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## ABSTRACT

**Objectives:** The purpose of this study was to identify abuse-related post-marketing reports associated with gabapentinoids use in the Middle East and North Africa (MENA) region countries. **Methods:** A retrospective cross-sectional analysis of abuse-related adverse drug event (ADE) reports from the Middle East and North Africa (MENA) region. It was performed using the Food and Drug Administration Adverse Event Reporting System (FAERS) database from January 2008 through June 2020. Abuse-related ADE reports for gabapentin and pregabalin were extracted from the FAERS database. Descriptive statistics were performed, and the proportional reporting ratio (PRR) was calculated to detect disproportional attribution of abuse-related ADEs for gabapentin versus pregabalin. **Results:** We identified 559 all-cause ADE reports for gabapentinoids, including 205 (36.7%) abuse-related ADE reports reported to FAERS in the period of analysis. FAERS included 139 (67.8%) pregabalin and 66 (32.2%) gabapentin abuse-related ADE reports. Among MENA region countries, Turkey (55, 39.6%) and Saudi Arabia (34, 23.7%) had the highest number of abuse-related ADE reports for pregabalin. The most pregabalin abuse-related ADE reports involved adult male patients. The PRR of pregabalin versus gabapentin abuse-related ADE reports was 1.11, indicating that the number of abuse-related events was higher for pregabalin compared to gabapentin. **Conclusion:** Over 200 cases of abuse-related gabapentinoids events were reported to FEARS from the MENA region in the study period. Further studies should assess risk factors and potential programs to reduce gabapentinoids abuse.
**Key words:** Gabapentin, Pregabalin, Adverse drug events, MENA, FAERS, Abuse.

## INTRODUCTION

Gabapentinoids (pregabalin and gabapentin) are widely prescribed in neurology and psychiatry and often prescribed off-label for a range of clinical conditions, including alcohol and narcotic withdrawal states, non-neuropathic pain disorders, and attention deficit hyperactivity disorder. Gabapentinoids act as gamma-aminobutyric acid (GABA) analogs, blocking alpha-2- delta subunit-containing voltage-dependent calcium channels.[1] Gabapentin was approved by the Food and Drug Administration (FDA) for post-herpetic neuralgia and epilepsy in 1993. Pregabalin was approved in 2004 for neuropathic pain, fibromyalgia, post-herpetic neuralgia, and seizures.[2-5] In the United States, the prescription rates for gabapentinoids increased significantly between 2002 and 2015 and pregabalin was a top 10 best-selling medication in 2017.[6,7] In Saudi Arabia, pregabalin was one of the top 10 sold drugs during 2010-2015.[8]

Recent systematic reviews documented gabapentinoid abuse-related adverse drug events (ADEs), including abuse, misuse, dependence, or overdose.[9,10] Studies have also shown gabapentinoids are likely to be abused among individuals with opioid dependence syndrome.[11-13] The abuse potential of gabapentinoids has been demonstrated in some clinical studies.[9,10] In Saudi Arabia, a study found that 12.4% of participants used pregabalin without a prescription.[14] Additionally, studies showed the potential risks for pregabalin misuse, abuse, and related harms in the United Arab Emirates and Jordan.[15,16] A few case reports also described pregabalin abuse in Turkey and Lebanon.[17-19]

The abuse of gabapentinoids is a serious public health problem.[6,13,14,16-20] There are some differences among countries in terms of gabapentinoids scheduling system. According to the United States Drug Enforcement Administration (DEA), pregabalin is classified as a Schedule V controlled substance, representing the least potential for abuse. In contrast, gabapentin is not classified as a controlled substance despite the evidence of abuse.[4,5,13] On the other hand, In Saudi Arabia, in May 2015, pregabalin was classified as a controlled substance by (SFDA). However, gabapentin is still a prescribed medication (Saudi Food and Drug Authority). The Jordan Food and Drug Administration (JFDA) also included pregabalin preparations in the restricted drug list in 2017.[21-23] On the other hand, gabapentinoids are not controlled medications in Turkey.[17]

Although gabapentinoids share many similar pharmacologic properties, such as interacting with the same binding site, renal excretion, comparable metabolic profiles, minimal protein binding, and negligible drug-drug interactions, they have significant absorption differences.[24-27] Gabapentin is absorbed less rapidly than pregabalin, with maximum plasma concentrations attained within 3-4 hr instead of 1

hr. Due to saturable absorption, gabapentin absorption drops from 68% to 36% after the dosage increases from 300mg to 1600 mg. In contrast, pregabalin's absolute bioavailability maintains ≥90% despite increasing doses.[24,26,28] That might explain why pregabalin is classified as a controlled medication while gabapentin is not.

