



# Gabapentinoids in penitentiaries: An abuse and addiction research

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## ABSTRACT

**Objectives:** This study aims to examine the abuse and addiction of gabapentinoids in penal institutions.

**Patients and methods:** Between September 2014 and November 2014, a total of 1,639 participants were administered an electronic questionnaire investigating the drug use and addiction. The questionnaire was requested to be asked and filled by the officers in charge for all voluntary convicts and prisoners in all penitentiaries throughout Turkey.

**Results:** The rate of answering the questions varied between 20.5% and 100%. It was found that 2% of the participants used pregabalin and gabapentin simultaneously, while 25.2% of them used multiple drugs. The usage rate of pregabalin and gabapentin was higher in some penitentiaries, compared to the normal population. There was a significant positive correlation between the use of gabapentinoids and multiple drugs and alcohol and drug addiction, various withdrawal symptoms, the number of going to the infirmary, and the number of referral to the hospital ( $p < 0.05$ ).

**Conclusion:** Although gabapentinoids seem to be used in the treatment of addiction, and are proved effective treatment agents. With a definite diagnosis, appropriate follow-up, and timely completion of the treatment, it is necessary to strictly control their use due to the probability of abuse and addiction.

**Keywords:** Abuse; addiction; gabapentin; gabapentinoid; pregabalin.

Gabapentinoids (gabapentin and pregabalin) are antiepileptic drugs used in the treatment of primary focal and secondary generalized epilepsy, the former of which makes N-type calcium channel modulation and is eliminated from the body 100% by kidneys and the latter of which acts by binding to  $\alpha 2\delta$  subunit of the voltage-gated calcium channel and is eliminated from the body 95% by kidneys. Pregabalin has a six times stronger binding affinity to this subunit of the calcium channels than gabapentin.<sup>[1-5]</sup> As a result of calcium release from the nerve endings, it reduces the release of various neurotransmitters such as glutamate, norepinephrine, and substance P.<sup>[6-8]</sup> Pregabalin does not act through the gamma-aminobutyric acid (GABA) receptors, and does not change the GABA uptake and degradation.<sup>[9,10]</sup> Neither drug binds to the plasma proteins, and interacts with liver enzymes and other drugs.<sup>[11]</sup> The well-known side effects of gabapentin are somnolence, dizziness, ataxia, fatigue, nystagmus,

weight gain, and behavior disorders in children and side effects of pregabalin are mild temporary elevations in the liver enzymes, somnolence, fatigue, dizziness, and weight gain.<sup>[1]</sup>

Pregabalin is primarily used in the treatment of epilepsy and neuropathic pain, and also in the treatment of addiction of alcohol and benzodiazepine.<sup>[12]</sup> Similarly, based on the central mechanisms in the etiopathogenesis of fibromyalgia syndrome, antiepileptics are considered to be tested in the treatment. Pregabalin is the first agent to be deemed suitable for the treatment of fibromyalgia syndrome by the United States Food and Drug Administration.<sup>[13]</sup> In regard to the use of gabapentin in fibromyalgia, a randomized placebo-controlled study is available in the literature.<sup>[14]</sup>

According to the data obtained by examining the commercial records (provided by the drug companies

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in Turkey), the use and institutional costs of these drugs have been gradually increasing worldwide (Figure 1). While the quantity of gabapentin sold in Turkey in 2011 was 3,725,927 boxes, this number increased up to 4,621,100 boxes in 2014. The quantity of pregabalin sold was 896,744 boxes in 2011, while this number was 2,997,515 boxes in 2014. The money spent for pregabalin was 13,130,220 US Dollars in 2011, while it was 23,433,991 US Dollars in 2014.

Gabapentin has been shown to be associated with euphoria as a side effect in 1 to 10% of patients.<sup>[15]</sup> Also, there are case reports of probable addiction of gabapentinoids.<sup>[16,17]</sup> Although they are considered as effective drugs, they are also regarded as the drugs potentially developing clinical abuse.<sup>[15-18]</sup>

In the present study, we aimed to examine the abuse and addiction of gabapentinoids which have been becoming more widespread around the world, in penal institutions where the probability of addiction is estimated to be higher, in terms of improving the health and training of the convicts and prisoners in the penal institutions, and developing the drug policies of the institutions.<sup>[19]</sup>

**PATIENTS AND METHODS**

Upon receiving the official and ethical approval of Turkish Republic Ministry of Justice General Directorate of Penitentiary and Detention Institutions, dated 25/08/2014 and numbered 57292265-204.06.03-1445/134224, a questionnaire investigating the drug use and addiction was prepared in the electronic environment, and it was requested to be asked and filled by officers in charge for all the convicts and prisoners who accepted to participate in the study and signed the written consent in all penitentiaries throughout Turkey. The study was conducted in accordance with the principles of the Declaration of Helsinki. By conforming to the privacy, it was ensured that the questionnaires were collected in a pool in electronic environment which can only be reached by the researchers. The data obtained was subjected to statistical analysis by an expert statistician. The results of this project were allowed to be published with the approval of Turkish Republic Ministry of Justice, dated 24/12/2015 and numbered 57292265-204.06.03-E.2013/188853.

