Original article / *Araştırma*

Abuse of prescribed psychoactive drugs

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ABSTRACT

Objective: *The abuse of psychoactive drugs and addiction to them have been a growing problem in the world. Article 188/6 of the Turkish Criminal Code numbered 5237 states 'The provisions of this article shall apply to any substance whose production is subject to the approval of official authorities or whose sales is subject to the prescription issued by the authorized physician, and to other substances causes a narcotic or stimulant effect. However, the imposed penalty can be reduced to half.' and warrants a penalty, indicating that such drugs will be considered in the context of 'narcotic drugs' in case of an abuse. The aim of this study was to investigate the types and frequency of psychoactive drug abuse cases which reflected to the judicial authorities in Turkey.* ***Methods:*** *The files that have been examined by the 5th Specialization Committee of the Turkish Council of Forensic Medicine between January 01st 2012 and January 01st 2019, within the scope of Article 188/6 of the Turkish Criminal Code numbered 5237, were reviewed in this study. The files were evaluated in respect to the distribution of the abused drugs, other narcotic substances detected with these drugs, drug forms and quantities.* ***Results:*** *A total of 1710 reports were examined in the study. The most frequently abused drug group was benzodiazepines, and the most frequently abused members were clonazepam, diazepam and alprazolam. Pregabalin, gabapentin, buprenorphine and quetiapine were the other drugs that took the first place in terms of abuse frequency. The most common narcotic substances detected with drugs were cannabis, synthetic cannabinoids and methylenedioxymethamphetamine. Buprenorphine and pregabalin were the most seized drugs at the crime scenes and on the suspects. Gabapentin was the one encountered most in the biological samples.* ***Discussion:*** *In the light of the data obtained, it can be said that the abused drug profiles may change over time and these changes may be affected by foreign currents. In order to reduce drug abuse, strict follow-up of psychoactive drug prescriptions, attention of the clinicians to the indications, dosage and usage of the drugs that may be abused, a detailed medical investigation of the patients' medical histories, briefing of the patients about the drugs with the potential for addiction, increasing the penalties on the persons who possess such drugs by prescription and then sell them on the streets, and detection and monitoring of the toxicity and death data related to psychoactive drugs are essential in fighting against drugs on a scientific basis.* ***(Anatolian Journal of Psychiatry 2020; 21(2):195-202)***

Keywords: *psychoactive drugs, abuse, pregabalin, gabapentin*

Reçete edilen psikoaktif ilaçların kötüye kullanılması

ÖZ

Amaç: *Psikoaktif ilaçların kötüye kullanılması ve bağımlılığı dünyada giderek artan bir sorun haline gelmiştir. 5237 sayılı Türk Ceza Kanunu'nun 188/6. maddesinde 'Üretimi resmi makamların iznine veya satışı yetkili tabip tarafından düzenlenen reçeteye bağlı olan ve uyuşturucu veya uyarıcı madde etkisi doğuran her türlü madde açısından da madde hükümleri uygulanır. Ancak, verilecek ceza yarısına kadar indirilebilir.' denilerek bu tür ilaçların suiistimali halinde uyuşturucu madde kapsamında değerlendirileceklerini müeyyide altına almıştır. Bu çalışmada Türkiye'deki suiistimal edilen ve adli makamlara yansıyan psikoaktif etkili ilaç olgularının çeşitleri ve sıklıklarının araştırılması*