A recent study, which used the United States data from the 2012-2016 Food and Drug Administration Adverse Event Reporting System (FAERS) data; found that a total of 576 cases out of 10,038 (5.7%) abuse-related events were reported to FAERS for gabapentin, and 58 cases out of 571 (10.2%) ADEs related to abuse were identified for pregabalin.[29]

This study has been conducted to evaluate epidemiological information regarding the scope of gabapentinoids abuse utilizing the FAERS database not to assess their abuse trends. To the authors' knowledge, there were no studies available at the time of this study that have identified abuse-related post-marketing reports associated with gabapentinoids (gabapentin and pregabalin) use in the Middle East and North Africa (MENA) region countries.This study aimed to identify abuse-related post-marketing reports associated with gabapentinoids (gabapentin and pregabalin) use in the MENA region countries reported to FAERS from January 2008 to June 2020.

## MATERIALS AND METHODS

### Data sources

A retrospective analysis of gabapentinoids (gabapentin and pregabalin) ADE reports from the MENA region was performed using the FAERS (U.S. Food and Drug Administration). The FAERS database contains ADE reports, medication error reports, and product quality complaints resulting in adverse events submitted to the FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biological products. In other words, FAERS data play a significant role in identifying early safety signals.[30-32]

The dataset is publicly available online and de-identified on the FDA website. Thus, no institutional review board approval is required. All ADE reports for pregabalin and gabapentin reported to FAERS from January 2008 to June 2020 were identified by searching the active ingredient names, dosage forms, and spellings with no specific reaction or outcome criteria.

The MENA region definition includes 23 countries: Afghanistan, Algeria, Bahrain, Djibouti, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, Turkey, United Arab Emirates, Yemen. The MENA region reports were extracted by using International Organization for Standardization (ISO) 3166-1 alpha-2 codes.[33-35]

FAERS classifies the reports expedited (reports from the manufacturer submitted to the FDA within 15 days of a serious and unexpected ADE not included in product labeling) and non-expedited reports of serious and non-serious adverse events for new molecular entity (NME) products within the first three years following FDA approval.[36] Serious outcomes include death, hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcomes. The primary sources of FAERS reports are categorized into healthcare professionals and consumers.

Abuse-related ADE reports were defined as reports with drug abuse, drug dependence, drug tolerance, withdrawal syndrome, euphoric mood, overdose, intentional overdose, intentional product misuse, product use in unapproved indication, maternal use an illicit drug, loss of personal independence in daily activities, substance-induced psychotic disorder, and intoxication.[25,29,37-39] The demographic characteristics of FAERS reports are limited. ADE reports were classified by patient gender (male, female) and age in years at the time of the report.

**Data analysis**Descriptive statistics were performed, and the proportional reporting ratio (PRR) was calculated to detect a disproportional attribution of ADEs for gabapentin versus pregabalin. The PRR was calculated using the following equation: $PRR=[P^a/P^t]/[G^a/G^t]$, where $P^a$ = number of ADEs reported for pregabalin abuse, $P^t$ = total number of ADEs reported for all pregabalin, $G^a$ = number of ADEs reported of gabapentin abuse, and $G^t$ = total number of ADEs reported for all gabapentin. The null value for a PRR is one, which means the higher the PRR, the greater the strength of the signal of abuse.[29,40] Descriptive statistical analyses, including frequencies and percentages, were performed using Microsoft Excel (2016 Version, Redmond, WA).

## RESULTS

We identified 559 all-cause FAERS ADE reports for gabapentinoids from January 2008 to June 2020, including 366 (65.5%) pregabalin and 193 (34.5%) gabapentin reports.

FAERS listed 66 (32.2%) abuse-related gabapentin ADE reports, of which 55 (83.3%) were reported by healthcare professionals, and 63 (95.5%) were expedited reports. There were 35 (53.0%) abuse-related ADEs reports of women patients. The mean patient age among abuse-related ADEs was 54.4±16.5 years (median=50). Among MENA region countries, Turkey (42, 63.6% of all MENA reports) had the greatest number of reports, followed by Iran (17, 25.8%) (Table 1).