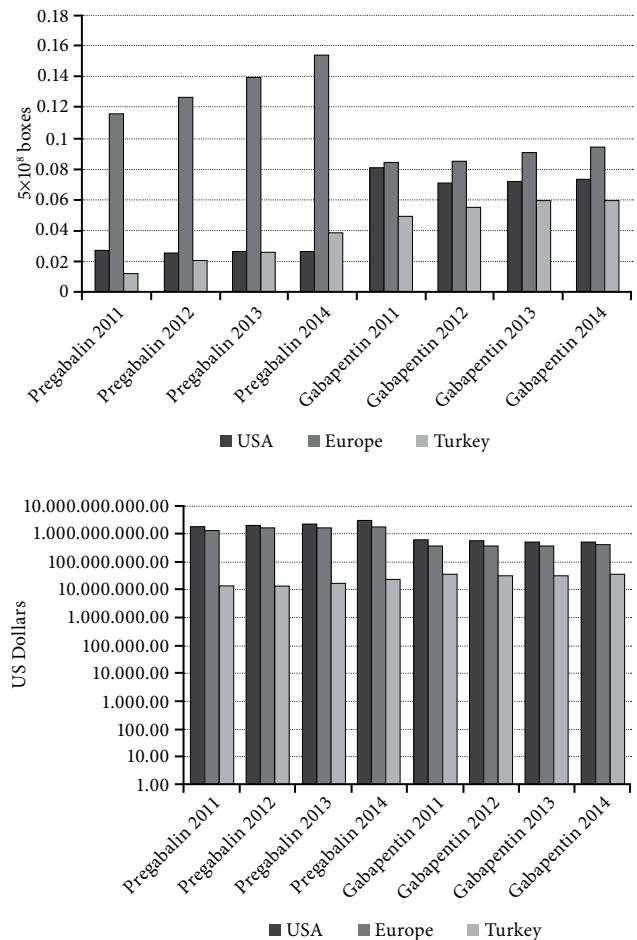
**Statistical analysis**

Statistical analysis was performed using the PASW version 17.0 statistical software (SPSS Inc., Chicago, IL,

USA). Descriptive statistics were expressed in median (min-max) values and number and percentage. The chi-square and Cramer’s V tests were used to assess the correlations. A *p* value of <0.05 was considered statistically significant.

**RESULTS**

A total of 1,639 participants attended to the questionnaire study. The response rate of the participants differed for each question, as it was based on volunteering (range, 20.5 to 100%; Table 1). According to the numbers of the individuals using pregabalin and gabapentin in each penal institution, it was found that the total number of the individuals using pregabalin and gabapentin was above the number of the participants in some institutions (e.g., Adana/Kozan and Nigde E type), which was due to the fact that some of the participants used pregabalin and gabapentin simultaneously (Table 2).



**Figure 1.** The population ratio of the sold pillbox numbers and institutional costs of pregabalin and gabapentin in US Dollars in the markets of USA, Europe and Turkey in 2011, 2012, 2013 and 2014.

The rate of the individuals participated in the questionnaire and using gabapentinoids are shown in Table 3.

A total of 302 (23.1%) participants were using pregabalin. Ninety seven (27.6%) of the participants had drug reports provided by the hospitals. The

question asking the usage frequency of pregabalin was answered as once a day by 25.8%, twice a day by 59.8%, three times a day by 14.0%, and four times a day by 0.3%. The median value of the duration of pregabalin use was five (range, 2 to 13) months. The percent of the individuals using pregabalin for  $\geq 6$  months was 48.5%.

**Table 1.** Number and percent of the participants to each question (n=1,639)

Question	Number of the participants	Percent of the participants (%)
Usage of pregabalin?	1567	95.5
Drug report for pregabalin?	352	21.5
Usage period for pregabalin (month)	336	20.5
Frequency of pregabalin usage	356	21.7
Dose of pregabalin	356	21.7
Pregabalin started before imprisonment?	366	22.3
Usage of gabapentin?	1559	95.1
Drug report for gabapentin?	414	25.2
Usage period for gabapentin (months)	371	22.6
Frequency of gabapentin usage	422	25.7
Dose of gabapentin	423	25.8
Gabapentin started before imprisonment?	428	26.1
Usage of antidepressant, antipsychotic or other antiepileptic drugs?	1621	98.9
Drug report for other drugs?	1078	65.8
Usage period for other drugs (months)	1003	61.2
Frequency of usage of other drugs	1071	65.3
Doses of other drugs	1061	64.7
Other drugs started before imprisonment?	1092	66.6
Diagnosis	1639	100
Name of the drugs	1639	100
Multiple drug usage	1634	99.6
In which step of health institution the drugs were started?	1498	91.3
Alcohol addiction	1411	86
Dope addiction	1446	88.2
Going to the infirmary (last 1 year)	1233	75.2
Going to the infirmary (last 6 months)	1639	100
Going to the infirmary (last 3 months)	1080	65.9
Referring to the hospital (last 1 year)	1171	71.4
Referring to the hospital (last 6 months)	950	57.9
Referring to the hospital (last 3 months)	946	57.7
Duration of imprisonment (intervals of months or years)	1377	84
Tend to engage in violence against others?	1559	95.1
Tend to engage in violence against the self?	1555	94.8
Withdrawal symptoms occurring when the drug is not used		
Sweating	985	60.1
Shivering	1021	62.3
Having fever	932	56.8
Stomachache	894	54.5
Nausea	900	54.9
Vomiting	880	53.7
Palpitation	960	58.5
Hallucination	954	58.2
Headache	1063	64.8
Dizziness	952	58
Nervousness	1294	78.9
Sleeplessness	1318	80.4
Nightmare	947	57.7
Epileptic seizure	883	53.8
Xerostomia	958	58.4
Restlessness	1368	83.4