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Received: June, 29th 2019, Accepted: September, 20th 2019, doi: 10.5455/apd.53469

amaçlanmıştır. ***Yöntem:*** *Bu çalışmada Adli Tıp Kurumu 5. İhtisas Kurulu'nda 01.01.2012-01.01.2019 tarihleri arasında 5237 sayılı Türk Ceza Kanunu'nun 188/6. maddesi kapsamında değerlendirilen dosyalar incelenmiştir. Dosyalar suiistimal edilen ilaçların dağılımları, bu ilaçlarla birlikte saptanan diğer uyuşturucu maddeler, ilaç formları ve miktarları yönüyle değerlendirilmiştir.* ***Bulgular:*** *Çalışmada 1710 rapor incelenmiştir. En sık kötüye kullanılan ilaç gurubu benzodiyazepinler olup bu grubun en sık kötüye kullanılan üyeleri ise sıklık sırası ile klonazepam, diyazepam ve alprazolam olmuştur. Pregabalin, gabapentin, buprenorfin ve ketiyapin suiistimal sıklığı açısından ilk sıralarda yer alan diğer ilaçlar olmuştur. İlaçlarla birlikte en sık saptanan uyuşturucu maddeler esrar, sentetik kannabinoidler ve metilendioksimetamfetamindir. Olay yerlerinde ve şüpheliler üzerinde en fazla buprenorfin ve pregabalin saptanmıştır. Biyolojik örneklerde ise en fazla gabapentin saptanmıştır.* ***Tartışma:*** *Elde edilen verilere göre, kötüye kullanılan ilaç profillerinin zaman içinde değişim gösterebildiği ve bu değişimlerin yurtdışı akımlardan etkilenebildiği söylenebilir. İlaçların kötüye kullanılmasını azaltmak için, psikoaktif ilaç reçetelerinin daha sıkı kontrol edilmesi, klinisyenlerin kötüye kullanılma olasılığı olan ilaçların endikasyon, doz ve kullanım takibi açısından daha dikkatli olmaları, hastaların tıbbi özgeçmişlerinin ayrıntılı olarak sorgulanması, bağımlılık potansiyeli olan ilaçlar konusunda hastaların bilgilendirilmesi, bu ilaçları reçeteyle alıp sokakta satan kişiler üzerindeki cezaların artırılması, psikoaktif ilaçlara bağlı toksisite ve ölüm verilerinin belirlenmesi ve izlenmesi uyuşturucu ile bilimsel temelli mücadele açısından önem taşımaktadır.* ***(Anadolu Psikiyatri Derg 2020; 21(2):195-202)***

Anahtar sözcükler: *Psikoaktif ilaçlar, suiistimal, pregabalin, gabapentin*

INTRODUCTION

Apart from the purpose of medical use, the abuse of psychoactive drugs has increased gradually and become a growing problem in many countries.[1-3] As a matter of fact, addiction to these drugs is defined as the 'fastest growing narcotic substance problem' in some countries.[4] These drugs are abused for their sedative and euphoric effects.[4,5]

The lack of information on the addiction potential of these drugs and the perception that they are safer than the illegal drugs have contributed to an increase in their consumption.[6] Abused drugs include mainly benzodiazepines (alprazolam, midazolam, diazepam, clonazepam, chlordiazepoxide), ketamine, opioids (buprenorphine, tramadol, hydromorphone), biperiden, quetiapine, pregabalin and gabapentin.[7-9]

Drugs may deviate from legal use at any point during the pharmaceutical production and distribution process and may be utilized for illegal use. Drugs may be stolen from the production facility, wholesale distributors, drug stores, pharmacies, hospitals, nursing homes or clinics, doctors, dentists, veterinary offices or the medicine cabinets of parents or friends.[10,11] In addition, the increasing demand comprise a basis for illegal production and trafficking.

Psychoactive drugs and substances are frequently used by people who want to experience mental and emotional pleasure.[12] These drugs have become the preferred alternatives by drug users, due to their psychotomimetic effects.[13] In dance parties and crazy parties called 'rave', these drugs can be abused together with other narcotic substances. They are also used to increase sexual pleasure and have more fun. In addition, drug users may prefer prescribed psychoactive drugs to suppress the symptoms of the abstinence syndrome.[1]

The use of these pleasure-inducing drugs on own initiative of the person for indications other than medical is evaluated within Article 188/6 of the Turkish Criminal Code (TCC) numbered 5237.[14]

In our study, we retrospectively evaluated the 1710 files that have arrived at the 5th Specialization Committee of the Turkish Council of Forensic Medicine, the highest authority in Turkey that draw an expert opinion in such cases, during the last seven years, and tried to establish scientific evidence-based policies and combat strategies taking the obtained data into account.

