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The impact of a restricted pregabalin prescription policy on drug utilization: An observational multicenter study

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ABSTRACT

Background: The Saudi Food and Drug Authority (SFDA) classified pregabalin as a controlled substance in 2018; however, whether this policy change has affected pregabalin use is unclear. This study examined the trends in pregabalin prescriptions before and after the SFDA restriction. In addition, the co-prescription of controlled analgesics and the use of pregabalin for approved indications were also evaluated.

Method: A cross-sectional study was conducted on outpatient pregabalin prescriptions from three healthcare centers in Saudi Arabia. Interrupted time series analysis was used to assess changes over time in pregabalin prescriptions and the number of patients receiving pregabalin. June 2016 to June 2017 was identified as the pre-restriction period, and July 2018 to July 2019 as the post-restriction period.

Results: In this study, 77,760 pregabalin prescriptions were identified. There were 9,076 patients on pregabalin in the pre-restriction period with 16,875 prescriptions, compared with 7,123 patients and 19,484 prescriptions post-restriction. The total number of pregabalin users decreased by 21.5% post-restriction, and prescriptions increased by 15.5%. There was no significant change in the monthly trends in pregabalin prescriptions before and after the restriction. However, the of tramadol and acetaminophen/codeine prescriptions in patients who were using pregabalin increased in the post-restriction period by 21% and 16.1%, respectively.

Conclusion: Pregabalin use was reduced after the SFDA-enforced prescription restriction was implemented. This was accompanied by increased narcotics use in the post-implementation phase.

1. Introduction

Pregabalin has commonly been prescribed for the treatment of neuropathic pain (NeP) associated with several conditions, such as post-herpetic neuralgia (PHN), painful diabetic peripheral neuropathy (PDPN), and spinal cord injury (Pfizer Canada Inc., 2016) (World health organization, 2017). In addition, pregabalin is also used to treat fibromyalgia (FM) and as an adjunct therapy for partial-onset seizures and generalized anxiety disorder (GAD) (Pfizer Canada Inc., 2016; World health organization, 2017). Pregabalin exerts its effect by binding with high affinity to the auxiliary subunit of the voltage-gated calcium channel site in the brain, known as the alpha2-delta (accessdata.fda.gov, 2018).

Pregabalin is recommended as a first-line agent in several treatment guidelines, including the International Association for the Study of Pain Treatment Guidelines for NeP, and by the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation for PDPN treatment. Pregabalin has several advantages (Raptis et al., 2014; Shrady et al., 2014). For example, in treating neuropathic cancer pain, pregabalin is associated with higher patient satisfaction, better tolerability, and fewer adverse events than opioids

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(Raptis et al., 2014).

With the widespread use of pregabalin, the number of records indicating pregabalin abuse was a warning in multiple pharmacovigilance databases, pointing to potential abuse liabilities and overdose fatalities (Bonnet and Scherbaum, 2017). Several countries have implemented various restriction policies, including prior authorization (PA) and step-up therapy (ST) policies, to tackle pregabalin abuse (Shrady et al., 2014; Stacey et al., 2017). Although these restriction policies can reduce pregabalin use, certain studies have shown that they are associated with an increased use of opioids and alternative pain management therapies (Shrady et al., 2014). Data from a systematic review revealed that restriction policies had no significant benefit in cost savings (Stacey et al., 2017). However, they are useful for drug utilization (Stacey et al., 2017).

In Saudi Arabia, pregabalin is a prescription medicine that community pharmacies formerly dispensed without the requirement for a prescription. In February 2018, the Saudi Food and Drug Authority (SFDA) initially required pregabalin to be dispensed only by a physician prescription due to the potential for misuse and abuse (Schjerning et al., 2016). Moreover, the SFDA changed pregabalin to a schedule II controlled substance, meaning that it can only be dispensed through a prescription with a clear indication and no refills are permitted (Ministry of Health, 2012; Saudi Food & Drug Authority, 2017).

This policy has the potential to impact pregabalin use in hospital settings. The consequence of this restriction was recently discovered to have resulted in a decline in overall pregabalin consumption, as indicated by sales data (Althunian et al., 2022).