**Table 2.** Penal institutions, number of participants and number of participants using pregabalin or gabapentin (n=1,639)

Institution	NP	P	G	Institution	NP	P	G	Institution	NP	P	G
Null	6	1	0	Diyarbakır	2	1	0	Kocaeli F type	30	2	2
Adana F type	6	0	2	Erzurum	18	3	2	Konya	13	6	3
Adana Karataş	9	0	1	Erzurum Oltu	48	4	7	Konya Beyşehir	5	1	2
Adana Kozan	5	4	4	Eskişehir Open	15	4	2	Konya Seydişehir	3	0	1
Adıyaman	2	0	2	Gaziantep	5	0	1	Manisa	45	5	12
Afyon	29	2	18	Giresun	33	6	27	Manisa Akhisar	4	0	1
Afyon Sandıklı	7	0	5	Hatay Closed	1	0	0	Manisa Alaşehir	1	0	0
Ağrı	14	0	3	Isparta Yalvaç	3	0	0	Mersin	149	2	6
Ankara	120	46	9	İstanbul	37	8	10	Muğla	60	39	6
Ankara Ayas	5	2	2	İstanbul L type	14	1	2	Nevşehir	7	0	7
Ankara Kızılcahamam	11	7	2	İstanbul Silivri	19	6	6	Niğde Open	10	2	4
Antalya	26	3	2	İzmir	24	3	3	Niğde E type	11	1	11
Ardahan	4	0	0	İzmir Aliağa	4	1	2	Osmaniye	6	0	2
Aydın	5	0	2	İzmir Bergama	50	18	4	Rize	13	1	2
Aydın Söke	1	0	0	İzmir Ödemiş	11	0	6	Samsun	58	11	8
Balıkesir	22	8	8	İzmir T type	7	7	0	Samsun Bafra	47	12	12
Balıkesir Bandırma	12	0	5	Kahramanmaraş	44	3	24	Samsun Çarşamba	6	0	0
Balıkesir L type	1	1	0	Karabük	15	6	1	Sinop	21	3	3
Batman	11	0	4	Karaman	5	0	5	Sinop Boyabat	4	1	2
Bitlis	25	2	9	Karaman Ermenek	6	0	6	Şanlıurfa	15	6	1
Bolu	53	15	8	Kastamonu	18	6	15	Şırnak	61	5	13
Bolu F type	27	9	6	Kastamonu Daday	4	0	3	Tekirdağ	8	0	1
Burdur	23	6	12	Kayseri	4	0	2	Tekirdağ Open	1	0	0
Bursa	4	1	0	Kırıkkale	46	9	16	Tekirdağ F type	16	0	8
Bursa H type	11	3	1	Kırıkkale Sulakyurt	6	4	2	Tokat	3	0	3
Çorum	12	4	4	Kırklareli	8	5	1	Tokat Zile	22	0	3
Çorum Sungurlu	5	4	1	Kırşehir	97	50	41	Tunceli	6	0	6
Çorum				Kırşehir	97	50	41	Tunceli	6	0	6
Sungurlu	5	4	1	Kocaeli	5	2	3	Yalova	5	0	0
Denizli	4	0	4								

NP: Number of participants; P: Pregabalin; G: Gabapentin.

**Table 3.** Percent of the individuals participated in the questionnaire, and percent of the individuals using gabapentinoids