METHODS

The Turkish Council of Forensic Medicine is an organization connected to the Ministry of Justice of the Republic of Turkey. The Council is headquartered in Istanbul and has subunits in the 81 provinces of the country, providing forensic expertise for some 150000 cases annually. The organization is composed of Specialization Committees that draw an expert opinion by evaluating the case with the participation of experts from different disciplines and from laboratories that provide analysis services. In total, there are eight committees which are specialized in certain areas, and each of them is assigned a number. In our study, 1710 files that have arrived at the 5th Specialization Committee of the Turkish Council of Forensic Medicine, which creates the scientific reports on drugs and psychoactive substances, between January 01st 2012 and January 01st 2019 were evaluated

within the scope of Article 188/6 of the TCC numbered 5237. The files were evaluated in respect to the types, forms and amounts of the abused drugs and their quantitative changes by years, other narcotic substances detected with these drugs and the frequency of detection of the drugs and the accompanying narcotic substances at the crime scene and/or in the biological samples.

RESULTS

The types of drugs abused due to its psychoactive effects and therefore evaluated within the scope of Article 188/6 and the number of cases are shown in Figure 1. In 614 cases, benzodiazepines were the most abused drugs, followed by pregabalin with 362, gabapentin with 310 and buprenorphine with 242 cases. Of the 24 cases listed under the heading 'others', dextromethorphan was detected in six cases, methylphenidate was detected in five, oxycodone in four, thiopental in three, trihexyphenidyl in five and remifentanil in one case.

Abused drugs were found on individuals, in the biological samples and/or at the crime scene. While only one psychoactive drug was detected in 1072 cases, more than one psychoactive drug or a narcotic substance in addition to the psychoactive drug was found in 638 cases. The narcotic substances seized together with psychoactive drugs and their frequency of detection are given in Figure 2. In Figure 2, the substances detected in 121 cases under the heading of 'synthetic cannabinoids' were; -5F-ADB, FUB-AMB, AMB-FUBINACA, AMB-CHMINACA, AB-CHMINACA, ADB-CHMINACA, etc. The group with the heading 'others' included three cases with propoxyphene, two cases with pethidine, and one case of each with methedrone, meta-chlorophenylpiperazine, 5-MeO-MiPT, alpha-pyrroli-

