Acta Pharm. Sci. Vol 60:(4), 2022
DOI: 10.23893/1307-2080.APS6021

Investigation of Hidden Crisis of Prescription Drug Abuse in Turkey: Pregabalin Monitoring

İsa BADUR[1*], Naciye BİLGİN BADUR[2], Barkın BERK[1]

1 Department of Clinical Pharmacy, Istanbul Medipol University, Istanbul, Turkey
2 Department of Neuroscience, Istanbul Medipol University, Istanbul, Turkey

ABSTRACT

This is a cross-sectional retrospective observational national study. Abuse/misuse of the pregabalin and related parameters analyzed. Pregabalin was mostly prescribed by general practitioners (26.2%). Pregabalin prescribing frequencies of other physicians were as follows, respectively: neurology (14.1%); mental health and illness (12%); physical therapy and rehabilitation (8.8%); internal medicine (4.8%). Accordingly, pregabalin (811.954box) and paracetamol, combinations excl. psycholeptics (1,131,069box) were the first two sales. In total cost of sales, pregabalin (57,721,322.00 TL) and methylphenidate (41,915,196.00 TL) were the top two sales rankings. According to the disposal results of ILAYS pharmaceuticals in 2020, pregabalin (2693box per year) and morphine (862box per year) were the most disposed drugs. It was determined that the frequency of pregabalin was followed by gabapentin. In conclusion, our study reveals the extent of abuse of pregabalin in Turkey with its data.

Key words: controlled drug pharmaco-economy, drug abuse, pregabalin, prescription drug monitoring

INTRODUCTION

In Turkey administrative regulations are made to ensure the rational use of drugs and to prevent drug abuse. In Turkey, red-colored prescriptions (opioids, methylphenidate etc.) are generally for the prescription of narcotic opioid drugs, while green-colored prescriptions (benzodiazepines, barbiturates, pre-

*Corresponding author: İsa BADUR
E-mail: haciisabadur@gmail.com
ORCIDs:
İsa BADUR: 0000-0002-0306-4259
Naciye BİLGİN BADUR: 0000-0001-6577-0100
Barkın BERK: 0000-0001-6047-2796
(Received 04 Jul 2022, Accepted 19 Jul 2022)

gabalin etc.) are generally for the prescription of psychotropic drugs, including pregabalin. Apart from these, there are also prescription drugs in white-controlled prescription (gabapentin), subject to control. After coloured-controlled paper prescriptions, the electronic colour-controlled prescription system became operational in Turkey. Electronic prescription data provides both pharmaco-epidemiological and pharmaco-economic benefits, considering the patient's comorbidity and literature data, which are thought to be predisposing factors in the disease, electronic records were used in this study.

The abuse of drugs is among the irrational drug parameters, and it is stated by the World Health Organization (WHO) that drugs should be prescribed and used rationally[1].

According to WHO estimates, more than 50% of medicines are improperly prescribed, procured or sold. Half of all patients cannot use their medications properly[2].

Drug abuse is defined as the use of drugs other than for medical purposes, especially when the physician does not see it necessary, on their own will or on the recommendation of unauthorized persons[3].

Pregabalin is an antagonist of voltage gated Ca^{2+} channels and specifically binds to alpha-2-delta subunit of the channel. It has antiepileptic and analgesic actions. It safe and efficous enough to be first line therapeutic agent for neuropathic pain. Pregabalin, (S)-3-(aminomethyl)-5-methylhexanoic acid, is a pharmacologically active S-enantiomer of a racemic 3- isobutyl gamma amino butyric acid analogue. It is the first frug to be approved by FDA for diabetic neuropathy and post-herpetic neuralgia[4].

Pregabalin is a GABA analogue, and this has direct or indirect effects on dopaminergic reward system. That is why pregabalin is a good candidate to be abused by the patients. The physicians must be aware of previous abuse history of the patients before prescription pregabalin[5].

Explaining the pharmacoeconomics and pharmacoepidemiology of prescription drug abuse will facilitate monitoring. Prescription drug abuse can be prevented by including results in electronic decision support mechanisms. It is aimed to attract attention of the pregabalin abuse and the role of health professionals including clinical pharmacists in prevention and awareness of the drug abuse.

METHODOLOGY

This national study is an observational retrospective research study based on electronic prescriptions of all individuals who have been declared to have abuse-controlled drug prescription drugs in Turkey between the years of 2017 and 2020.