It's worth digging deeper into the impact to see whether the restriction of pregabalin prescriptions in community pharmacies influenced its utilization in hospital settings and the effect of such restrictions on utilizing alternative pain therapies, such as opioids. Therefore, our study aimed to examine the trends in pregabalin use pre-and post-restriction and the co-prescription rates of other controlled analgesics (tramadol and acetaminophen with codeine). In addition, the use of pregabalin for approved indications was also evaluated.

2. Materials and methods

2.1. Study design

This was a cross-sectional study using electronic health records (EHRs) from three large tertiary care medical centers in Riyadh, Saudi Arabia, namely King Faisal Specialist Hospital and Research Center (H1), King Fahad Medical City (H2), and King Saud University Medical City (H3). These hospitals serve as referral centers for patients from all Saudi Arabian regions.

2.2. Ethical consideration

Ethical approval was obtained from each center before study initiation. This study was approved by the King Saud University Medical City Institute review board (IRB; Research Project No.: E-19–4146), King Fahd Medical City IRB (IRB Log No. 19–427), and King Faisal Specialist Hospital & Research Center Research Ethics Committee (REF: C380/59/41).

2.3. Data source

Data were extracted from the EHRs database of each hospital. June 2016 to June 2017 was considered the baseline period (one-year pre-restriction), and July 2018 to July 2019 was considered the follow-up period (one-year post-restriction). The month of June 2018 was considered a grace period for implementing pregabalin restrictions between the two periods.

The EHRs data included demographics, clinical diagnosis, and information on prescription drugs from hospital outpatient pharmacies (e.g., drug name, ensing date, quantity dispensed, days of supply, and refills). Personal identifiers were removed from all analytical data files.

2.4. Study participants

Eligible individuals included adults and children who were prescribed at least one pregabalin prescription in the outpatient setting during the study period, either pre-or post-restriction. Patients who only received pregabalin prior to June 2016 and after July 2019, or during the month of June 2018, were excluded.

2.5. Study outcomes

The primary outcome was pregabalin utilization, defined as the number of pregabalin prescriptions and the number of patients who received pregabalin. Any pre- or post-restriction change in alternative medications, such as opioids, was considered a secondary outcome. The following information was collected to measure pregabalin utilization: the number of filled pregabalin prescriptions, date of prescription, indication for use, number of pills, dosage, and duration per prescription for each eligible patient.

Approved indications for pregabalin use were defined as NeP associated with DPN, PHN, FM, spinal cord injury, and adjunctive therapy to treat partial-onset seizures. Pregabalin prescription was considered an approved indication if any of these diagnoses were listed in the patient EHRs, and prescriptions were labeled as unapproved indications if none of these diagnoses were listed in the patient EHRs. Clinical diagnosis was reported using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes, in addition to diagnoses manually entered in the system as "free text.".

For opioid use, we collected data on the number of filled prescriptions, date of prescription, dosage, and duration per prescription. Only tramadol and acetaminophen/codeine prescriptions were collected, as they represent the most used agents in outpatient settings at the included hospitals.

2.6. Statistical analysis

Descriptive statistics were used to summarize the data, including the counts and percentages. Patient data were divided into two groups: 1) pre- and 2) post-policy implementation. The effect of the restriction was estimated using an interrupted time series (ITS) analysis. We used segmented linear regression to evaluate the significance of changes in the level and slope of the regression lines pre-and post-restriction (Wagner et al., 2002). Data management and analysis were conducted using Microsoft Excel 2010 and R statistical software.

ITS analysis was used to assess changes in study outcomes pre- and post-restriction. Data were aggregated by calendar month. The units of analysis were prescriptions per month and patients per month. To understand the impact of the restriction, the ITS analysis included two measures of time: (1) 12 months pre-restriction and (2) 12 months post-restriction, to test for changes in slope post-restriction.

Our model is based on the equation $Y_t = \beta_0 + \beta_1 * \text{Time} + \beta_2 \text{Restriction}_t + \beta_3 \text{TimeSinceRestriction}$.

β_0 represents the baseline level, β_1 is the change in outcome associated with the monthly increase, β_2 is the level of change following the restriction, and β_3 is the slope change following the restriction using the interaction between time and intervention: TimeSinceRestriction.