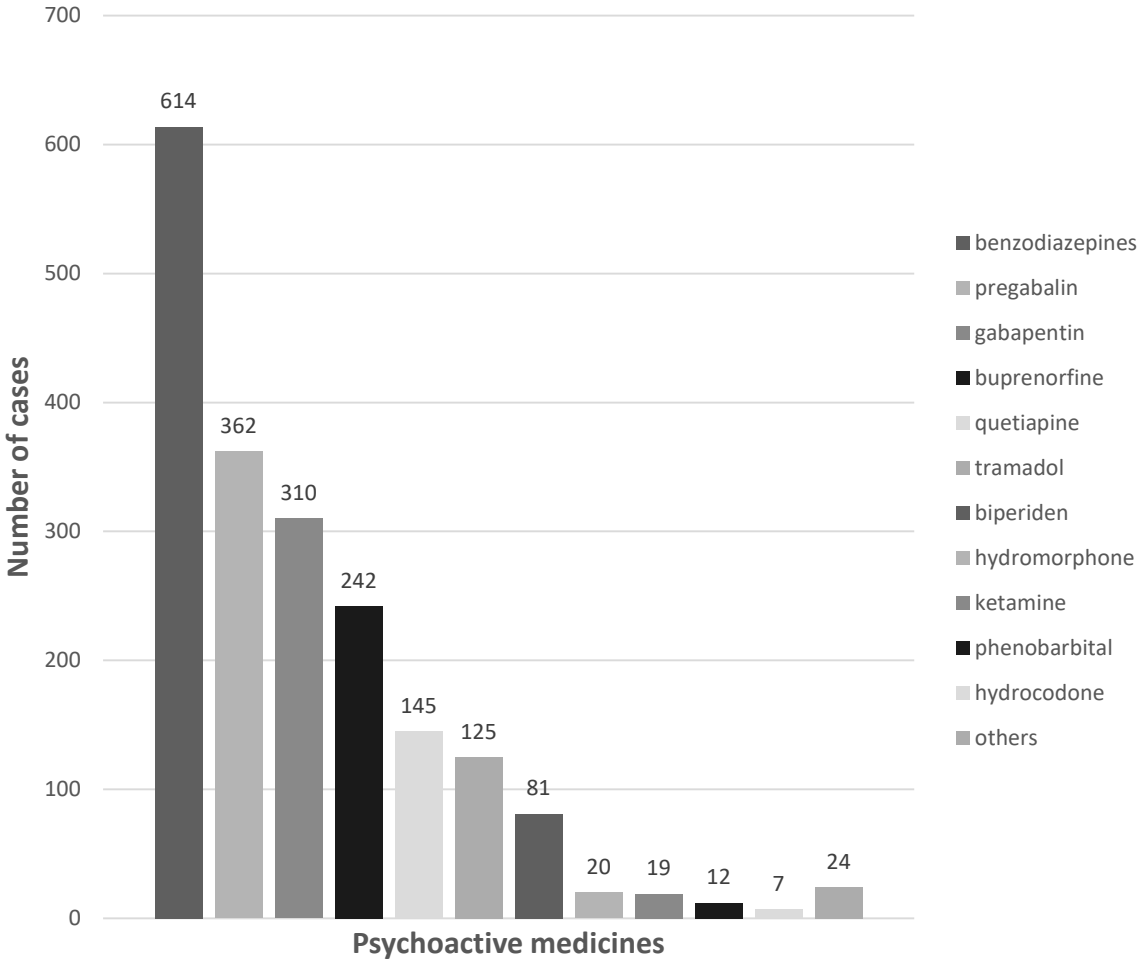

Figure 1. Types of abused psychoactive medicines

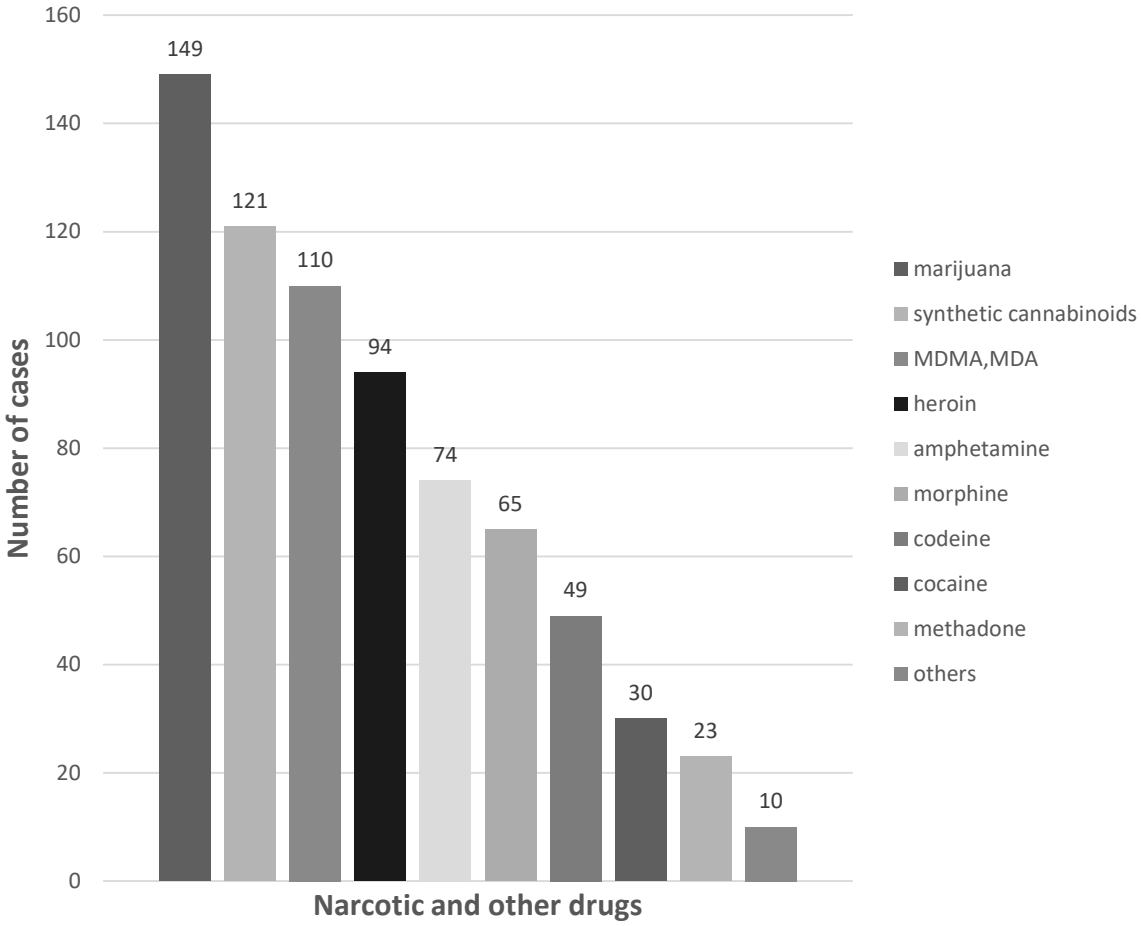

Figure 2. Drugs seizured/detected with psychoactive medicines

dinovalerophenone (α-PVP) and 4-MEC.

As demonstrated in Figure 1, the most frequently abused substances belonged to the benzodiazepine family. It was observed that 86% of the abused benzodiazepine-type drugs consisted of clonazepam, diazepam and alprazolam.

Although there was a gradual increase in all drugs in which an abuse has been observed, gabapentin and pregabalin has shown a significant increase since 2014, when they were first detected. This increase is given in Figure 3. While the number of cases related to pregabalin was one in 2014, it has increased steadily over the last years, reaching 261 in 2018. In 2014, there were three cases associated with gabapentin, and in 2016, a significant increase was observed with 194 cases.

In 42% of the cases (732 cases), the detection was made in the biological samples such as blood, urine, hair and nail of the individuals and in 58% of the cases (978 cases) the detection was made at the crime scene. The materials seized on the individuals were in the form of tablets, capsules, powders, ampoules and tablet fragments.

Table 1 shows the distribution of the psychoactive drugs seized at the crime scenes and on the suspects according to weight. Of the 736 cases, in which tablets were seized at the crime scene or on the individuals, 315 (43%) had less than 10 tablets. In such cases, if the drug is prescribed to the individual and if the drug and/or its metabolite is detected in the biological samples of the individual, the courts conclude that the individual is a user and there is no abuse. If the seized amount is between 11 and 50 tablets and if the individual can prove that the drug is prescribed in this amount, no legal action is taken under Article 188/6 of the TCC. In case the seized amount exceeds 50 tablets, the presence of the drug active substance in the biological sample of the individual is not sufficient and legal action is taken for the individual for selling and

