https://doi.org/10.31925/farmacia.2021.6.25 **ORIGINAL ARTICLE**

PREGABALIN CONSUMPTION IN TURKEY: WAS IT AN ABUSE?

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Abstract

The gabapentinoids (pregabalin and gabapentin) have been developed as anticonvulsants and have been prescribed increasingly for more than one different medical indication in recent years. Although the risks of addiction and the abuse of them were considered as low probability in the past, recent studies have shown that the situation is very different about them. Especially, pregabalin consumption has become remarkable about its adverse effects. The main purpose of this study is to investigate the presence of the abuse related to pregabalin consumption data between 2004 and 2019. Due to the warnings made by the World Health Organization, the pregabalin consumption has decreased by approximately 50% all around the world in 2019. According to our results, the pregabalin consumption in Turkey has increased by 36 times between 2007 and 2018. After the prescription status was changed in 2019, its consumption has decreased by about 50%, the same as the world. The data obtained in this research indicate that pregabalin has been abused. This abuse has been caused by more than one factor/determinant. The diagnosis treatment guides and the reimbursement rules should be constantly updated and especially the physicians' prescriptions should be controlled more effectively. Otherwise, experiencing similar abuses in the future it will be inevitable.

Rezumat

Gabapentinoidele (pregabalin și gabapentin) au fost dezvoltate ca anticonvulsivante și sunt din ce în ce mai prescrise pentru diferite indicații în ultimii ani. Deși riscurile de dependență și abuz au fost considerate probabilități reduse în trecut, studiile au arătat că situația este foarte diferită. Consumul de pregabalin a devenit remarcabil. Scopul principal al acestui studiu este investigarea abuzului în funcție de datele privind consumul anual de pregabalină. Analiza a fost realizată folosind datele înregistrate pentru consumul din perioada 2004-2019. Datorită avertismentelor Organizației Mondiale a Sănătății, consumul de pregabalină a scăzut cu aproximativ 50% în întreaga lume în 2019. Potrivit rezultatelor cercetării, consumul de pregabalină în Turcia a crescut de 36 de ori între 2007-2018. După schimbarea statutului de prescripție medicală în 2019, consumul a scăzut cu aproximativ 50%, similar cu cel la nivel mondial. Datele obținute indică faptul că s-a abuzat de tratamentul cu pregabalin, acest aspect fiind cauzat de mai mulți factori. Ghidurile de tratament pentru diagnosticare și regulile de rambursare ar trebui să fie actualizate constant și mai ales prescripțiile medicilor ar trebui să fie controlate mai eficient. În caz contrar, experimentarea unor abuzuri similare în viitor este inevitabilă.

Keywords: abuse, Turkey, pregabalin, gabapentin, gabapentinoids

Introduction

In general, drug abuse refers to the use of drugs in indications other than those approved, but it also includes unnecessary use of addictive drugs [32]. In addition to the medical use, the abuse of psycho-active drugs has increased in many countries and it has become a growing problem [13, 15]. Such drugs are misused due to their sedative and euphoric effects on the human central nervous system [7, 22]. These abused drugs may or may not have an addiction potential [32]. They can be psychotropic or from different drug groups [29]. People have no knowledge about the addictive potential of drugs. They have perceptions that the prescribed drugs are safer than illegal substances. This situation contributed to the increase in the consumption of such drugs [10, 19]. The prescription of central nervous system drugs, particularly opioids, sedative and stimulant groups, have increased dramatically in the United States since the early 2000s [20, 28]. In the reports of five European countries, it was stated that the opioid, sedative and stimulant group drugs were mostly used outside the common indications [20]. On the other hand, there are no systematic data for Turkey [19].

Pregabalin, structurally related to gabapentin, is an alkylated analogue of gamma-aminobutyric acid (GABA). It holds on to the a2d type 1 protein of the P /Q voltage-dependent calcium channel and reduces the central release of stimulating molecules [18]. Pregabalin was originally developed as an anticonvulsant, like gabapentin [30]. Both drugs have been increasingly prescribed for a number of clinical conditions [16]. In the past 10 years, gabapentinoids have been widely prescribed, as well as being sold on the global black market and even on the internet and have been causing many serious side effects on their users. They are misused between therapeutic or non-therapeutic doses

by orally, intranasal and intravenously [6]. As it has a faster onset of impact than gabapentin, pregabalin has a higher potential for abuse [9].

In Europe, pregabalin has marketing authorisations for epilepsy, neuropathic pain (NP) and general anxiety disorder (GAD). It has also marketing authorisations for fibromyalgia, post-herpetic neuralgia and neuropathic pain after spinal cord injury, but has not been approved for GAD in the USA [36]. In Turkey, it has marketing authorisations for epilepsy, peripheral NA, GAD and fibromyalgia [8].