3. Results

3.1. Changes in prescription patterns

In this study, 77,760 pregabalin prescriptions were identified from all the included hospitals (Fig. 1). There were 9,076 patients using pregabalin with 16,875 prescriptions pre-restriction, compared to 7,123

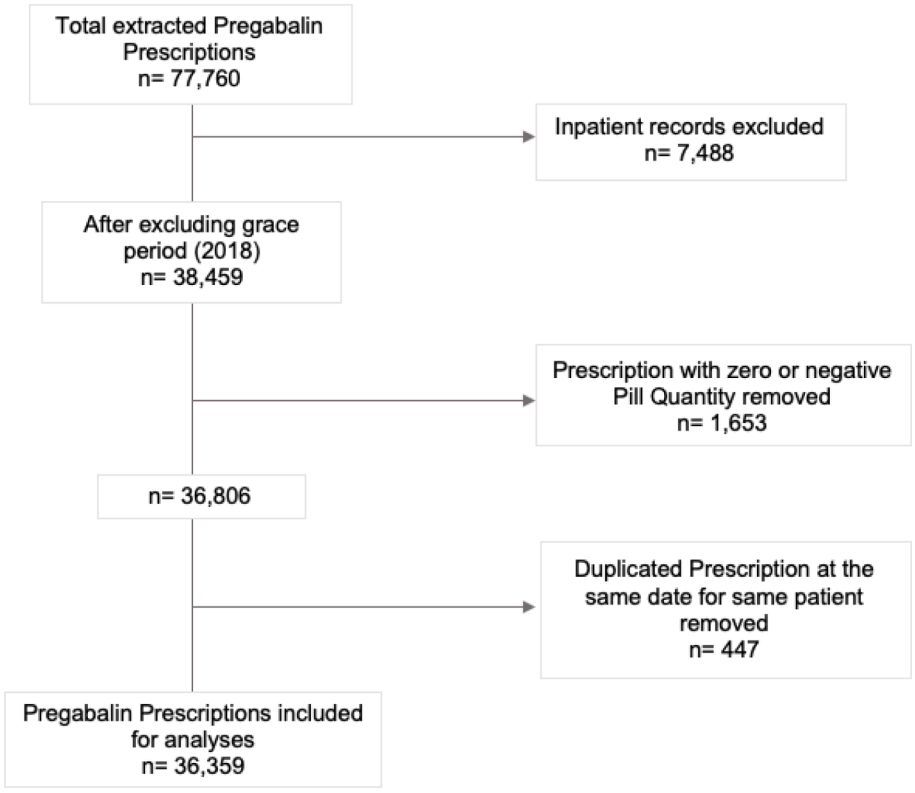

Fig. 1. Flow chart illustrating the process of evaluating prescriptions for inclusion in the review.

patients and 19,484 prescriptions post-restriction.

Following the enforcement of the pregabalin restriction policy, the total number of pregabalin users decreased by 21.5 %. However, there was a 15.5 % increase in pregabalin dispensation. Among the three hospitals, H1 had a 4.3 % reduction in the number of patients (n = 3563 vs. n = 3410) and a 16.5 % increase in prescriptions (n = 7033 vs. n = 8193) post-restriction. In H2, there was a reduction in both the number of patients and prescriptions equal to 33.9 % (n = 3,260 vs. n = 2,154) and 16.1 % (n = 5,981 vs. n = 5,018), respectively. H3 had a 30.8 % decrease in patients (n = 2,253 vs. n = 1,559) and 62.5 % increase in prescriptions (n = 3,861 vs. n = 6,273). These results are summarized in Figs. 2 and 3.

The ITS analysis results (Table 1) indicate that the starting level of prescribing pre-restriction was estimated at 1,372, with a decrease in prescribing trend over time by seven prescriptions monthly (p = 0.8). The estimated average number of monthly prescriptions decreased by 155 (level change, p = 0.8) post-restriction. The trend of prescribing increased by approximately 25 prescriptions per month post-restriction (p = 0.7). However, these values were not statistically significant (Fig. 4).