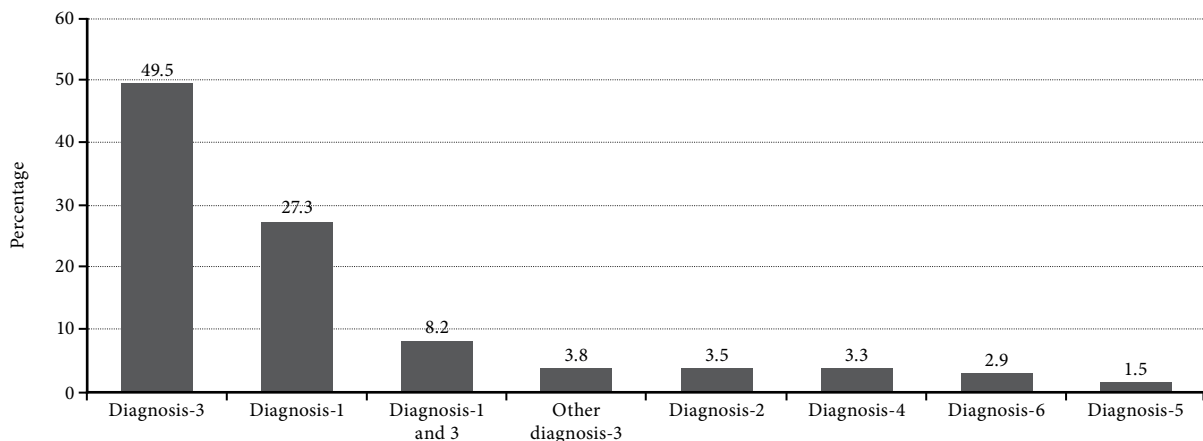
City	A	B	C	D	E	City	A	B	C	D	E
Adana	20	4,457	0.45	11	0.25	Kahramanmaraş	44	1966	2.24	27	1.37
Adıyaman	2	1,427	0.14	2	0.14	Karabük	15	1121	1.34	7	0.62
Afyon	36	2,269	1.59	25	1.1	Karaman	11	1099	1	11	1
Ağrı	14	531	2.64	3	0.56	Kastamonu	22	1159	1.9	22	1.9
Ankara	136	6,661	2.04	68	1.02	Kayseri	4	1710	0.23	2	0.12
Antalya	26	3,817	0.68	5	0.13	Kırıkkale	52	607	8.57	31	5.11
Ardahan	4	70	5.71	0	0	Kırklareli	8	1694	0.47	6	0.35
Aydın	6	2,754	0.22	2	0.07	Kırşehir	97	1257	7.7	91	7.24
Balıkesir	35	4,823	0.73	22	0.46	Kocaeli	35	3595	0.97	9	0.25
Batman	11	453	2.43	4	0.88	Konya	21	2380	0.88	13	0.55
Bitlis	25	626	4	11	1.76	Manisa	50	3148	1.59	18	0.57
Bolu	80	1,657	4.83	38	2.3	Mersin	149	3321	4.49	8	0.24
Burdur	23	1,162	1.98	18	1.55	Muğla	60	2102	2.85	45	2.14
Bursa	15	3,598	0.42	5	0.14	Nevşehir	7	667	1.05	7	1.05
Çorum	17	1,903	0.9	13	0.68	Niğde	21	1269	1.65	18	1.42
Denizli	4	2,481	0.16	4	0.16	Osmaniye	6	2159	0.28	2	0.09
Diyarbakır	2	2,580	0.08	1	0.04	Rize	13	983	1.32	3	0.31
Erzurum	66	2,131	3.1	16	0.75	Samsun	111	2492	4.45	43	1.73
Eskişehir	15	1,967	0.76	6	0.31	Sinop	25	852	2.93	9	1.06
Gaziantep	5	3,409	0.15	1	0.03	Şanlıurfa	15	1722	0.87	7	0.41
Giresun	33	856	3.86	33	3.86	Şırnak	61	1193	5.11	18	1.51
Hatay	1	2,551	0.04	0	0	Tekirdağ	25	3156	0.8	9	0.29
Isparta	3	1,219	0.25	0	0	Tokat	25	1673	1.5	6	0.36
İstanbul	70	19,338	0.36	33	0.17	Tunceli	6	51	11.76	6	11.76
İzmir	96	10,051	0.96	42	0.42	Yalova	5	51	9.8	0	0

A: Total number of the prisoners and convicts participated in the questionnaire on the basis of city; B: Total number of the prisoners and convicts on the basis of city; C: Percent of the individuals participated in the questionnaire; D: Number of the individuals using gabapentinoids; E: Percent of the individuals using gabapentinoids.

The question about when pregabalin was started was answered as after imprisonment by 59% of the participants. The question asking the daily pregabalin dose was answered as below: 50 mg by 1.7%, 50-150 mg by 20.2%, 150-300 mg by 34.3%, 300-600 mg by 31.2%, 600-1,200 mg by 10.4%, 1,200-1,800 mg by 1.7%, and more than 1,800 mg by 0.6%.

A total of 425 (27.3%) participants were using gabapentin. A hundred and seventy eight (43%) of them

had a drug report. A total of 14.9% of the participants used gabapentin once a day, 31.8% twice a day, 49.5% three times a day, 3.8% four times a day. According to the total daily dose of gabapentin, those using it below 300 mg were 6.6%, 300-600 mg were 12.8%, 600-1,200 mg were 32.9%, 1,200-1,800 mg were 17.3% and more than 1,800 mg were 30.5%. The question about when gabapentin was started was answered as after imprisonment by 54.4% of the participants.



**Figure 2.** Percents of the diagnosis of the participants (n=1,639). Diagnosis-1: Neuropathic pain; Diagnosis-2: Chronic pain; Diagnosis-3: Depression; Diagnosis-4: Psychosis; Diagnosis-5: Fibromyalgia syndrome; Diagnosis-6: Epilepsy; Other diagnosis: Allergy etc.

The median value of the duration of gabapentin use was 10 (range, 4 to 20) months. The percent of the individuals using gabapentin for  $\geq 6$  months was 64.7%. It was shown that 36 participants (2%) were using both pregabalin and gabapentin simultaneously.

A total of 1,067 participants (65.8%) were using an antidepressant, antipsychotic, or other antiepileptic drugs (other than pregabalin and gabapentin). A total of 14.7% of the participants had a drug report. The question asking the usage frequency of these drugs was answered as once a day by 71%, twice by 25%, three times by 3.5% and four times by 0.4%. While 43.1% of the participants were using the drugs at a dose  $\leq 50$  mg, 56.9% of them were using them at a dose above 50 mg. Also, 52.9% of the participants started these drugs after imprisonment. The rate of those who used these drugs for  $\geq 6$  months was 56.5% and median value of the duration of the drug use was eight (range, 3 to 20) months.

The rates of the diagnosis are shown in Figure 2. The percent of gabapentinoid users was 33.7%, antidepressant users was 20.4%, antipsychotic users was 15.9%, gabapentinoid + antipsychotic users was 8.1%, gabapentinoid + antidepressant users was 6.5%, gabapentinoid + antidepressant + antipsychotic users was 2%. However, 25.2% of the participants gave the answer 'Yes' to the question of multiple drug use.

While the percent of alcohol use was 58.2% (415 social drinkers and 407 addicted), the percent of

those who were addicted was 28.8%. Also, 50.9% of the participants used dope (164 social drinkers and 573 addicted), while 39.6% were addicted. In addition, 27.6% of the participants tended to engage in violence against others, while 28.9% of them tended to engage in violence against the self.

