathy	24 (32.9)	23 (34.3)	
Fibromyalgia	24 (32.9)	8 (11.9)	
Polyneuropathy	12 (16.4)	17 (25.4)	
Neurological disease	5 (6.8)	10 (14.9)	
Attempt to quit (n, %)			
Yes	25 (34.2)	12 (17.9)	0.035***
No	48 (65.8)	55 (82.1)	

(Table continued)

Table III *(Continued).* Comparison of some sociodemographic and clinical parameters by gender.

Parameters	Female (n = 73)	Male (n = 67)	p
Dose reduction trial (n, %)			
Yes	34 (46.6)	29 (43.3)	0.696***
No	39 (53.4)	38 (56.7)	
Drug used (n, %)			
Pregabalin	46 (63.0)	35 (52.2)	0.197***
Gabapentin	27 (37.0)	32 (47.8)	
Pregabalin dose (mg/day) [median (min-max)]	300 (50-600)	300 (150-600)	0.816**
Gabapentin dose (mg/day) [median (min-max)]	900 (300-1,200)	900 (300-2,400)	0.315**
Quit trial period (months) (Mean ± SD)	14.4 ± 30.4	7.6 ± 19.4	0.041**
Dose reduction trial time (months) (Mean ± SD)	29.6 ± 50.7	29.6 ± 40.6	0.936**
Symptom duration (months) [median (min-max)]	60 (9-180)	60 (12-216)	0.241**
Medication duration (months) [median (min-max)]	24 (6-120)	24 (5-120)	0.905**
Beck Anxiety Inventory Scores [median (min-max)]	20 (3-44)	14 (0-47)	0.012**
Beck Depression Inventory Scores [median (min-max)]	15 (3-40)	14 (0-37)	0.081**
MedDRA classification (n, %)			
Therapeutic	52 (71.2)	51 (76.1)	0.521***
Misuse	5 (6.8)	3 (4.5)	
Abuse	15 (20.5)	10 (14.9)	
Addiction	1 (1.4)	3 (4.5)	

*t-test in Independent Groups. **Mann-Whitney U-Test. ***Chi-square Test (Fisher's Exact Test).

Table IV. Comparison of some sociodemographic and clinical parameters according to therapeutic use and drug abuse status.

Parameters	Therapeutic drug use (n = 103)	Drug abuse (n = 25)	p
Age (years) (Mean ± SD)	59.2 ± 12.6	51.8 ± 16.0	0.014*
BMI (kg/m^2) (Mean ± SD)	27.9 ± 4.4	26.8 ± 3.8	0.254*
Gender (n, %)			
Female	52 (50.5)	15 (60.0)	0.393***
Male	51 (49.5)	10 (40.0)	
Educational status (n, %)			
Primary school	52 (50.5)	14 (56.0)	0.582***
Secondary education	40 (38.8)	10 (40.0)	
University	11 (10.7)	1 (4.0)	
Occupational status (n, %)			
Physical	24 (23.3)	11 (44.0)	0.107***
Desk-job	27 (26.2)	4 (16.0)	
Housewife	52 (50.5)	10 (40.0)	
Marital status (n, %)			
Single	3 (2.9)	6 (24.0)	< 0.001***
Married	88 (85.4)	13 (52.0)	
Widow	12 (11.7)	6 (24.0)	
Living alone (n, %)			
Yes	4 (3.9)	8 (32.0)	< 0.001***
No	99 (96.1)	17 (68.0)	
Systemic disease (n, %)			
Yes	73 (70.9)	12 (48.0)	0.036***[a]
No	30 (29.1)	13 (52.0)	
Smoking (n, %)			
Yes	27 (26.2)	14 (56.0)	< 0.008***
No	76 (73.8)	11 (44.0)	
Alcohol use (n, %)			
Yes	2 (1.9)	3 (12.0)	0.051***[a]
No	101 (98.1)	22 (88.0)	
Antidepressant use (n, %)			
Yes	33 (32.0)	14 (56.0)	0.026***
No	70 (68.0)	11 (44.0)	

(Table continued)

Table IV. *(Continued).* Comparison of some sociodemographic and clinical parameters according to therapeutic use and drug abuse status.