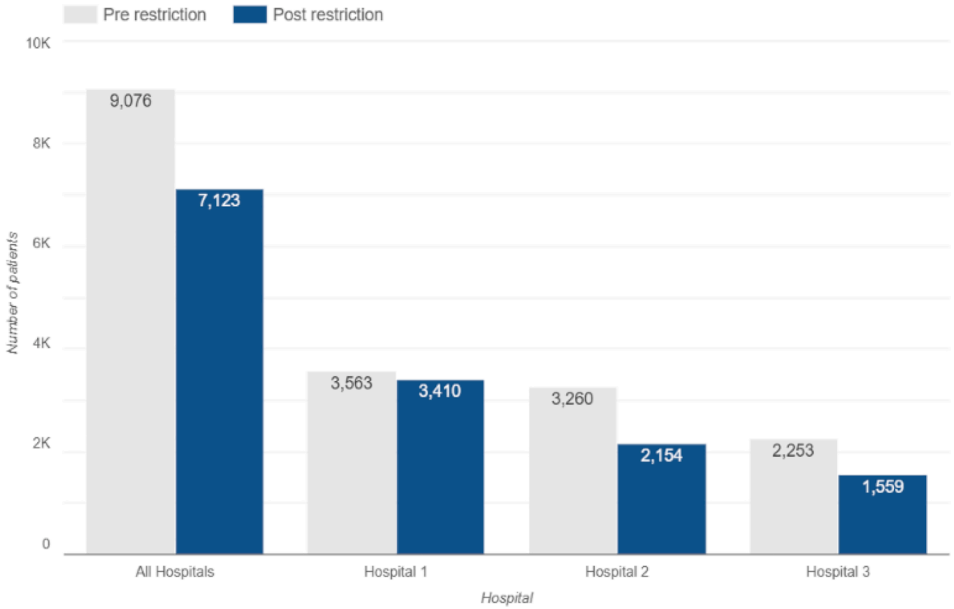

Fig. 2. Differences in prescription utilization (number of patients).

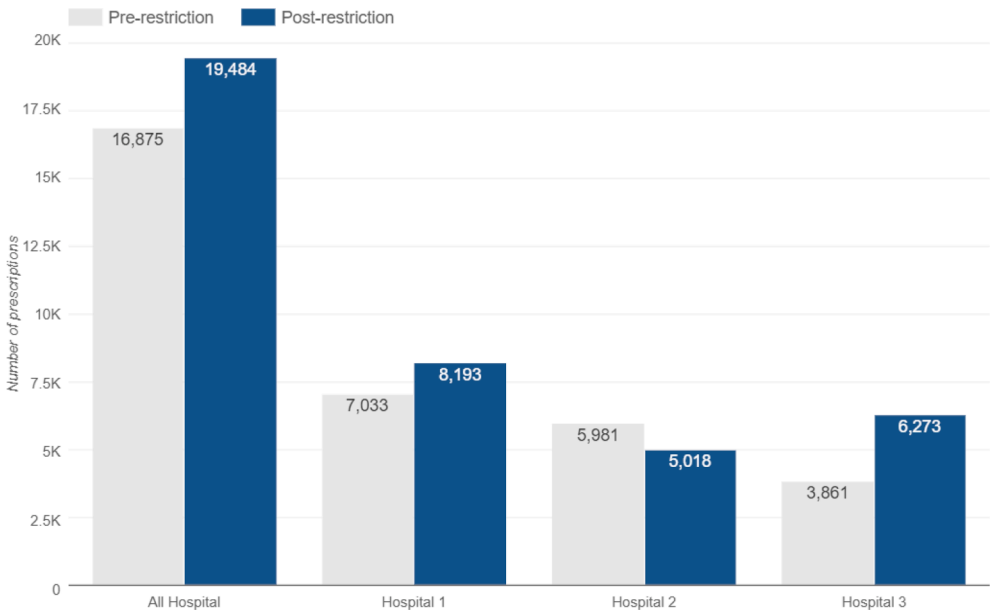

Fig. 3. Differences in number of prescriptions pre- and post-restriction.

Table 1
Coefficient estimation from the regression model for both the level and trend of monthly pregabalin prescriptions pre- and post-restriction.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	1372.033	293.978	4.667	0.000118
time	−7.275	41.575	−0.175	0.862696
restriction	−155.527	857.086	−0.181	0.857667
time: restriction	24.912	58.796	0.424	0.675894

The analysis of monthly patients on pregabalin levels showed that the pre-restriction starting level of patients was estimated at 1297, with a slight decreasing trend of approximately eight patients monthly ($p = 0.8$). The estimated average number of patients immediately increased by 358 patients monthly post-restriction (level change, $p = 0.8$; Table 2). The patient utilization trend showed that the number of patients decreased by 13 patients per month ($p = 0.8$) (Fig. 5).