The rates of going to the infirmary and referring to the hospital numbers of participants are given in Table 4.

The highest rates among the withdrawal symptoms were seen in restlessness (75.7%), sleeplessness (73.5%), and nervousness (73.0%). Other withdrawal symptoms were headache (50.5%), shivering (42.1%), sweating (39.1%), xerostomia (33.4%), palpitation (31%), nightmare (28.9%), having fever (28.4%), hallucination (26.4%), dizziness (24.9%), nausea (15.2%), stomachache (13.1%), epileptic seizure (11.2%), and vomiting (9.7%). Withdrawal symptoms reported by the participants with their individual expressions apart from the questions asked were pain in different regions of the body, thinking of bad things, allergic symptoms and acnes in the body, anti-sociality, hyper-reflection, paresthesia in the feet, burning and itching, contractions and cramping, fainting, biting lips, fatigue, depression, reluctance to work, discouragement and fear, urinary incontinence at night, restless leg syndrome, melancholy, tendency to be asocial, diarrhea, lack of appetite, teeth grinding, self-destruction and giving harm to others, panic

**Table 4.** Percents of going to the infirmary and referring to the hospital numbers of participants in last three months, six months and one year

Number of going to the infirmary	Last 3 months (n=1,080) (%)	Last 6 months (n=1,639) (%)	Last 1 year (n=1,233) (%)
0	0	36.2	0.2
1-3	32.1	11.0	14.4
4-7	42.5	14.3	13.1
8-11	16.0	17.6	13.0
12-15	5.2	9.8	15.7
16-20	3.0	5.9	13.9
21-26	1.2	4.9	29.1
>26	0	0.2	0.6
Number of referring to the hospital	Last 3 months (n=946) (%)	Last 6 months (n=950) (%)	Last 1 year (n=1,171) (%)
0	0.2	0.1	0.2
1-3	67.8	46.4	31.5
4-7	23.4	31.1	31.1
8-11	5.7	12.1	17.2
12-15	2.3	5.6	8.4
16-20	0.4	3.4	4.4
21-26	0.2	1.1	6.9
>26	0	0.3	0.3

attack, impatience, suicide attempt, skepticism, becoming seduced, obsession, and being cold.

There was a positive correlation between the pregabalin use and alcohol addiction (Cramer's  $V=0.212$ ), dope addiction (Cramer's  $V=0.147$ ), number of going to the infirmary in the last one year (Cramer's  $V=0.241$ ), last six months (Cramer's  $V=0.229$ ) and last three months (Cramer's  $V=0.223$ ) and number of referring to the hospital in the last one year ( $r=0.245$ ), last six months (Cramer's  $V=0.258$ ) and last three months (Cramer's  $V=0.196$ ). While there was no correlation between pregabalin use and tendency to engage in violence against others (Cramer's  $V=0.030$ ), there was positive correlation between pregabalin use and tendency to engage in violence against the self (Cramer's  $V=0.072$ ). There was a positive correlation between pregabalin use and withdrawal symptoms such as sweating (Cramer's  $V=0.059$ ), having fever (Cramer's  $V=0.091$ ), stomachache (Cramer's  $V=0.076$ ), nausea (Cramer's  $V=0.107$ ), vomiting (Cramer's  $V=0.101$ ), hallucination (Cramer's  $V=0.058$ ), headache (Cramer's  $V=0.066$ ), nervousness (Cramer's  $V=0.061$ ), sleeplessness (Cramer's  $V=0.139$ ), nightmare (Cramer's  $V=0.095$ ) and restlessness (Cramer's  $V=0.087$ ).

There was a positive correlation between the duration of pregabalin use and alcohol addiction (Cramer's  $V=0.186$ ), dope addiction (Cramer's  $V=0.166$ ), number of going to the infirmary in the last one year (Cramer's  $V=0.268$ ) and last six months (Cramer's  $V=0.201$ ), number of referring to the hospital in the last three months (Cramer's  $V=0.273$ ). While there was no correlation between the duration of pregabalin use and tendency to engage in violence against others (Cramer's  $V=0.066$ ), there was a positive correlation between the duration of pregabalin use and tendency to engage in violence against the self (Cramer's  $V=0.100$ ).

There was a positive correlation between the duration of pregabalin use and withdrawal symptoms such as stomachache (Cramer's  $V=0.183$ ), palpitation (Cramer's  $V=0.151$ ), hallucination (Cramer's  $V=0.330$ ), dizziness (Cramer's  $V=0.221$ ), nervousness (Cramer's  $V=0.153$ ), sleeplessness (Cramer's  $V=0.183$ ), epileptic seizure (Cramer's  $V=0.258$ ), xerostomia (Cramer's  $V=0.178$ ) and restlessness (Cramer's  $V=0.134$ ).

In addition, there was a positive correlation between the dose of pregabalin and alcohol addiction (Cramer's  $V=0.152$ ), dope addiction (Cramer's  $V=0.132$ ), number of going to the infirmary in the last six months (Cramer's  $V=0.268$ ), number of referring to the hospital in the last six months (Cramer's  $V=0.245$ ) and last three months

(Cramer's  $V=0.229$ ). However, there was no correlation between the dose of pregabalin and tendency to engage in violence either against others or the self (Cramer's  $V=0.073$  and Cramer's  $V=0.020$ , respectively). There was a positive correlation between the dose of pregabalin and withdrawal symptoms such as sweating (Cramer's  $V=0.155$ ), stomachache (Cramer's  $V=0.166$ ), nausea (Cramer's  $V=0.154$ ), vomiting (Cramer's  $V=0.201$ ), palpitation (Cramer's  $V=0.163$ ), hallucination (Cramer's  $V=0.226$ ), dizziness (Cramer's  $V=0.245$ ), sleeplessness (Cramer's  $V=0.194$ ), nightmare (Cramer's  $V=0.257$ ), epileptic seizure (Cramer's  $V=0.240$ ), and xerostomia (Cramer's  $V=0.245$ ).