Parameters	Therapeutic drug use (n=103)	Drug abuse (n=25)	p
Substance use (n, %)			
Yes	1 (1.0)	1 (4.0)	0.354***
No	102 (99.0)	24 (96.0)	
Diagnosis (n, %)			
Cervical radiculopathy	13 (12.6)	2 (8.0)	0.141***
Lumbar radiculopathy	39 (37.9)	5 (20.0)	
Fibromyalgia	18 (17.5)	10 (40.0)	
Polyneuropathy	21 (20.4)	5 (20.0)	
Neurological disease	12 (11.7)	3 (12.0)	
Attempt to quit (n, %)			
Yes	29 (28.2)	5 (20.0)	0.462***[a]
No	74 (71.8)	20 (80.0)	
Dose reduction trial (n, %)			
Yes	47 (45.6)	11 (44.0)	0.883***
No	56 (54.4)	14 (56.0)	
Drug used (n, %)			
Pregabalin	54 (52.4)	19 (76.0)	0.042***
Gabapentin	49 (47.6)	6 (24.0)	
Pregabalin dose (mg/day) [median (min-max)]	300 (50-600)	375 (150-600)	< 0.001**
Gabapentin dose (mg/day) [median (min-max)]	900 (300-1,200)	1,500 (600-2,400)	0.022**
Quit trial period (months) (Mean ± SD)	13.3 ± 29.0	3.3 ± 8.2	0.252**
Dose reduction trial time (months) (Mean ± SD)	33.6 ± 49.6	14.1 ± 27.7	0.245**
Symptom duration (months) [median (min-max)]	60 (9-216)	72 (24-180)	0.216**
Medication duration (months) [median (min-max)]	18 (5-96)	54 (12-120)	< 0.001**
Beck Anxiety Inventory Scores [median (min-max)]	14 (0-40)	23 (4-27)	0.004**
Beck Depression Inventory Scores [median (min-max)]	12 (0-39)	22 (3-40)	< 0.001**

*t-test in Independent Groups. **Mann-Whitney U-Test. ***Chi-square Test (Fisher's Exact Test).

cohol use, antidepressant use, drug type, duration of drug use, Beck Anxiety Inventory score, and Beck Depression Inventory score were included. Of these, age, living alone, duration of drug use, and Beck Depression Inventory score remained significant in the model (Table VI).

Discussion

The misuse and abuse of gabapentinoids appear to have increased in recent years. In the study by Chiappini and Schifano[4], when the misuse, abuse, and addiction reports between 2004 and 2015 were examined, more than 75% of the reports were found to have been published after 2012. The prevalence of the misuse or abuse of gabapentinoids has been shown[13] in Sweden to be 40-65% in prescribed individuals, 15-22% in opioid-abused individuals, and 1% in the general population. In a UK study[14], the lifetime prevalence of misuse was found to be 1.1% for gabapentin and 0.5% for pregabalin. In our study, 73.6% of the patients were therapeutic users of these drugs, while 17.9% abused them, 5.7% misused them, and 2.9% had an addiction to them.

Almost all of the studies in the literature on the abuse of gabapentinoids have been conducted on substance and alcohol users or their records in health databases. A recently published study[15] examined a group of patients with spinal cord lesions who were prescribed gabapentinoids for neuropathic pain symptoms. In this study, abuse was reported at 81.9% for pregabalin and 69.7% for gabapentin. The reasons for such high abuse rates may be that the damage is permanent in patients with spinal cord lesions, neuropathic pain is more common in this patient group. In addition, they benefit more from these drugs, which are used at higher doses, because their pain is more resistant to other treatments.

In literature, drug abusers were identified regardless of the source of the gabapentinoids. In a study[14], in which 1,500 people were evaluated, gabapentinoid abuse was found in 13.1% of those with individual legal prescriptions for the drug.

Evidence suggests that gabapentinoid abuse is more common among patients with substance use disorder, particularly opioid abuse, psychiatric

Table V. Univariate Logistic Regression Analysis to identify risk factors for drug abuse.