The most common gabapentin abuse-related ADEs reactions were for indications that are non-FDA approved, which were mentioned in 16 (23.2%) reports (Table 2). Other gabapentin abuse-related ADEs included 15 (21.7%) substance-induced psychotic disorder, 14 (20.3%) intoxication, 8 (11.6%) withdrawal syndrome and 8 (11.6%) maternal use of illicit drugs reactions. The outcomes reported for gabapentin abuse-related ADE included 6 (9.1%) death, 8 (12.1%) hospitalizations, and 46 (69.7%) other serious outcomes (Table 3).

Moreover, from January 2008 to June 2020, FAERS listed 139 (67.8%) abuse-related pregabalin ADE reports. There were 106 (76.3%) cases were reported by healthcare professionals to the FAERS database, and 137 (98.6%) were expedited reports. There were 67 (48.2%) abuse-related ADEs reports of male patients. The mean patient age among abuse-related ADEs was (36.0 ± 19.1) years (median=28). Among MENA region countries, Turkey (55, 39.6%) had the greatest number of reports, followed by Saudi Arabia (34, 23.7%) and Jordan (19, 13.7%) (Table 1).

Drug abuse was mentioned in 77 (39.1%) reports and was the most frequent pregabalin abuse-related ADE, followed by overdose (24, 12.2%), intentional overdose (12, 6.1%), and drug dependence reactions (12, 6.1%) (Table 2). The outcomes reported for pregabalin abuse-related ADE included 4 (2.9%) death, 24 (17.3%) hospitalizations, 2 (1.4%) congenital anomalies, and 103 (74.1%) other serious outcomes (Table 3).

The PRR of pregabalin versus gabapentin abuse-related events was 1.11, indicating that the number of abuse-related ADEs and the strength of the signal of abuse were slightly higher for pregabalin than for gabapentin.

## DISCUSSION

This study's results indicate that most of the gabapentinoids abuse-related events reported in some of the MENA region countries in the study period were associated with pregabalin use. This finding could be due to the distinct pharmacokinetic advantages of pregabalin over gabapentin. These advantages have been linked to the superiority of pregabalin pharmacodynamic properties such as higher bioavailability, faster absorption, and rapid onset of action with higher potency than gabapentin, which may explain the higher addiction potential of pregabalin.[24-28]We also noted that Turkey, Saudi Arabia, and Jordan had the greatest number of pregabalin abuse-related ADE reports among MENA region countries. In most MENA region countries, gabapentinoids are prescribed as non-controlled medications.[16,41] However, some of the MENA countries have taken serious actions to

prevent the risk of gabapentinoids abuse. For instance, in Saudi Arabia, the SFDA classified pregabalin as a controlled substance in May 2015, but gabapentin has not been classified as a controlled substance yet (Saudi Food and Drug Authority). In Jordan, the JFDA added pregabalin to the restricted drug list in 2017.[21-23]Previous studies show that gabapentinoid abuse events seem to be more likely in young adults; however, data about gender differences are conflicting.[10,29,39] Our study found that most of the gabapentin abuse-related ADE reports involved adult women patients, while the majority of pregabalin abuse-related ADE reports were for young adult male patients.

Some MENA region countries did not report any gabapentinoids ADE to FAERS. This may be attributed to variations in policies and characteristics of reporting systems in the region because each country has its adverse event reporting system. For example, Saudi Adverse Event Reporting System (SAERS) was launched by SFDA in March 2009 to monitor the safety of post-marketed medications. Also, the Turkish Pharmacovigilance Center (TUFAM) was established in 2015.[42]The analysis also revealed that abuse-related ADEs were higher for pregabalin than gabapentin. This result confirms the findings by Evoy *et al.* 2019. Although this study did not assess the concomitant medications,