Until recently, the risk of misuse of gabapentinoids was thought to be low (pregabalin) or none (gabapentin). However, abuse of gabapentinoids is based in 2010 on data from studies involving prisoners and people involved in the drug addiction treatments [31]. Since then, the reports of abuse, poisoning and drug discontinuation syndrome have increased on gabapentinoids [6, 26]. Gabapentinoids have been placed on the "Substances to be Used Controlled V" list by the American Food and Drug Administration (FDA) [21]. In the UK, it has been included in the "Class C Controlled Substances" list due to the increased mortality related to abuse [17]. By order of the Turkish Ministry of Health, pregabalin and gabapentin were placed on the "Controlled Drugs That Should Be Given with a Normal Prescription" list in 2013 [2], and only pregabalin was included in the "Controlled Drugs That Should Be Given with a Green Prescription" list in 2019 [3, 6]. However, the reimbursement agency has left pregabalin to the personal preferences of some group of specialist physicians despite treatment guides [5].

In this study, the presence of abuse by pregabalin and other drugs repaid at the same indication was investigated over the consumption amounts by the years in Turkey.

Materials and Methods

In this paper, previous studies that were done after 2005 on prescription drugs and pregabalin abuse have been scanned in the PubMed, Scopus and Ebsco indices. In addition, the drug consumption data of Turkey, from 2004 to 2019, of the active substances included in the study were provided with an official letter from Iqvia Turkey/IMS-Health institution. Because, IQVIA keeps records of all the movements of the drug market from the production to the consumption. Pregabalin is reimbursed only in diagnoses of NA and fibromyalgia in Turkey. For this reason, other active substances (gabapentin and alpha lipoic acid) that are only repaid in the NA indication, like pregabalin, are also included in the study. It is aimed to better understand the consumption movements of the drugs by using the data of the whole market in which pregabalin is located. The analysis was carried out over the consumption data of the active substances by years.

Results and Discussion

Gabapentin is found to be presented in 6 different dosage forms in the Turkey pharmaceutical market. In 2004, its consumption was of 522.950 boxes; it was raised to 2.462.443 boxes in 2009, to 5.131.479 boxes in 2018; but after the regulation on dispensing it with green prescription, it was dropped to 4.199.922 boxes; that means of almost 20% reduction in its consumption by 2019 (Table I).

Table I

Unit box consumption of gabapentin in Turkey by years [12]

Gabapentin	100 mg	250 mg	300 mg	400 mg	600 mg	800 mg	Total
2004	68.859	0	345.933	107.733	0	425	522.950
2005	68.729	0	492.018	13.144	19.447	150.528	743.866
2006	81.098	0	56.592	13.684	496.181	329.969	977.524
2007	87.321	0	150.308	141.068	649.305	422.058	1.450.060
2008	121.379	0	245.689	276.310	827.165	502.892	1.973.435
2009	164.275	0	323.953	316.168	1.066.540	591.507	2.462.443
2010	210.287	0	391.955	304.163	1.416.194	728.721	3.051.320
2011	234.167	0	474.894	300.017	1.888.962	886.256	3.784.296
2012	268.093	0	474.437	236.526	2.222.027	930.642	4.131.725
2013	287.468	0	671.932	277.600	2.380.923	971.714	4.589.637
2014	308.394	3.377	692.123	279.631	2.420.919	996.099	4.700.543
2015	335.671	7.041	814.321	326.072	2.475.620	1.015.292	4.974.017
2016	340.433	12.032	920.970	329.204	2.303.583	999.997	4.906.219
2017	354.043	8.048	993.064	354.246	2.432.080	1.027.707	5.169.188
2018	322.753	6.561	1.034.319	357.735	2.411.470	998.641	5.131.479
2019	194.311	4.353	921.976	307.895	1.949.248	822.139	4.199.922

Pregabalin was introduced to the market in 2007 in 3 different dosage forms. It was marketed in 8 different dosage forms by 2019. A total of 165.286 boxes of it were consumed in 2007, 1.528.352 boxes in 2012, and a total of 5.974.838 boxes in 2018. Its consumption increased 36 times from 2007 to 2018. In 2013, pregabalin and gabapentin were included in the list of "Controlled Drugs that Should Be Given with a Normal Prescription",

but despite this decision, pregabalin sales continued to increase. 2.938.047 boxes of pregabalin were consumed with a 50% decrease, after it was included in the list of "Controlled Drugs That Should Be Given with a Green Prescription" in 2019 (Table II).