	OR	95% CI	p
Age (years)	0.959	0.926-0.993	0.017*
Marital status			
Single	1.0		
Married	13.65	3.011-60.875	0.001*
Widow	3.38	1.083-10.583	0.036*
Living alone			
Yes	1.0		
No	11.64	3.156-42.988	< 0.001*
Systemic disease			
Yes	1.0		
No	0.38	0.155-0.926	0.033*
Smoking			
Yes	1.0		
No	3.58	1.453-8.843	0.006*
Alcohol use			
Yes	1.0		
No	6.88	1.085-43.696	0.041*
Antidepressant use			
Yes	1.0		
No	2.70	1.107-6.585	0.029*
Drug used			
Pregabalin	1.0		
Gabapentin	2.87	1.061-7.779	0.038*
Pregabalin dose (mg/day)	1.012	1.005-1.020	0.001*
Gabapentin dose (mg/day)	1.004	1.001-1.006	0.012*
Medication duration (months)	1.050	1.028-1.073	< 0.001*
Beck Anxiety Inventory Scores	1.069	1.026-1.125	0.001*
Beck Depression Inventory Scores	1.125	1.061-1.193	< 0.001*

*Binary Logistic Regression Test (Enter method). **OR = Odds Ratio, CI = Confidence Interval.

Table VI. Multivariable Logistic Regression Analysis to identify risk factors for drug abuse.

	OR**	95% CI**	p
Age	0.891	0.827-0.960	0.003*
Living alone (yes)	129.85	3.444-4896.519	0.009*
Medication duration (months)	1.073	1.038-1.109	< 0.001*
The Beck Depression Inventory score	1.144	1.052-1.243	0.002*

*Binary Logistic Regression Test (Backward: LR). (Omnibus Tests of Model Coefficients < 0.001, Nagelkerke R Square = 0.727, Hosmer and Lemeshow Test = 0.876). **OR = Odds Ratio, CI = Confidence Interval.

comorbidities, and younger age. It has been reported[16,17] that 15-22% and 3-68% of patients with opioid use disorder abuse gabapentin and pregabalin, respectively. Although concurrent cocaine, benzodiazepine, and cannabis use has been reported, opioid use disorder is known as the most common one associated with gabapanoid abuse[18].

Anxiety has been shown[19] to be an important diagnosis in predicting gabapentinoid abuse without concomitant substance use. In the study by Sason et al[20], the severity of depression was found to be associated with the risk of drug abuse. In addition, diagnoses such as cancer, multiple sclerosis, neuropathy, or personality disorder are thought[21] to increase this risk of drug abuse. In our study, we determined that smoking, alcohol use, and antidepressant use were risk factors for gabapentinoid abuse. Substance use was not found to be a risk factor. We believe that this was due to the small number of patients using substances in our

study. In addition, anxiety and depression levels were significantly higher in the pregabalin users. This group of psychologically sensitive patients may be considered more prone to abuse or addiction. For this reason, patients who are planning to be prescribed gabapentinoids or are using them should be evaluated, especially in terms of anxiety and depression.

The abuse of gabapentinoids typically occurs at supratherapeutic doses (i.e., pregabalin > 600 mg and gabapentin > 3600 mg). Since tachyphylaxis develops rapidly, it has been reported[22] that the dose used is increased in repeated abuses. In our study, abuse and duration of drug use as well as median values of gabapentin and pregabalin doses, were significantly correlated. In addition, abuse was 2.8 times higher in pregabalin users, 13.6 times in singles, 11.6 times in those living alone, 3.3 times in widows, 3.5 times in smokers, 6.9 times in alcohol users, and 2.7 times in antidepressant users. Here, it should be considered that the risk was also higher in those who did not have a supportive family or a supportive environment. In their study, Driot et al[23] showed that more than 10% of gabapentin and pregabalin abusers developed a primary addiction without any other substance-related disorders. They determined that more than 10% of new pregabalin users and 6% of new gabapentin users abused the drug within two years of the first prescription.

Given its faster onset of action, higher bioavailability, and potency, the pharmacokinetics of pregabalin theoretically increase the likelihood of abuse *vs.* gabapentin[24]. Although the adverse effects of gabapentinoid ingestion alone are relatively limited, growing evidence[25] has indicated that when used together, gabapentinoids significantly increase opioid-related morbidity and mortality.

Previous studies[26,27] have confirmed the increased potential for pregabalin abuse and health problems associated with gabapentinoid abuse (hospitalization, dependency support requests, and deaths due to serious neurological, psychiatric, or cardiac effects). Findings[28] that gabapentinoids play a role in fatal poisonings, mostly together with opioids, are proof that more care should be taken in this regard.