**Table 1: Characteristics of Gabapentinoids Abuse-Related ADEs Reported to FAERS (January 2008-June 2020).**

| Characteristics | Gabapentin n (%) | Pregabalin n (%) |
|---|---|---|
| Total | 66 (32.2%) | 139 (67.8%) |
| Male | 11 (16.7%) | 67 (48.2%) |
| Female | 35 (53.0%) | 37 (26.6%) |
| Not Specified | 20 (30.3%) | 35 (25.2%) |
| Age | | |
| Mean | 54.4 | 36.0 |
| Median | 50 | 28 |
| Standard Deviation | ±16.5 | ±19.1 |
| Type | | |
| Expedited | 63 (95.5%) | 137 (98.6%) |
| Non-Expedited | 3 (4.5%) | 2 (1.4%) |
| Source | | |
| Consumer | 11 (16.7%) | 33 (23.7%) |
| Healthcare Professional | 55 (83.3%) | 106 (76.3%) |
| MENA Region Countries (Includes Only Countries with FAERS Reports) | | |
| Algeria | - | 7 (5.0%) |
| Bahrain | - | 1 (0.7%) |
| Egypt | 1 (1.5%) | 3 (2.2%) |
| Iran | 17 (25.8%) | 1(0.7%) |
| Israel | 2 (3.0%) | 13 (9.4%) |
| Jordan | - | 19 (13.7%) |
| Lebanon | 2 (3.0%) | 3 (2.2%) |
| Morocco | - | 1 (0.7%) |
| Saudi Arabia | 2 (3.0%) | 33 (23.7%) |
| Tunisia | - | 1 (0.7%) |
| Turkey | 42 (63.6%) | 55 (39.6%) |
| United Arab Emirates | - | 2 (1.4%) |

**Table 2: Type of Gabapentinoids Abuse-related ADE Reactions Reported to FAERS (January 2008-June 2020).**

| ADE Reactions | Gabapentin n (%) | Pregabalin n (%) |
|---|---|---|
| TOTAL | 69 (25.9%) | 197 (74.1%) |
| Drug Abuse | - | 77 (39.1%) |
| Overdose | 2 (2.9%) | 24 (12.2%) |
| Intentional Overdose | - | 12 (6.1%) |
| Drug Dependence | 4 (5.8%) | 12 (6.1%) |
| Withdrawal Syndrome | 8 (11.6%) | 10 (5.1%) |
| Intentional Product Misuse | - | 9 (4.6%) |
| Product Use in Unapproved Indication | 16 (23.2%) | 9 (4.6%) |
| Intoxication | 14 (20.3%) | 8 (4.1%) |
| Drug Tolerance | 1 (1.4%) | 6 (3.0%) |
| Euphoric Mood | 1 (1.4%) | 4 (2.0%) |
| Loss of Personal Independence in Daily Activities | - | 4 (2.0%) |
| Maternal use of the illicit drug | 8 (11.6%) | 8 (4.1%) |
| Substance-Induced Psychotic Disorder | 15 (21.7%) | 14 (7.1%) |

**Multiple reactions were listed for some cases*

**Table 3: Outcomes of Gabapentinoids Abuse-related ADE Reported to FAERS (January 2008-June 2020).**

| Reactions | Gabapentin events n (%) | Pregabalin events n (%) |
|---|---|---|
| TOTAL | 66 (32.2%) | 139 (67.8%) |
| Death | 6 (9.1%) | 4 (2.9%) |
| Hospitalization | 8 (12.1%) | 24 (17.3%) |
| Life-threatening | 2 (3.0%) | - |
| Disability | 1 (1.5%) | - |
| Congenital anomaly | - | 2 (1.4%) |
| Other serious outcomes | 46 (69.7%) | 103 (74.1%) |
| Non-serious outcomes | 3 (4.5%) | 6 (4.3%) |

Chiappini *et al.* 2016 and Evoy *et al.* 2019 studies found that most deaths occurred in patients who were also taken opioids.[29,39]

This study has some limitations. First, there is no certainty that the ADE reports were due to gabapentinoids themselves; it might be due to the concomitant medications. Second, since ADE reporting from consumers or healthcare professionals is voluntary, the FDA does not receive reports for every adverse event or medication error that occurs with a product. Therefore, FAERS data can detect safety signals but cannot be used to estimate the incidence of adverse events or medication errors.

## CONCLUSION

Over 200 cases of abuse-related gabapentinoids events were reported to FEARS from the MENA region in the study period. Further studies should assess risk factors and potential programs to reduce gabapentinoids abuse.

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## Declarations of interest
None

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## CONFLICT OF INTEREST
The authors declare no conflict of interest.

## Ethical approval
This study does not involve the use of any human or animal subjects.

## Data availability
The data used to support the findings of this study will be available upon request.

## Authors contributions
**Mona Alsheikh:** Writing- original draft preparation, methodology, data curation. **Ali Alshahrani:** Software, reviewing, and editing. Reem Almutairi: Conceptualization, reviewing, and editing. **Hana** Althobait: Methodology, investigation. Validation. **Ahmed Ibrahim Fathelrahman:** Editing and proofreading, **Enrique Seoane-Vazquez:** visualization, supervision, and editing. Moudi Alasmari: Writing- original draft, methodology, reviewing, and editing.

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