Table II

Unit box consumption of pregabalin in Turkey by years [12]

Pregabalin	20 mg	25 mg	50 mg	75 mg	100 mg	150 mg	225 mg	300 mg	Total
2004	0	0	0	0	0	0	0	0	0
2005	0	0	0	0	0	0	0	0	0
2006	0	0	0	0	0	0	0	0	0
2007	0	653	0	88.905	0	70.544	0	0	165.286
2008	0	2.682	0	154.515	0	140.196	0	0	311.240
2009	0	5.507	0	236.092	0	198.501	0	22.376	462.476
2010	0	11.505	0	346.096	0	251.149	0	33.810	642.560
2011	0	13.539	0	551.606	0	332.254	0	47.898	945.297
2012	0	32.984	0	950.442	0	467.795	0	77.131	1.528.352
2013	0	58.497	2	1.199.037	0	636.426	0	109.293	2.003.255
2014	0	159.950	0	1.866.478	0	925.437	6.598	163.463	3.121.926
2015	0	278.999	36.103	2.766.828	0	1.165.203	44.403	232.525	4.524.061
2016	0	345.136	129.336	3.389.565	0	1.275.172	67.691	303.050	5.509.950
2017	6	401.247	117.807	3.786.762	512	1.457.854	99.887	486.644	6.350.719
2018	2	398.892	229.916	3.177.011	38.200	1.364.642	130.370	635.807	5.974.838
2019	0	184.286	108.330	1.270.886	24.987	795.037	100.789	453.732	2.938.047

Table III

Unit box consumption of alpha lipoic acid and combinations in Turkey by years [12]

Alpha lipoic acid and combinations	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Total Unit box consumption	279.783	419.396	526.434	967.994	1.358.411	1.903.341	2.278.335	2.721.185	3.485.684	3.613.291	3.380.173

The drugs containing alpha lipoic acid, which are reimbursed only in the NP indication, were consumed 279.783 boxes in 2009, 3.613.291 boxes in 2018, and 3.380.173 boxes in 2019 when pregabalin was included in the green prescription (Table III).

While gabapentin had 4 different generics in 2009, this number was raised at 8 in 2019. There was a remarkable increase in the generic number of pregabalin between 2009 and 2019. 15 generics of pregabalin, which had only one generic in 2009, were identified in the market in 2019. While one generic containing alpha lipoic acid was found in 2009, its 7 generics were determined in 2019 (Table IV).

Table IV

Number of generics on the market by years [12]

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Gabapentin	4	5	6	7	8	8	8	7	7	7	7
Pregabalin	1	1	4	7	14	15	16	14	15	15	15
Alpha l. acid	1	1	1	3	4	5	6	6	7	7	7

The consumed total volumes of these drugs were 3.204.702 boxes in 2009, but them raised to 14.726.956 boxes in 2018. While the total market volumes increased approximately 5 times between 2009 and 2018, the sales of pregabalin increased cumulatively about 15 times. After pregabalin was included in the green prescription in 2019, gabapentin sales decreased by 25%, pregabalin by 50%, alpha lipoic acid by 6.5%, and the total market volumes by 28% (Table V).

In the literature, a systematic review of preclinical (n = 17), clinical (n = 19), epidemiological (n = 13) studies and case reports (n = 9) addressing the potential for abuse of pregabalin has been found [27]. The clinical studies have reported euphoria as a common side effect in the patients treated with pregabalin. As a result, with their studies in 2016, Schjerning *et al*., decided that pregabalin had an important clinical abuse potential and that prescribers should be especially careful in the patients with a history of substance abuse [27]. According to a study, between 2004 and 2015, 7.639 reports for pregabalin and 4.301 reports for gabapentin were detected (misuse/abuse/addiction), 75% of them are after 2012 [4].

Table V

Total market consumption by years [12]

Years	Gabapentinoids			Alpha lipoic acid	Total market
	Gabapentin	Pregabalin	Total		
2009	2.462.443	462.476	2.924.919	279.783	3.204.702
2010	3.051.320	642.560	3.693.880	419.396	4.113.276
2011	3.784.296	945.297	4.729.593	526.434	5.256.027
2012	4.131.725	1.528.352	5.660.077	967.994	6.628.071
2013	4.589.637	2.003.255	6.592.892	1.358.411	7.951.303
2014	4.700.543	3.121.926	7.822.469	1.903.341	9.725.810
2015	4.974.017	4.524.061	9.498.078	2.278.335	11.776.413
2016	4.906.219	5.509.950	10.416.169	2.721.185	13.137.354
2017	5.169.188	6.350.719	11.519.907	2.934.684	14.454.591
2018	5.131.479	5.974.838	11.106.317	3.613.291	14.726.956
2019	4.199.922	2.938.047	7.137.969	3.380.173	10.518.142