All electronic records of the people who were mentioned in the announcements of the Ministry of Health, which they have made drug abuse for five years between 2016-2020, about the need to be careful against abuse to health institutions, until 31 December 2020, were examined.

The extent of this abuse has been examined from the perspective of pregabalin drug with active ingredient, for which special restrictions have been imposed due to the unusual increase in abuse across Turkey.

Detailed 18-month sales reports of one of Turkey's three largest pharmaceutical distribution warehouses and ILAYS (national licensed disposal center), that is, the year 2020, 12-month report of drugs that pharmacies are liable to destroy were examined.

The first of the 216 announcements, which were detected to have abused drugs and distributed to health institutions/organizations in Turkey, was on 24.02.2016 and the last one was on 04.09.2020. When missing/wrong information, duplicate person/articles were accepted as exclusion criteria in these articles, 199 articles were evaluated. The limitations of our study are the distribution of only 216 abuse detection official announcements across Turkey, between the years 2016-2020, the deficiencies/inaccuracies in 17 articles, and the context problems between electronic prescriptions. These prescriptions are excluded.

The Microsoft Excel document of our study was determined to be 5,506 kilobytes, consisting of approximately 700 thousand cells.

Statistical program was used for statistical analysis. In our study, "$p<0.05$ value" was accepted as a significant value.

RESULTS and DISCUSSION

199 people were included in the study as abusers. After the first warning letter belonging to this patient, the electronic prescription records of the person were examined with all the prescribing details since 2017 (the start of e-prescription in Turkey). 725 health institutions in 76 different provinces; It was determined that a total 6610 prescriptions were prescribed, 3262 green colour-controlled-controlled prescriptions 680 of which were red colour-controlled-controlled

prescriptions, and prescriptions were dispensed from 1222 different pharmacies in 69 different cities.

Table 1. Grouping of controlled drugs in our study according to ATC codes and number of patients/prescriptions

ATC	ATC NAME	ATC CODE	PRESCRIBED ABUSE (n)		ABUSED PRESCRIPTION (n)	
Benzodiazepine derivatives	clonazepam	N03AE01	65	109	907	1.819
	alprazolam	N05BA12	66		659	
	diazepam	N05BA01	36		227	
	lorazepam	N05BA06	21		106	
Other antiepileptics (pregabalin)	pregabalin	N03AX16	98	98	548	548
Tertiary amines	biperiden	N04AA02	36	36	400	400
Opium alkaloids and derivatives	combinations (codein+dionin)	R05DA20	4	4	44	44
Drugs used in opioid dependence	buprenorphine, combinations	N07BC51	11	11	86	86
Barbiturates and derivatives	phenobarbital	N03AA02	2	2	22	22
Opioids	tramadol	N02AX02	23	40	305	818
	pethidine	N02AB02	24		218	
	morphine	N02AA01	8		119	
	oxycodone	N02AA05	12		96	
	fentanyl	N02AB03	11		88	
	tramadol and paracetamol	N02AJ13	11		23	
	hydromorphone	N02AA03	1		1	
Centrally acting sympathomimetics	methylphenidate	N06BA04	4	4	28	28
Benzodiazepine related drugs	zopiclone	N05CF01	4	4	7	7

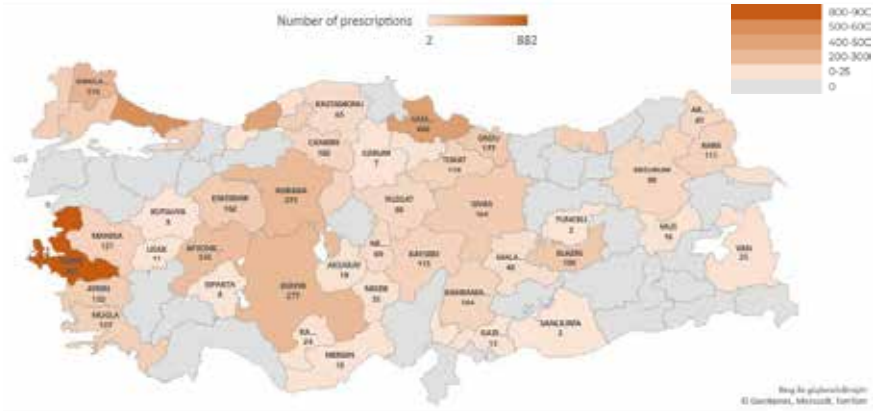

Figure 1. Number of abuse prescriptions by province

All drugs taken by abusers for approximately 4 years (17.3.2017- 31.12.3020) are limited according to ATC group and active substance name and code. Benzodiazepines are followed by opioids, followed by pregabalin. Considering that pregabalin is not a drug group but only an active ingredient, abuse seems to be much greater.