There was a positive correlation between the usage frequency of pregabalin and alcohol addiction (Cramer's  $V=0.147$ ), number of going to the infirmary in the last one year (Cramer's  $V=0.209$ ), last six months (Cramer's  $V=0.219$ ), and last three months (Cramer's  $V=0.186$ ), and number of referring to the hospital in the last three months (Cramer's  $V=0.160$ ). While there was a correlation between the usage frequency of pregabalin and tendency to engage in violence against others (Cramer's  $V=0.120$ ), there was no correlation between the usage frequency of pregabalin and tendency to engage in violence against the self (Cramer's  $V=0.006$ ). There was a positive correlation between the usage frequency of pregabalin and withdrawal symptoms such as sweating (Cramer's  $V=0.229$ ), having fever (Cramer's  $V=0.226$ ), nausea (Cramer's  $V=0.212$ ), vomiting (Cramer's  $V=0.294$ ), hallucination (Cramer's  $V=0.236$ ), dizziness (Cramer's  $V=0.215$ ), sleeplessness (Cramer's  $V=0.211$ ), nightmare (Cramer's  $V=0.231$ ), epileptic seizure (Cramer's  $V=0.224$ ), and xerostomia (Cramer's  $V=0.167$ ).

There was a positive correlation between the gabapentin use and alcohol addiction (Cramer's  $V=0.125$ ), dope addiction (Cramer's  $V=0.135$ ), number of going to the infirmary in the last one year (Cramer's  $V=0.275$ ), last six months (Cramer's  $V=0.260$ ) and last three months (Cramer's  $V=0.251$ ), and number of referring to the hospital in the last one year (Cramer's  $V=0.179$ ). While there was no correlation between gabapentin use and tendency to engage in violence against others (Cramer's  $V=0.025$ ), there was positive correlation between gabapentin use and tendency to engage in violence against the self (Cramer's  $V=0.046$ ). There was a positive correlation between gabapentin use and withdrawal symptoms such as sweating (Cramer's  $V=0.060$ ), having fever (Cramer's  $V=0.097$ ), palpitation (Cramer's  $V=0.056$ ), headache (Cramer's  $V=0.120$ ), nervousness (Cramer's  $V=0.094$ ), sleeplessness (Cramer's  $V=0.085$ ), and restlessness (Cramer's  $V=0.076$ ).

There was positive correlation between the duration of gabapentin use and alcohol addiction (Cramer's  $V=0.227$ ), dope addiction (Cramer's  $V=0.239$ ), number of going to the infirmary in the last one year (Cramer's  $V=0.216$ ) and last six months (Cramer's  $V=0.198$ ), and number of referring to the hospital in the last six months (Cramer's  $V=0.200$ ). There was a positive correlation between the duration of gabapentin use and tendency to engage in violence against others and against the self (Cramer's  $V=0.156$  and Cramer's  $V=0.188$ , respectively). There was a positive correlation between the duration of gabapentin use and withdrawal symptoms such as palpitation (Cramer's  $V=0.110$ ), hallucination (Cramer's  $V=0.128$ ), dizziness (Cramer's  $V=0.169$ ), nervousness (Cramer's  $V=0.149$ ), sleeplessness (Cramer's  $V=0.170$ ), xerostomia (Cramer's  $V=0.136$ ), and restlessness (Cramer's  $V=0.117$ ).

On the other hand, there was no correlation between the dose of gabapentin and alcohol addiction, dope addiction, number of going to the infirmary and referring to the hospital, tendency to engage in violence against others or the self ( $p>0.05$ ). There was a positive correlation between the dose of gabapentin and withdrawal symptoms such as sweating (Cramer's  $V=0.133$ ), vomiting (Cramer's  $V=0.196$ ), palpitation (Cramer's  $V=0.149$ ), headache (Cramer's  $V=0.149$ ), and nervousness (Cramer's  $V=0.125$ ).

There was a positive correlation between the frequency of gabapentin usage and dope addiction (Cramer's  $V=0.120$ ), number of going to the infirmary in the last one year (Cramer's  $V=0.190$ ) and last six months (Cramer's  $V=0.239$ ). There was a positive correlation between the frequency of gabapentin usage and tendency to engage in violence against others and against the self (Cramer's  $V=0.129$  and Cramer's  $V=0.184$ , respectively). There was a positive correlation between the frequency of gabapentin usage and withdrawal symptom of sleeplessness (Cramer's  $V=0.120$ ).