In a normal situation, while gabapentin, whose primary competitor is diminished from the market, was expected to fill this gap, its consumption decreased rather than increasing in 2019 [Table I]. This can be explained by the general hesitations of the physicians against gabapentinoids. Gabapentin is thought to have a lower risk of abuse than pregabalin [7]. There are also studies related to which gabapentin is misused with the opioids and sedative drugs. For this reason, the consumption of gabapentin should be carefully monitored. Pregabalin consumption increased about 72 times in Finland from 2004 to 2012. However, there was no increase in gabapentin consumption in the same period [9]. In Denmark, while gabapentin entered the market in 1997 and reached 8.6 million boxes sales figure in 2018; pregabalin entered the market in 2005 and reached 9 million boxes sales figure in 2018 [24]. In the UK, pregabalin and gabapentin prescriptions increased by approximately 24% each year from 2004 to 2015, and increased from 1 million to 10.5 million annually [14]. In Turkey, gabapentin consumption increased by 10 times between 2004 and 2018 (Table I). Pregabalin consumption increased by 36 times between 2007 and 2018 (Table II).

Many factors are thought to be effective in the cumulative increase of pregabalin consumption in Turkey. For example, while there was one drug containing pregabalin on the market in 2007, there were 15 different generics in 2018 (Table IV). The main purpose in generic drug application is the economic benefit. However, each new generic creates its own market rather than taking a share from the total market. With the inclusion of new manufacturers in the market, which has grown uncontrolled, the total number of generics has increased. For this reason, it is thought that new generics increase pregabalin consumption over the years. In this process, gabapentin remained only in 7 generics. A second reason is that pregabalin had 3 different dosage forms in 2007, while 8 different dosage forms were available in 2018 (Table II). Continuously introducing their different dosage forms to the market can be explained by the manufacturers' strategies to make more profit from the growing market and to get rid of the generic drug pressure. The Ministry of Health has not been able to implement a licensing policy in line with the needs of the public health. Licensing of different dosage forms with the manufacturer's demands increased their consumptions. Another reason for their increased consumption is that it can be prescribed in fibromyalgia without any reimburse rules [1]. Similarly, in Finland, counting pregabalin through the antiepileptic drugs paved the way for easy prescription and increased the abuse [34]. It is an optimistic approach to think that pregabalin is abused only by malicious individuals. There is more than one factor in the abuse. Bureaucratic mistakes made it possible for the physicians to prescribe approximately 6 million boxes of pregabalin until 1 year ago. Its inclusion on the green prescription in 2019 is a delayed and neglected decision.

In the prison environment, pregabalin and gabapentin are highly sought after for enhancing the effects of opiates or abusing them solely. It is stated that the improper prescription of gabapentin and pregabalin for non-specific mechanical back pain, which is frequently encountered in prison patients, causes problems for the clinicians [25]. In a study conducted in Turkey, the physicians working in the prison were asked the question “the first five drugs that you think abused by inmates” and in their answers to the question, gabapentin and pregabalin were found in 80% of the “top 5 drug” list [33]. In a study by İlhanlı *et al*. (2017) in the prison population, in some prisons, the rate of gabapentinoid use was found higher than the normal population. There was a significant correlation between the multiple drug use, alcohol and the drug addiction, various withdrawal symptoms, the number of visits to the infirmary and the number of referrals to the hospital [11].

Following the warnings of the WHO (World Health Organization) in 2018 [37], pregabalin consumption has decreased by 45 - 50% worldwide [23]. Similarly, in Turkey, after being included in the green prescription coverage in 2019, the consumption has decreased by approximately 50% regarding all the dosage forms

(Table II). The fact that the decrease in consumption of gabapentin and alpha lipoic acid after the precautions taken was not as strong as in the case of pregabalin, supports the fact that pregabalin was abused (Tables I, II, III and V).

For these reasons, pharmacists should always be ready to advise their patients on prescription drugs. Because patients often only seek counseling from them [35].

Conclusions

The patients expect the best treatment from their physicians and they trust them. Government agencies are obliged to make all necessary arrangements and take the necessary measures on time to protect the health of their citizens. Manufacturers should understand that the drugs are not goods that must be sold under every circumstance. According to the data obtained in this study, at pregabalin consumption in Turkey, its abuse is seen effective. Many factors are responsible for its abuse, from the production to the prescription. The effects of its abuse on the society must be investigated. Furthermore, this study is a remarkable example of the abuse that occurs when psychoactive drugs are left uncontrolled to the market dynamics. In Turkey, the prescription of psychoactive drugs should be controlled more effectively. The physicians should be more careful and should prescribe this group of medications by researching their patients' medical history. Constantly updated national and scientific treatment diagnostic guides for the psychoactive drugs should be created by the Ministry of Health in order to protect the public health. Reimbursement rules should be reorganized according to these guidelines. Otherwise, it is inevitable to experience similar abuses in the future.

Conflict of interest

The authors declare no conflict of interest.

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