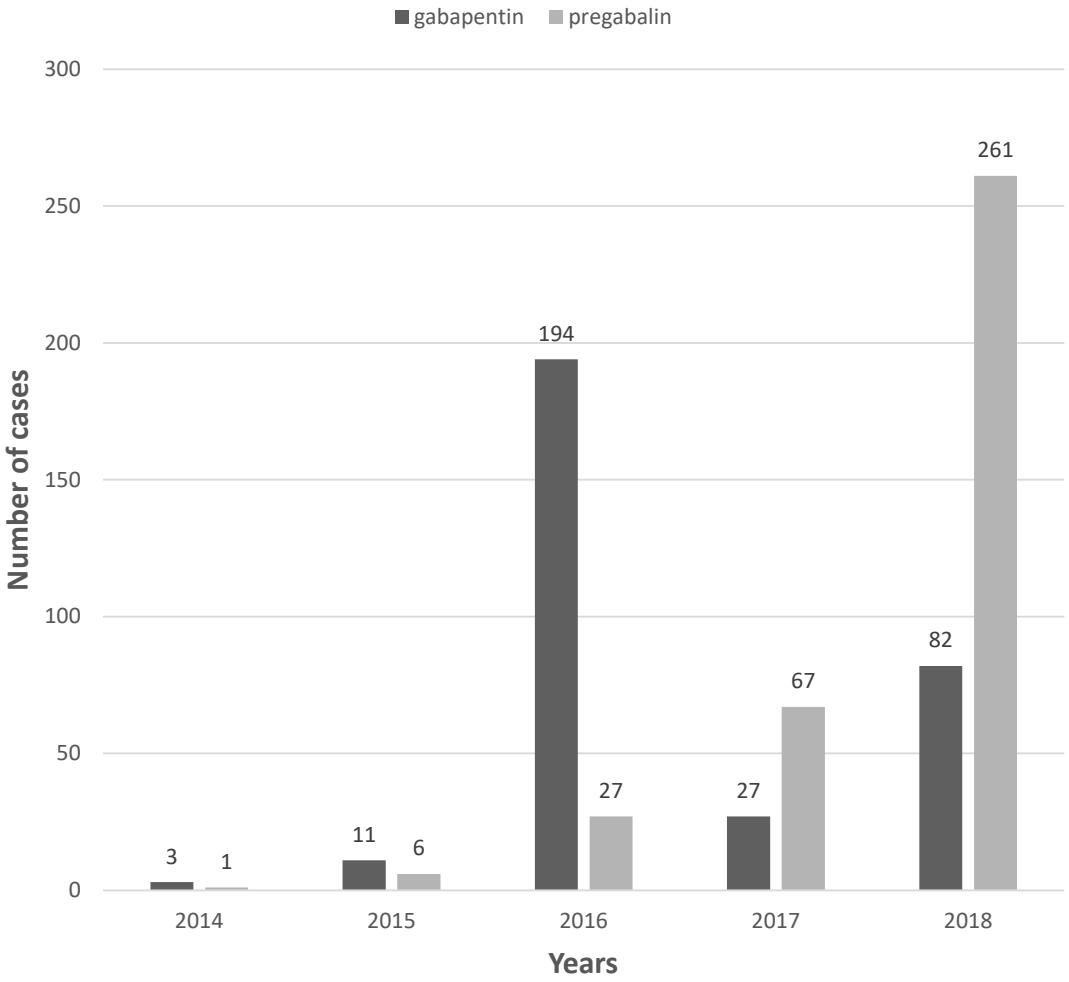

Figure 3. Comparison of gabapentin and pregabalin seizures and detection

Table 1. The forms and amounts of the seized psychoactive drugs

	Prega-balin	Gaba-pentin	Clona-zepam	Diaze-pam	Alpra-zolam	Bupre-norphine	Quetia-pine	Tramadol	Total
Number of tablets 10	65	20	42	10	22	116	19	21	315
Number of tablets 11-50	69	21	26	6	18	24	5	14	183
Number of tablets 51-100	27	9	12	3	8	6	1	4	70
Number of tablets 101-500	49	6	12	0	5	13	0	12	97
Number of tablets 501-1000	9	4	3	1	4	2	0	6	29
Number of tablets ≥1000	8	3	2	1	6	6	0	16	42
Fractures of tablets parts	5	1	9	1	6	29	2	2	55
Powder	9	5	0	0	1	5	1	0	21
Ampules	0	0	0	1	0	0	0	0	1
Total	241	69	106	23	70	201	28	75	813

trading, to the extent in parallel with the increase in the number of tablets seized.