3.2. Changes in other pain medications prescription patterns

The number of tramadol and acetaminophen/codeine prescriptions in patients who were simultaneously using pregabalin increased in the post-restriction period by 21 % and 16.1 %, respectively. Moreover, there were post-restriction increases in the number of tramadol and acetaminophen/codeine patients who were on pregabalin of 10.5 % and 10.7 %, respectively. Data were only available for H1 and H3 (Figs. 6 and 7).

3.3. Labeled approved indications

When looking at data on whether pregabalin was prescribed for approved versus unapproved indications, the collective percentage of prescriptions labeled for an approved indication in H2 and H3 during the pre-restriction phase was 2.25 % (n = 121/5379), 1.9 % (n = 91/4853) in H2, and 5.70 % (n = 30/526) in H3 separately. In the post-restriction phase, the rate of prescriptions with labeled approved indications increased to 9.07 % (n = 631/6958) in H2 and H3 jointly, 4.4 % (n = 208/4722) in H2 and 18.92 % (n = 423/2236) in H3 independently (Table 3).

4. Discussion

Our study compared pregabalin prescription patterns one year before and one year after the SFDA policy enforcement in Saudi Arabia. The patterns of co-prescription of other controlled analgesics were also evaluated during both periods. The use of pregabalin for approved indications was also evaluated based on pharmacy and clinical information available from the electronic medical records of the three hospitals. To our knowledge, this is the first study that provides insights on the impact of SFDA restriction policies across large institutions in Saudi Arabia.

Our study results suggest that the SFDA pregabalin restriction policy enforcement was effective in reducing the overall number of patients using pregabalin. This reduction was accompanied by an increase in the number of pregabalin prescriptions. When we compared the number of refills and pill quantities between the two phases, the post-restriction phase was associated with increased refills and increased pill quantities. These results support the hypothesis that schedule II controlled substance refill bans, one-month limit coverage, and the restriction of prescriptions in community pharmacies led to more frequent prescriptions in hospital settings. However, this reduction did not appear to have a consistent pattern among the different hospitals. For instance, there was a reduction in both users and prescription numbers in only one hospital, while the other hospitals showed only a reduction in the number of patients who were prescribed pregabalin. Several factors may explain these differences. For instance, the hospitals had variations in internal adherence to implemented prescription restrictions.

Similar approaches have been used to restrict access to pregabalin worldwide, such as ST and PA, which have been associated with a net decrease in pregabalin use (Stacey et al., 2017; Suehs et al., 2014; Udall et al., 2013). ST is defined as a formulary policy intended to encourage the use of less expensive medications and is often considered first-line therapy prior to a patient progressing to higher-cost treatment options (Suehs et al., 2014). PA requires a prescriber to obtain prior approval from a specific authority (payer, specialty, etc.) to prescribe the medication (Udall et al., 2013). The ST restriction on pregabalin was demonstrated in two studies to be effective in reducing pregabalin utilization. However, it was also associated with a notable increase in the use of other medications, such as gabapentin, tricyclic antidepressants (TCA), serotonin–norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), and local anesthetics such as lidocaine