It is aimed to collect relevant data for the contribution of the e-prescription system to drug abuse as the stages of pregabalin in e-prescription systems:

• Neither colour-controlled nor e-prescription

• E-prescription but not colour-controlled

• Both colour-controlled and e-prescription

While the active ingredient of Pregabalin (ATC: N03AX16) was in the system as a controlled drug as of February 1, 2018, it was included in the colour-controlled prescription class as of 01.04.2019. While the e-prescription requirement was on 17.03.2017, this requirement for pregabalin started on 01.04.2019. In terms of prescription history, prescriptions were examined according to drug ATC names.

In addition, the obligation to write pregabalin in the e-prescription system is different from other coloured-controlled prescription drugs. In other words, while other drugs were already controlled, they had to be in the system as soon as the e-prescription system started, but this was not the case for pregabalin, and it was included in the system approximately 2 years after the e-prescription system started.

The active ingredient of pregabalin can be used as an index-marker for controlling drug abuse and waste, in a way, for the control of the e-prescription system in Turkey, due to the above-mentioned features. Because this drug with active substance was passed in all layers of the prescription monitoring system (it was not in the system, it was subject to control in the system, it was as a green prescription in the system) with certain date intervals.

Unlike other coloured-controlled prescriptions, the fact that pregabalin is in all the following stages provides the opportunity to use it as an indicator:

• While neither colour-controlled nor e-prescription (n=18), the average prescription date is September 12, 2017 (±98,073 days)

• Coloured-controlled but non-e-prescription (n=175) while the average prescription date was September 20, 2018 (±110,84 days)

• Average January 27, 2020 (±191,57 days) for both e-prescription and colour-controlled (n=364)

The differences in dates between the prescription phases of the active ingredient of pregabalin were examined by one-way ANOVA. Since the equality of variances could not be achieved, Tamhene test was applied for post hoc for pairwise comparisons. Accordingly, the difference between all paired groups was found to be significant ($p<0.001$).

The following results were found to be statistically significant for the other mean prescription differences of pregabalin:

• Both e-prescription and colour-controlled prescription date averages - 866 days more than neither colour-controlled nor e-prescription date average

• Both e-prescription and colour-controlled prescription date average - 493 days more than the colour-controlled but non-e-prescription date average

• Colour-controlled but non-e-prescription date average - 372 days more than neither colour-controlled nor e-prescription date average

By taking the date of April 2019, the relevant figure was created so that a general view would be more accurate so that the course of all drugs that are taken by patients who abuse drugs and that are required to be registered in the system.

The decision to take urgent measures for pregabalin was given by the scientific advisory commission with the announcement of the Department of Pharmacovigilance and Controlled Substances of the Ministry of Health[6]. In our study, we have created the following figure for a visual overview in order to take a holistic view of the drug course taken by individuals who abuse drugs according to drug pregabalin.