The amounts of the psychoactive drugs detected in the biological samples are given in Table 2. Quantitative analyses were performed in the blood. Among the drugs whose quantitative analysis in the blood was performed, gabapentin took the first place with the highest amount. The

Table 2. The level of psychoactive drugs in the biological samples

Narcotic drug	Number of cases	Minimum level (ng/ml)(blood)	Maximum level (ng/ml)(blood)	Therapeutic interval (ng/ml)
Gabapentin	185	3	49022	2000-10000
Diazepam	86	1	590	20-4000
Quetiapine	55	1	822	195-632
Clonazepam	55	0.1	600	7-75
Alprazolam	33	1	572	25-102
Biperiden	17	1	130	5-100
Midazolam	15	2.63	90	80-250
Tramadol	14	2.26	550	100-600
Ketamine	5	1.5	1312	200-6300
Phenobarbital	4	3.7	416	1000-3000
Pregabalin	3	8.7	19	500-16000
Buprenorphine	2	1.3	5636	14-110

second most quantitatively analyzed drug was diazepam. Although the number of cases with pregabalin was higher, there were only two cases that were performed a quantitative analysis in the blood. In some cases, since the pregabalin was not the pure standard form, quantification could not be performed. The level of gabapentin, quetiapine, clonazepam, alprazolam, biperiden and buprenorphine in the blood was found above the therapeutic level in some cases.

DISCUSSION

It is known that individuals who use these drugs due to psychiatric disorders may start to abuse them over time. On the other hand, the initial use of such drugs with the intention of abuse is not uncommon. Health professionals with a relatively easy access to psychoactive drugs, such as anesthesiologists, emergency physicians, family/general practitioners, and psychiatrists have a high potential to exploit these drugs.[15,16]

In our study, when the drug abuse over the years were reviewed, pregabalin, gabapentin, buprenorphine in particular were seen to have a tendency to increase, and benzodiazepines exhibited similar distributions and formed the most abused group of drugs in general. The abuse of benzodiazepines to this extent may be due to the fact that they are well known by health professionals and the community, and are the most commonly prescribed sedative-hypnotics. Clonazepam, diazepam and alprazolam were among the most frequently abused benzodiazepines.

If we are to speculate about the forms of the abused drugs detected at the crime scene, the seizure of tablets in large quantities, accompanied by tablet fractures and drugs in the powder form, may be considered as findings that support the illegal trade and abuse of the substances. In addition, during drug abuse, the user usually takes the drugs at a higher dose than the therapeutic dose in order to experience its euphoric and sedative effects. Therefore, the drug level in the blood detected above the therapeutic range may be considered as a finding that supports abuse.

In our study, the most commonly abused opioid was buprenorphine (Figure 1). The detection of this drug in five cases in the powder form suggests that it can be abused using different methods of administration or mixed with other substances. Heroin was the most common drug found along buprenorphine. The use of buprenorphine in the treatment of heroin addiction may provide evidence that this drug has been abused over time by addicts who were getting treatment.

In the Middle East, especially in Iran and Egypt, tramadol abuse has increased considerably.[17] The prevalence of lifetime tramadol abuse among Iranian adolescents was reported as 4.8%.[17] In our study, the number of files related to cases in whom tramadol was detected increased over the years. Especially the 15 cases, in which over 1000 tablets of tramadol were seized at the crime scene, provide a strong evidence that support the trafficking and illegal trade of this drug. In one case, tramadol dextromethorphan and biperiden were detected within the same tablet, which shows that different formulations of tramadol with other psychoactive drug constituents have been prepared, that is,

they have been also used in illegal manufacturing. Furthermore, the seizure of the drug in the powder form may be an important finding that it has been tested and abused via a different method of administration.

In our study, however, it was observed that ketamine abuse did not tend to increase over the years. In one case, ketamine and caffeine were found within the same tablet, and in our country, this data can be considered as an evidence to the use of ketamine in the production of illicit substances.