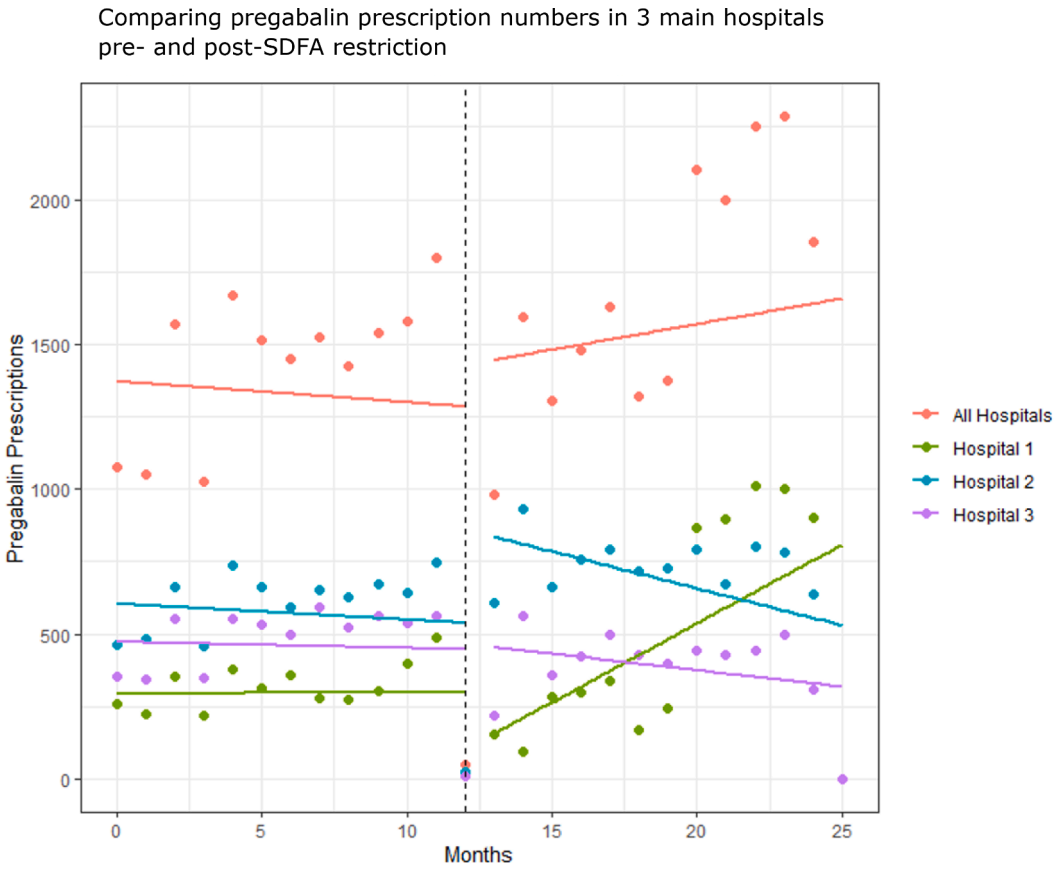

Fig. 4. Time series analysis of pregabalin prescriptions.

Table 2
Coefficient estimation from the regression model for both the level and trend of monthly pregabalin-treated patients pre- and post-restriction.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	1296.989	229.217	5.658	1.09e-05
time	−7.665	32.416	−0.236	0.815
restriction	358.104	668.276	0.536	0.597
time: restriction	−13.385	45.843	−0.292	0.773

(Suehs et al., 2014; Udall et al., 2013). A recent study that evaluated the impact of pregabalin restriction by SFDA on the overall utilization in Saudi Arabia based on sales data showed a significant reduction in sales with higher use of gabapentin (Althunian et al., 2022). Unlike our study, Althunian, et al study did not evaluate the prescribing patterns in hospitals including the use of pregabalin for approved indications. Rather, it only focused on sales data which do not necessarily translate into actual utilization by patients. Another limitation of the Althunian, et al study is that it did not address the impact on the use of other controlled substances such as codeine and its combinations. A systematic review of the potential impact of pregabalin restriction policies included published health economic studies suggesting that PA and ST are effective in reducing pregabalin use without a clear benefit in terms of cost savings (Stacey et al., 2017).

Pregabalin and opioids used together carry a high risk of abuse and fatalities (Bonnet and Scherbaum, 2017). Our study evaluated the co-prescription of opioids among pregabalin users in hospital outpatient settings. There was an overall decrease in the number of patients using pregabalin among the three hospitals; however, there was an increase in co-prescriptions with other pain medications in hospital outpatient settings. An increase in opioid prescriptions can be a major factor contributing to opioid misuse. In addition, several studies have demonstrated the consequences of implementing pregabalin restrictions, such as increased analgesic, antidepressant, and anxiolytic use among patients (Margolis et al., 2009; Suehs et al., 2014).