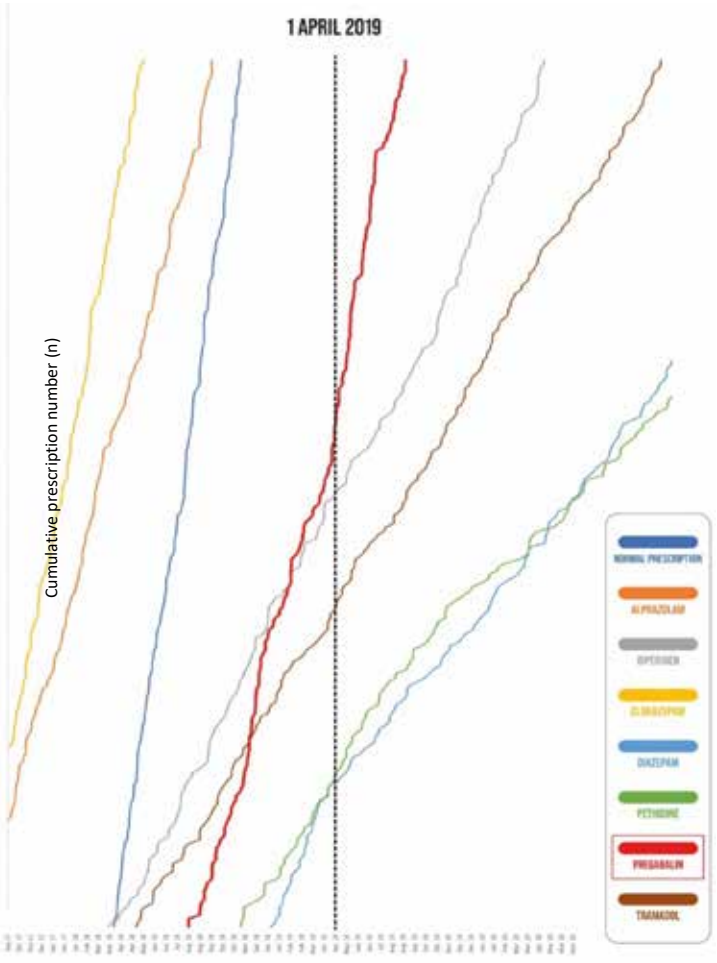

Figure 2. Pregabalin, cumulative prescription number graph by other drugs in the e-prescription system between September 2017 and June 2020

It was understood that the decision of the Ministry of Health's scientific committee was correct, but since there was no decrease in the slope of the pregabalin curve before the decision, we can say that we have concluded that the e-prescription system is not sufficient to prevent drug abuse, and perhaps it is sufficient to register the prescription.

The fact that it almost intersects with the perpendicular line on the block just after 1 April date may have shown the accumulation in the relevant dates, but the fact that this hunger does not go away even though months have passed reveals the seriousness of the problem.

As a result, we can say that monitoring is not enough. However, since the literature detailed below mentions that this may not be easy, we can emphasize that a reaction should be taken according to the relevant literature from now on.

Monitoring has an important place in the identification, evaluation and treatment of drug abuse or misuse. All monitoring tools have some limitations. At the beginning of these constraints are the ignorance of age and cultural differences. The healthcare industry and patients benefit greatly if abuse and misuse can be detected with monitoring tools. Monitoring tools are cost-effective in identifying patients at risk, and the use of these tools provides therapeutic benefits[7].

However, these monitoring tools should be age and population compatible[8].

With the use of monitoring tools, early diagnosis of substance use can be made, so that young people can be prevented from encountering larger problems in the future[9].

The use of computerized monitoring tools is both speed and cost-effective[10].

In our study, these three aspects were supported and explained. It is thought that we can get better results with better opportunities.

For example, we can say that our study, which we started to work on before the publication of the following study and which is Turkey-wide, shows results in line with the literature, but it is more comprehensive than those in the literature. Rose et al. The risk factors of abuse in the study, in which data on more than three million adults were examined, are similar to those in our study and support our study. These risk factors include frequent visits to the pharmacy and frequent visits to the same doctor[11].

In order to prevent the abuse of prescription drugs in the world, laws are made on how to collect and dispose of prescription drugs[12].

In our country, the destruction of these drugs can be given as examples of licensed disposal centers with the determination of the Ministry of Health officials. The Pharmaceutical Waste Management System (ILAYS), managed by pharmacists, is one of them, and first of all, a list of drugs is created for drug disposal, and transactions are carried out by pharmacists. As a result of the delivery of the drugs subject to control, together with the drug lists and the report prepared in the Health Directorates, they are directed to the disposal centers[13].

In our study, detailed 18-month sales reports of one of Turkey's three largest pharmaceutical distribution warehouses and ILAYS, that is, the year 2020, 12-month report of the drugs that pharmacies are obliged to dispose were examined.

Accordingly, pregabalin (811,954box for 18 months) and paracetamol, combinations excl. psycholeptics (1,131,069box for 18 month) are the first two sales. In total cost of sales, pregabalin (57,721,322.00 TL for 18 months) and methylphenidate (41,915,196.00 TL for 18 months) were the top two sales rankings.

According to the drug dispose report of ILAYS, pregabalin (2693box per year) and morphine (862 box per year) were the most destroyed drugs in 2020. According to the same report, when the costs of disposed controlled drugs for 2020 were calculated, pregabalin and morphine were determined as two values.

It has been observed that the most common active ingredients of clonazepam, alprazolam, pregabalin and biperiden are included in the prescriptions of these abusers. The fact that these patients continue to use drugs that may be the subject of abuse reveals that the e-prescription system in our country is not sufficient to follow these patients.

Pregabalin was the highest number of general practitioners (26.2%), respectively; neurology (14.1%); mental health and illness (12%); physical therapy and rehabilitation (8.8%); internal medicine (4.8%); It was prescribed by family medicine specialist (2.3%).