In Denmark, the use of pregabalin has been reported to have increased 10-fold during the last 10 years.[8] Based on the pharmaceutical sector data, the pregabalin sales in the world in 2014 was reported to have progressed to the 12th place in gross sales, with a 12% growth rate.[8] In the UK, an online survey with 1,500 participants aged between 16 and 59 years reported a 0.5% prevalence of pregabalin abuse.[18] In a sample population of patients who wanted to be treated for opioid addiction, 7% of the patients were reported to use pregabalin in amounts greater than the non-prescribed or prescribed dose.[19]

In the current study, the cases with pregabalin showed a tendency to increase as in abroad, which proves that the tendencies of substance and drug abuse abroad also affect our country. In particular, pregabalin was one of the most seized drugs at the crime scenes and on the suspects, in tablet, tablet fragment and powder form. Its seizure in the powder form is a finding that suggest the use of the drug via a different method of administration, or the use, production or illicit trading of the drug by mixing it with other psychoactive components. Again in the current study, the quantitative analysis of pregabalin in the biological samples was performed in a limited number of cases, suggesting a lack of quantitative analysis of pregabalin in our country. This drawback can lead to failure in determining the status of the pregabalin-related deaths in our country.

When the crime scene data were reviewed, 49 cases were found to possess 100 to 500 tablets, nine cases were found to possess over 500 and eight cases over 1000 tablets, bringing up the total to 66 cases and more than 100 pregabalin tablets. Another noteworthy observation was about the seizure of more than 1000 tramadol tablets on 16 cases. Similarly, alprazolam and buprenorphine in the amount of more than 1000 tablets were detected on six cases. The seizure of tablets over the number of tablets that are usually contained in a box or a blister indicates the trade of abuse.

Similar to the findings in the literature, gabapentin cases tended to increase over the years in our study. The most frequently quantitatively analyzed drug in the biological samples was gabapentin. In some cases, the level of the drug in the blood was above the therapeutic level.

In a study where online reports of pregabalin and gabapentin abuse from 2008 to 2015 were analyzed, the researchers stated that pregabalin was an ideal psychotropic drug used for recreational purposes, could lead to a mixed type of euphoria similar to alcohol/gamma-hydroxybutyrate and benzodiazepine, could cause empathogenic effects and dissociation similar to dextromethorphan, and helped cope with the abstinence of opioids.[20]

In a report on the intravenous use of quetiapine, a 33-year-old male patient who presented to the emergency ward for detoxification and rehabilitation and had addiction to multiple substances (cocaine, alcohol, heroin and benzodiazepine), told that he had stolen the quetiapine prescribed for his wife (400-800 mg/day), crushed it into powder and mixed it with cocaine, dissolved it in water, filtered it with bandages, and then injected it to himself. Researchers have reported that patients used quetiapine in this manner in order to experience its hallucinogenic effects.[21] In our study, quetiapine abuse cases have also increased over the years, and the drug has been frequently detected in the biological samples. This result suggests that the drug is more abused in patients receiving psychiatric treatment.

In order to reduce the risk of drug abuse, care must be taken in patient selection, treatment and follow-up. The medical history of the patient should be questioned in detail. For example, the use of opioids in the treatment of pain in a patient who is an alcohol or substance addict carries a risk for the potential for abuse. The medical records of the patients should be examined, the treatment goals should be determined, and the patient's condition should be recorded in detail before and after the treatment.

The side effects of the drugs in psychiatric patients with multiple drug use should be followed up through clinical examinations and laboratory tests, and when the patient takes a drug with the potential of addiction for treatment, close monitoring of the patient for drug abuse or addiction,

investigation of the presence of the accompanying general medical condition, and evaluation of the patient with other specialties when necessary are of great importance.

Authors' contributions: *E.M.: Finding subject, literature review, design, gathering data; F.A.: Finding subject, design, writing manuscript.*

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