Our study only evaluated whether pregabalin prescriptions were labeled with approved indications and found that this was true only for a small percentage of prescriptions across study centers. Other studies examining the appropriateness of pregabalin prescriptions and whether they were prescribed for approved indications revealed generally sub-optimal rates (Viñas-Bastart et al., 2018). For instance, a study in Spain found that 68.2 % of patients prescribed pregabalin had appropriate indications, which were defined as NeP, GAD, or epilepsy according to the summary of product characteristics of pregabalin (Viñas-Bastart et al., 2018). Viñas-Bastart et al study also showed that epilepsy was the least common indication (0.7 %), while off-label and unlicensed indications were more frequent (Viñas-Bastart et al., 2018).

Even though we merely covered pregabalin prescribing in outpatient settings, our results tie well with the recent local study that analyzed pregabalin sale data covering inpatient and outpatient settings (Althunian et al., 2022). The impact was measured using the daily defined dose per 1,000 inhabitant-days (DDD/TID) estimation and showed a direct decrease of Pregabalin overall use by −1.85 DDD/TID (95 %CI −2.71 to −0.99) with a prolonged declining effect (DDD/TID: −0.22, CI to −0.37 to −0.05) (Althunian et al., 2022). These results lead to similar conclusion supporting our findings that SFDA restrictions was associated with an overall reduced use of pregabalin.

5. Limitations

This study was limited by including hospital outpatient settings in only three hospitals; therefore, our findings may not apply to the entire population and cannot be generalized to inpatient settings. However, the evidence in the literature and comparison with similar studies

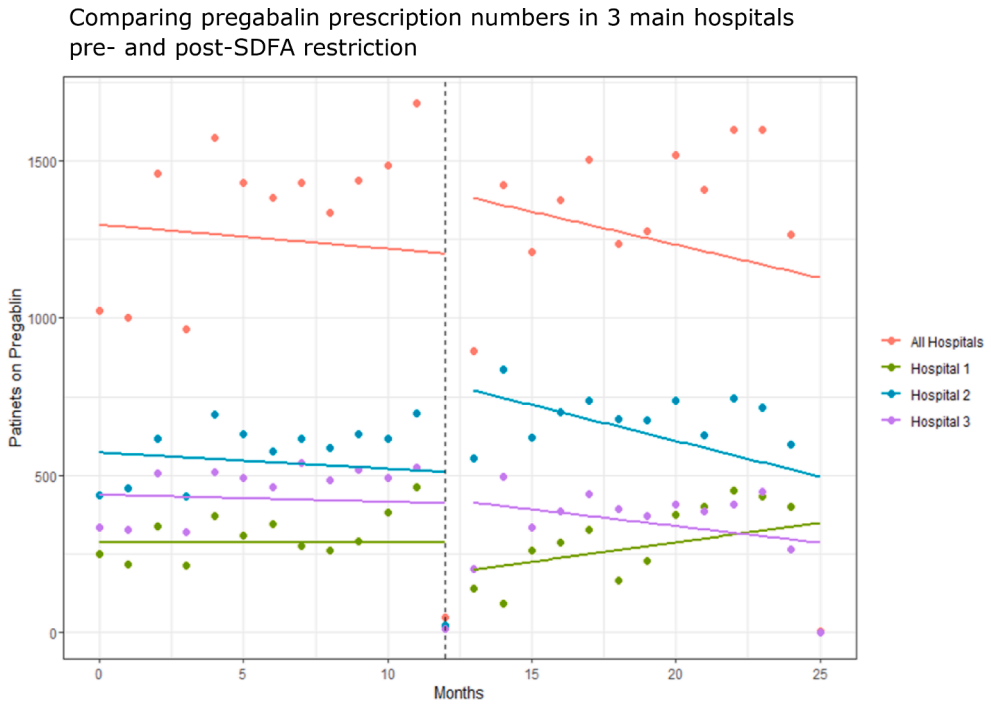

Fig. 5. Time series analysis of patients using pregabalin.