There was a positive correlation between the use of other drugs comprising antidepressant, antipsychotic, and antiepileptics (other than gabapentinoids) and alcohol addiction (Cramer's  $V=0.136$ ), dope addiction (Cramer's  $V=0.084$ ), number of going to the infirmary in the last one year (Cramer's  $V=0.286$ ), last six months (Cramer's  $V=0.277$ ) and last three months (Cramer's  $V=0.259$ ), and number of referring to the hospital in the last one year (Cramer's  $V=0.210$ ). While there was no correlation between the use of these drugs and tendency to engage in violence against others (Cramer's  $V=0.033$ ), there was a positive correlation between the use of these drugs and tendency to engage

in violence against the self (Cramer's  $V=0.057$ ). There was also a positive correlation between the use of these drugs and withdrawal symptoms such as sweating (Cramer's  $V=0.068$ ), having fever (Cramer's  $V=0.095$ ), vomiting (Cramer's  $V=0.072$ ), hallucination (Cramer's  $V=0.120$ ), headache (Cramer's  $V=0.088$ ), sleeplessness (Cramer's  $V=0.276$ ), nightmare (Cramer's  $V=0.133$ ), and epileptic seizure (Cramer's  $V=0.096$ ).

There was a positive correlation between the multiple drug use and alcohol addiction (Cramer's  $V=0.056$ ), dope addiction (Cramer's  $V=0.033$ ), number of going to the infirmary in the last one year (Cramer's  $V=0.137$ ), last six months (Cramer's  $V=0.129$ ) and last three months (Cramer's  $V=0.087$ ) and number of referring to the hospital in the last one year (Cramer's  $V=0.124$ ), last six months (Cramer's  $V=0.120$ ), and last three months (Cramer's  $V=0.070$ ). While there was no correlation between the multiple drug use and tendency to engage in violence against others (Cramer's  $V=0.76$ ), there was a positive correlation between the multiple drug use and tendency to engage in violence against the self (Cramer's  $V=0.075$ ). There was a positive correlation between the multiple drug use and withdrawal symptoms such as sweating (Cramer's  $V=0.068$ ), having fever (Cramer's  $V=0.086$ ), stomachache (Cramer's  $V=0.127$ ), nausea (Cramer's  $V=0.147$ ), vomiting (Cramer's  $V=0.151$ ), hallucination (Cramer's  $V=0.223$ ), headache (Cramer's  $V=0.087$ ), nervousness (Cramer's  $V=0.076$ ), sleeplessness (Cramer's  $V=0.151$ ), nightmare (Cramer's  $V=0.189$ ), and restlessness (Cramer's  $V=0.075$ ).

However, there was no significant correlation between the duration of imprisonment (<6 months in 14.7%, 6 months-1 year in 16%, 1-3 years in 30.3%, 3-6 years in 13.9%, 6-10 years in 11.9% and >10 years in 13.2%) and other variables.

## DISCUSSION

The major finding of our study is that it is the first study about the use of gabapentinoids and addiction in penal institutions. One of the limitations of our study is that since the participants were completely free in participating in the questionnaire and answering the questions, there was a high dependence on participants, particularly about not telling the truth in terms of drug addiction and abuse. By a higher participation and application of a stricter questionnaire accompanied by medical records, independent of participants, the results would be much realistic. The response rate was low to some questions, as they were concerning the small part of the participants who were using



gabapentinoids. For instance, the question asking the pregabalin drug report or the question asking the duration of pregabalin use had response rates about 20%, as the participants who did not use pregabalin previously did not answer these questions. However, the response rates in the questions that concern all the participants were high (Table 1).

According to the drug market data, it was estimated that the number of individuals using gabapentin was about 240,682, while the number of individuals using pregabalin was about 249,793. Considering that the population above 18 years old was 52,314,553 individuals (according to 2014 data of Turkish Statistical Institute),<sup>[20]</sup> it was thought that the rate of gabapentinoid usage of normal population was about 0.94%. At the E column in Table 3, it is seen that the rate of gabapentinoid usage was quite above the normal population, particularly in some institutions.

It was found that pregabalin, which is recommended to be used twice a day, was used at a percent of 14.3% three times a day and more. While ideal daily dose of pregabalin is accepted as 300 mg (rarely can be increased up to 600 mg/day), it was used at a percent of 43.9% more than 300 mg daily. This may be due to the fact that the drug was abused or that the patients and infirmary personnel were not sufficiently informed by physicians. Moreover, that 59% started pregabalin after imprisonment and 48.5% used it for  $\geq 6$  months can be interpreted as to be careful in terms of abuse and addiction. It was found that gabapentin, which is recommended to be used as at least 1,800 mg daily in three divided doses, was used in true frequency only by 49.5% of the participants and in true doses only by 47.8%. Similar to pregabalin, that 54.4% started gabapentin after imprisonment and 64.7% used it for  $\geq 6$  months can be interpreted as to be careful in terms of abuse and addiction.

The fact that 36 participants (2%) have used these two groups of drugs simultaneously, although simultaneous use of pregabalin and gabapentin is not recommended, shows the importance of questioning drug use by physicians, sufficiently informing the patient and considering drug abuse. Besides, the rate of high usage of antidepressant, antipsychotic, or other antiepileptic drugs, and mostly starting these drugs after imprisonment and their long duration of use indicate that the physicians should be careful while managing the treatments. That 16.6% of the participants have used drugs simultaneously in more than one group and 2% of them have used gabapentinoid + antidepressant + antipsychotic simultaneously revealed the requirement for being

careful about multiple drug use and drug abuse and addiction.

Neuropathic pain examples encountered in the clinic can be considered as post herpetic neuralgia, diabetic neuropathy, post-traumatic neuralgia and central post-stroke pain syndrome. Frequently encountered symptoms in neuropathic pain cases are spontaneous pain, allodynia, hyperalgesia, and paresthesia in the painful region.<sup>[21]</sup> The presence of neuropathic pain in 35.5% of the participants suggests the question whether the necessary criteria were adequately questioned for this diagnosis, as the maximum prevalence of neuropathic pain is 1% in the Western societies.<sup>[21]</sup>

The high rate of those reporting that they were alcohol and/or drug addicted strengthen the predictions regarding that probability of addiction may be high in penal institutions, and reveal the possibility that use of gabapentinoids which can also be used in the treatment of addiction can be more than predicted in penal institutions.