For these reasons, the treatment processes of patients using gabapentinoid should be followed closely. After the therapeutic dose is determined, patients should be called for control at regular intervals, and dose adjustments should be made by the physician according to the decrease or increase in symptoms. In our study, the fact that 45% of the patients tried to reduce their dose, 26.4% tried to stop the drug, and the doses used (gabapentin 900 mg, pregabalin 300 mg) were at reasonable therapeutic levels may indicate that physicians are aware of this issue.

The results of a study[29] conducted in New Zealand made the following recommendations: attempt dose reduction in a controlled manner, increase the use of non-pharmaceutical pain management, develop clinical decision-making processes in prescribing gabapentinoids, and try the short-term use of pharmaceutical opioids and benzodiazepines in a controlled manner.

There are several measures that can be taken to reduce the risk of drug abuse. One of the most important is to take advantage of different methods of pain management, rather than relying solely on opioids. When prescribing opioids, it is important to question their use carefully and obtain a thorough medical history from the patient. Patients should be closely followed up in terms of their drug use, and prescribed amounts should be limited when necessary. When a patient's symptoms subside, attempts should be made to reduce or discontinue the dose of opioids, while ensuring that withdrawal symptoms are prevented. By implementing these measures, the risk of drug abuse can be reduced, and patients can receive effective pain management while minimizing the risk of addiction.

Our study identified several risk factors for drug abuse. Participants who were young, single, and lived alone, as well as those who smoked and used alcohol, used antidepressants, experienced increased anxiety and depression levels, and took drugs at higher doses and for longer durations, were found to be at higher risk of drug abuse. Additionally, lack of family support was also identified as a risk factor in our study. Therefore, we recommend that patients are evaluated in terms of these factors before prescribing gabapentinoids. It should also be considered whether the benefits of gabapentinoids outweigh the potential harms.

This study was conducted on patients admitted to the hospital for neuropathic pain and who were prescribed gabapentinoids for therapeutic purposes. In this respect, the strength of our study is that it is the first to evaluate many factors in terms of gabapentinoid abuse. The risk factors we have identified can be evaluated together with the previously determined risk factors in the prescription of the drug and in the treatment process, as well as contribute to the creation of an algorithm to prevent the risk of abuse.

Since our study was single-centered, the results cannot be generalized to the population. In our study, the number of patients in disease groups in which neuropathic pain is more common, and gabapentinoids are used for longer periods and at higher doses was limited (spinal cord lesion, multiple sclerosis, traumatic nerve injury, etc.). Information on how often patients visited the hospital, whether they were informed about the drug use process, the frequency of disease follow-up, and which symptoms (increased pain/withdrawal) occurred during the periods of dose reduction and drug withdrawal was not obtained. These are the limitations of the present work.

Conclusions

In conclusion, the rate of gabapentinoid abuse was 17.9% in our study. Smoking, alcohol and antidepressant use, duration of drug use, the dose of gabapentin and pregabalin, being single, and living alone were determined to be risk factors for gabapentinoid abuse. Questioning patients in terms of these risk factors before prescribing drugs and managing the treatment process in a controlled manner can reduce the rate of abuse.

Conflict of Interest
The Authors declare that they have no conflict of interest.

Ethics Approval
Ethical approval was obtained for this study from the Clinical Research Ethics Committee (09.01.2019/16). The study was conducted according to the World Medical Association Declaration of Helsinki.

Informed Consent
All patients read the informed consent form and accepted to participate in this study.

Availability of Data and Materials
All generated data were presented in this study.

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Authors' Contributions
Conceptualization and design: ZK, EAÖ; experiments: drafting and writing: ZK, EAÖ; editing: ZK, EAÖ.