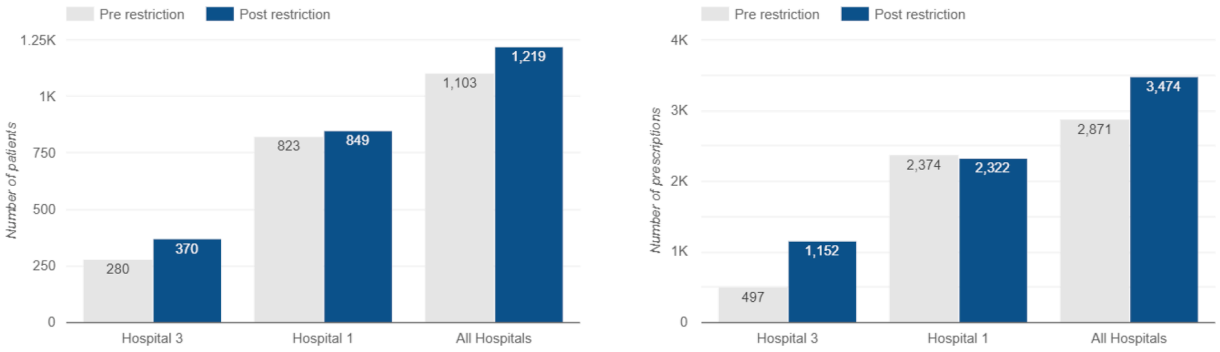

Fig. 6. Differences in acetaminophen/codeine prescription utilization (number of patients) and prescription writing (number of prescriptions) among the hospitals.

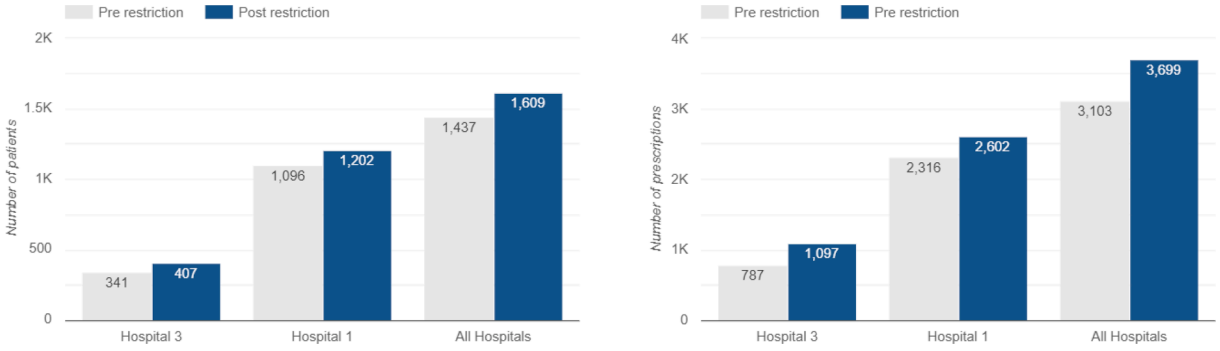

Fig. 7. Differences in tramadol utilization (number of patients) and prescription writing (number of prescriptions) among the hospitals.

Table 3
Percentage of prescriptions with approved indication per hospital.

	Pre-restriction phase	Post-restriction phase
H2	91/4853 (1.9 %)	208/4722 (4.4 %)
H3	30/526 (5.7 %)	423/2236 (18.92 %)

carried out in different countries support our findings. Although there were missing data and not all the hospitals provided information on indications, we observed similarities between the findings of the two hospitals included in our study in terms of the changes in the appropriateness of indications after implementing the restriction policy. Notably, all data were extracted from electronic pharmacy records and

may not reflect the patient's actual use. In addition, our data did not include effectiveness and safety outcomes, nor did it cover the impact of other pregabalin alternative agents, such as SSRIs, gabapentin, and TCA. Another limitation of our study is the low documentation rate for pregabalin indications in-hospital prescriptions, which might have resulted in the overestimation of pregabalin use for unapproved indications in our findings. Although tramadol and acetaminophen/codeine comprise most agents utilized in outpatient setting, it is worth mentioning they are the only opioids included in our study. Also, Pregabalin-independent opioid prescription trends are not present, hence it is unclear whether they are related.

6. Conclusion

Restricting pregabalin prescriptions in Saudi Arabia has led to a reduction in overall usage in hospital outpatient settings. However, there has been an increased use of opioids and other analgesics. Encouraging clinicians to document indications for each pregabalin prescription is an essential aspect of evaluating the appropriateness of pregabalin in patients. Future studies evaluating the appropriate use of pregabalin pre-and post-restriction, including indication, dosage, and duration, may provide a better understanding of the impact of restricting pregabalin use.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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