In accordance with the decisions taken by the Scientific Advisory Commissions, "Medicines Containing the Active Substance of Pregabalin", which is in the status of a drug subject to monitoring that must be given with a normal prescription, will be included in the list of "Green Drugs to be Given by Prescription" as of 01.04.2019. In addition, provided that it is valid from the specified date, "Medicines Containing Pregabalin Active Substance" can be prescribed only by the relevant specialist physicians within the therapeutic indications specified in the Approved Short Product Information, in case it is desired to be prescribed without a Drug Use Report[6].

However, both addicts and abusers put pressure, including violence, on healthcare professionals to take this drug. According to the results of the second half of 2020, people who abused prescription drugs in our study took gabapentin after pregabalin. We think that the reason for this is that after pregabalin was counted as a controlled drug, abusers turned to gabapentin. Because gabapentin shows similar effects to pregabalin[14].

Considering the fact that overuse of gabapentin leads to deaths in an article published in JAMA in 2022, it will be seen from another perspective that the magnitude of the prescription drug crisis in Turkey are much larger[15].

As a result, our study revealed that pregabalin cannot be adequately controlled in Turkey and it would be beneficial to incorporate the data in this publication in e-prescription decision-making processes immediately.

STATEMENT OF ETHICS

Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee date is 25/04/2018 and number is 272. This investigation is ethically approved.

REFERENCES

1. World Health Organisation (11 June 2021), Achieving Better Health Outcomes and Efficiency Gains Through Rational Use of Medicine, Brief No 3 https://www.who.int/publications/m/item/achieving-better-health-outcomes-and-efficiency-gains-through-rational-use-of-medicine, Access date: 01.02.2022

2. Turkish Medicines and Medical Devices Agency, http://www.titck.gov.tr/Ilac/AkilciIlacKullanimi Access date: 01.02.2022

3. Glossary of Pharmaceutical and Pharmaceutical Terms, Ankara 2014, TDK

4. Verma V, Singh N, Singh Jaggi A. Pregabalin in neuropathic pain: evidences and possible mechanisms. Curr. Neuropharmacol. 2014; Jan 1; 12(1):44-56.

5. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS drugs. 2014; Jun;28(6):491-6.

6. Department of Pharmacovigilance and Controlled Substances of the Ministry of Health, https://www.titck.gov.tr/duyuru/il-saglik-mudurluklerinin-dikkatine-07032019145613, Access date: 01.05.2022

7. Babor TF, McRee BG, Kassebaum PA, Grimaldi PL, Ahmed K, Bray J. Screening, Brief Intervention, and Referral to Treatment (SBIRT) toward a public health approach to the management of substance abuse. Substance abuse. 2007; Nov 21;28(3):7-30.

8. Rumpf HJ, Wohlert T, Freyer-Adam J, Grothues J, Bischof G. Screening questionnaires for problem drinking in adolescents: performance of AUDIT, AUDIT-C, CRAFFT and POSIT. European addiction research. 2013;19(3):121-7.

9. Harris SK, Louis-Jacques J, Knight JR. Screening and brief intervention for alcohol and other abuse. Adolescent medicine: state of the art reviews. 2014; Apr 1;25(1):126-56.

10. Levy S, Weiss R, Sherritt L, Ziemnik R, Spalding A, Van Hook S, Shrier LA. An electronic screen for triaging adolescent substance use by risk levels. JAMA pediatrics. 2014 Sep 1;168(9):822-8.

11. Rose AJ, McBain R, Schuler MS, LaRochelle MR, Ganz DA, Kilambi V, Stein BD, Bernson D, Chui KK, Land T, Walley AY. Effect of age on opioid prescribing, overdose, and mortality in Massachusetts, 2011 to 2015. JAGS. 2019; Jan;67(1):128-32.

12. P Peterson DM. New DEA rules expand options for controlled substance disposal. J. Pain Palliat. Care Pharmacother. 2015; Jan 2;29(1):22-6.

13. Pharmaceutical Waste Management System, https://ILAYS.ieo.org.tr/, Access date: 01.01.2022

14. The green prescription drug mentioned in the razor attack puts many pharmacists and doctors in a difficult situation, https://medimagazin.com.tr/guncel/jiletli-saldirida-adi-gecen-yesil-receteli-ilac-bircok-eczaci-ve-doktoru-zor-durumda-birakiyor-83800, Access date: 01.01.2022

15. Kuehn BM. Gabapentin Increasingly Implicated in Overdose Deaths. JAMA. 2022 Jun 28;327(24):2387-.