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References

1) Kremer M, Salvat E, Muller A, Yalcin I, Barrot M. Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights. Neuroscience 2016; 338: 183-206.
2) Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet 2010; 49: 661-669.
3) Zaccara G, Gangemi P, Perucca P, Specchio L. The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. Epilepsia 2011; 52 : 826-836.
4) Chiappini S, Schifano F. A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. CNS Drugs 2016; 30: 647-654.
5) Piskorska B, Miziak B, Czuczwar SJ, Borowicz KK. Safety issues around misuse of antiepileptics. Expert Opin Drug Saf 2013; 12: 647-657.
6) Schwan S, Sundström A, Stjernberg E, Hallberg E, Hallberg P. A signal for an abuse liability for pregabalin--results from the Swedish spontaneous adverse drug reaction reporting system. Eur J Clin Pharmacol 2010; 66: 947-953.
7) Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-571.
8) Hıslı, N. A study on the validity of the Beck Depression Inventory. Turk Psychol J 1998; 6: 118-123.
9) Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988; 56: 893-897.
10) Ulusoy M. Sahın NH, Erkmen H. Turkish version of the Beck Anxiety Inventory: psychometric properties. J Cogn Psychother 1998; 12: 163.
11) Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, Comer SD, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain 2013; 154: 2287-2296.
12) Arya R, Antonisamy B, Kumar S. Sample Size Estimation in Prevalence Studies. Indian J Pediatr 2012; 79: 1482-1488.

13) Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse and diversion: a systematic review. Addiction 2016; 111: 1160-1174.
14) Kapil V, Green JL, Le Lait MC, Wood DM, Dargan PI. Misuse of the γ-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. Br J Clin Pharmacol 2014; 78: 190-191.
15) Polat CS, Konak HE, Akıncı MG, Onat SS, Altas EU. Misuse of gabapentinoids (pregabalin and gabapentin) in patients with neuropathic pain related to spinal cord injury. J Spinal Cord Med 2022; 2: 1-6.
16) Hägg S, Jönsson AK, Ahlner J. Current Evidence on Abuse and Misuse of Gabapentinoids. Drug Saf 2020; 43: 1235-1254.
17) Evoy KE, Morrison MD, Saklad SR. Abuse and Misuse of Pregabalin and Gabapentin. Drugs 2017; 77: 403-426.
18) Evoy KE, Sadrameli S, Contreras J, Covvey JR, Peckham AM, Morrison MD. Abuse and Misuse of Pregabalin and Gabapentin: A Systematic Review Update. Drugs 2021; 81: 125-156.
19) Peckham AM, Evoy KE, Covvey JR, Ochs L, Fairman KA, Sclar DA. Predictors of Gabapentin Overuse With or Without Concomitant Opioids in a Commercially Insured U.S. Population. Pharmacotherapy 2018; 38: 436-443.
20) Sason A, Adelson M, Schreiber S, Peles E. Pregabalin misuse in methadone maintenance treatment patients in Israel: Prevalence and risk factors. Drug Alcohol Depend 2018; 1; 189: 8-11.
21) Driot D, Jouanjus E, Oustric S, Dupouy J, Lapeyre-Mestre M. Patterns of gabapentin and pregabalin use and misuse: Results of a population-based cohort study in France. Br J Clin Pharmacol 2019; 85: 1260-1269.
22) Schifano F, D'Offizi S, Piccione M, Corazza O, Deluca P, Davey Z. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother Psychosom 2011; 80: 118-122.
23) Driot D, Jouanjus E, Oustric S, Dupouy J, Lapeyre-Mestre M. Patterns of gabapentin and pregabalin use and misuse: Results of a population-based cohort study in France. Br J Clin Pharmacol 2019; 85: 1260-1269.
24) Bussa M, Mascaro A, Sbacchi E, Dourandish M, Rinaldi S. Understanding peripheral neuropathic pain in primary care: diagnosis and management. Eur Rev Med Pharmacol Sci 2021; 25: 1990-1996.
25) Evoy KE, Peckham AM, Covvey JR, Tidgewell KJ. Gabapentinoid Pharmacology in the Context of Emerging Misuse Liability. J Clin Pharmacol 2021; 61: 89-99.
26) Tambon M, Ponté C, Jouanjus E, Fouilhé N, Micallef J, Lapeyre-Mestre M; French Addictovigilance Network (FAN). Gabapentinoid Abuse in France: Evidence on Health Consequences and New Points of Vigilance. Front Psychiatry 2021; 12: 639780.
27) Goins A, Patel K, Alles SRA. The gabapentinoid drugs and their abuse potential. Pharmacol Ther 2021; 227: 107926.
28) Kriikku P, Ojanperä I. Pregabalin and gabapentin in non-opioid poisoning deaths. Forensic Sci Int 2021; 324: 110830.
29) Aindow S, Crossin R, Toop L, Hudson B. Managing the misuse potential and risk of psychological harm from gabapentinoids in primary care in New Zealand. J Prim Health Care 2021; 13: 302-307.