The numbers of going to the infirmary and referring to the hospital were generally high in participants. However, the rates of referring to the hospital were lower in the last three months, compared to the last one year. This can be interpreted in a way that condition of the patients becomes more stabilized as a result of the treatment.

Withdrawal symptoms such as restlessness, sleeplessness and nervousness show that abuse and addiction potential of these drugs should be kept in mind. Significant correlations between the gabapentinoid use, dose, usage frequency, duration of use and alcohol/dope addiction, number of going to the infirmary, referring to the hospital and also various withdrawal symptoms suggest abuse and addiction potential of these drugs, and also it should be noted that they may have a role in the treatment of addiction.

There was a significant correlation between the use of other drugs comprising antidepressant, antipsychotics, other antiepileptics, and alcohol/dope addiction, the number of going to the infirmary and referring to the hospital and also various withdrawal symptoms. Also, multiple drug use was high and there was significant correlation between the multiple drug use and alcohol/dope addiction, number of going to the infirmary and referring to the hospital and also various withdrawal symptoms.

The presence of the results which can be accepted as contradictory in the questions about violence against others or violence against the self were attributed to

the accuracy and consistency levels of the answers given by the participants to these questions.

Addiction is a chronic neurobiological disease involving genetic, psychosocial, and environmental factors in its development. Addiction is a manifestation occurring when a substance is taken for the wrong purposes and in gradually increasing amounts as a result of the tolerance developing against that substance, when it is continued to be used although it causes problems in the life of the person, and as withdrawal symptoms appear, when substance intake is reduced or quitted. The common feature of the addictive substances is that they have a reinforcing effect on their intake. Due to the effects on the reward system in brain, the person is addicted to pleasure-inducing feature of the substance and becomes addicted upon using it repeatedly. Addicted person continues to use substance s/he is addicted compulsively despite negative results s/he experienced.

It is shown that the usage rates of antipsychotic and antidepressant were quite high among those participating in our study. The studies conducted with antidepressant drugs have shown that these drugs back up the treatment in the presence of comorbid depression in alcohol addicts, they treat depression and reduce alcohol intake.<sup>[22-25]</sup> Although typical antipsychotics relieve the psychotic symptoms originating from drug addictions, usage frequency of substance may increase in these patients due to the side effects. Studies on olanzapine, clozapine, and quetiapine in regard to the use of antipsychotics in the treatment of alcohol addiction are available. In previous studies, the results regarding that olanzapine, clozapine treatments decreased the desire for alcohol in patients diagnosed with schizophrenia and schizoaffective disorder.<sup>[26-28]</sup> The studies examining the effects of quetiapine on alcohol and substance intake were conducted primarily in the patient populations accompanied by bipolar and schizophrenia diagnoses. Quetiapine was associated with the days of staying sober in the alcohol addiction and is shown to have reduced anxiety, depression and food craving. Several studies have shown that it increases substance abuse in patients only with substance use disorders. On the other hand, cases about the abuse of quetiapine and risk of addiction are increasing more and more in the literature. The most promising antipsychotic agent in the treatment of alcohol addiction seems to be aripiprazole. In a study comparing the aripiprazole, a partial dopamine agonist, with naltrexone, it is reported that aripiprazole is as effective as naltrexone in reducing alcohol use and food craving.<sup>[29-31]</sup> Antiepileptic drugs are known

to be used frequently in the treatment of cleaning in alcohol addiction, withdrawal symptoms and epileptic seizures.<sup>[32]</sup> Data regarding that valproate and lamotrigine reduce the desire for and intake of alcohol in the patients with bipolar disorder are obtained.<sup>[32-34]</sup> The GABA and gabapentin are among the agents the use of which would be considered in the treatment of alcohol addiction, particularly in the withdrawal period in the future.<sup>[22,35]</sup>

Several studies have concluded that pregabalin does not show apparent drug interactions, and there is not any tolerance and abuse;<sup>[36]</sup> however Grosshans et al.<sup>[17]</sup> presented the first pregabalin addiction case in 2010. A 47-year-old male patient in whom pregabalin was started due to alcohol addiction used 7,500 mg/day pregabalin to eliminate alcohol withdrawal symptoms. Although no toxic finding was encountered, sweating, shivering, restlessness, and hypertension were seen in its deprivation and these findings were treated with benzodiazepines; however, the patient continued to use 6,000 mg/day pregabalin again. It is concluded that it is necessary to pay attention, particularly to those who have an addiction history in regard to the abuse of pregabalin.<sup>[17]</sup> There was a significant correlation between the pregabalin use and various withdrawal symptoms in our study.

It is found that the usage rate of pregabalin and gabapentin together with antipsychotic/antidepressants was high in our study. This situation gives rise to the thought that gabapentinoids can be used off-label with neuropathic pain or epilepsy diagnoses, although they have not taken the aforementioned indications yet in Turkey.

In conclusion, although gabapentinoids seem to be used in the treatment of addiction and are proved effective treatment agents in terms of true diagnosis, suitable follow-up and timely completion of the treatment, it is necessary to strictly control their use due to the probability of abuse and addiction.

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