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BRIEF REPORT

Assessment of gabapentin misuse using prescription drug monitoring program data

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ABSTRACT

Background: Gabapentin is an anticonvulsant medication with potential misuse reported in case reports and population studies, highlighting the need to reexamine its abuse liability. The purpose of this study was to describe gabapentin dispensing patterns and assess potential misuse. *Methods:* We used data from Ohio's Prescription Drug Monitoring Program (PDMP) from December 1, 2016 to March 31, 2017 and restricted the population to adults who filled at least one gabapentin prescription ($N = 379{,}372$). Gabapentin dispensing patterns are described and multiple strategies were used to assess potential misuse, including Lorenz-1 curve analysis. Supratherapeutic dosing, number of prescribers and number of pharmacies used were compared for individuals who were co-dispensed medications for opioid use disorder (MOUD) and those who were not. *Results:* More than one million gabapentin prescriptions were dispensed during the 4-month period, with a mean dose of 1103.8 mg. While few individuals received supratherapeutic dosing, exceptionally high doses were observed. Half of the individuals (50.9%) were co-dispensed gabapentin and opioids. The Lorenz-1 value for gabapentin (5.5%) did not exceed the threshold for misuse potential. Individuals co-dispensed MOUD were more likely to have supratherapeutic dosing; however, they had a lower Lorenz-1 value compared to individuals not co-dispensed MOUD. *Conclusions:* Among Ohio residents dispensed gabapentin, there was no evidence of misuse using PDMP data based on the Lorenz-1 value, yet supratherapeutic dosing of gabapentin was observed and was associated with OUD. New strategies may be needed to identify the non-medical use of gabapentin.

KEYWORDS
Gabapentin; misuse; non-medical use; abuse liability; PDMP

Introduction

Gabapentin is an analog of Gamma-Aminobutyric Acid (GABA), that increases glutamate decarboxylase activity and indirectly increases GABA levels.[1,2] It was approved by the U.S. Food and Drug Administration (FDA) for the treatment of partial seizures,[3] postherpetic neuralgia, and restless leg syndrome.[4] The prevalence of gabapentin prescribing and gabapentin use increased steadily in recent years.[5,6] As of September 2017, gabapentin was ranked as the seventh most prescribed medication in the United States.[4] Currently, gabapentin is prescribed off-label for a variety of indications,[7] including substance use disorders (SUD).[8–10] Off-label use is estimated to account for 83–95% of gabapentin use.[11–13]

Gabapentin was once believed to be safe and have a low potential for abuse.[14] However, there has been an increasing number of case reports and epidemiological studies suggesting that gabapentin is being misused for its subjective pleasurable effects.[15,16] In the Social Networks Among Appalachian People (SNAP) study, 15% of participants with illicit opioid use self-reported using gabapentin "to get high" in 2014; a 165% increase in use compared to reports from 1-year prior, and a 2950% increase since 2008.[17] A study conducted in France reported that the cumulative incidence of gabapentin misuse was 6.6% in new patients over the first 2 years.[18]

Gabapentin appears to most frequently be misused in combination with opioids,[17,19–22] alcohol[23] or benzodiazepines[7]. While the mechanism of its abuse potential is not well understood, it may be partially explained by the increased bioavailability resulting from co-administration with opioids.[24] Further, an animal study showed that gabapentin prevented and reversed the development of antinociceptive tolerance to morphine.[25] Little evidence supports gabapentin misuse in patients without a history of SUDs,[26] suggesting that gabapentin misuse occurs more frequently when it is used in combination with other central nervous system drugs and among individuals with a history of substance misuse or addiction. However, the combined use of prescription opioids and gabapentin could increase the risk of overdose.[27,28] Sustained overuse of opioids and gabapentin quadrupled the odds of all-cause inpatient hospital or emergency department services use.[29] Public health officials, in response to increasing reports of gabapentin misuse, have

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increased surveillance of gabapentin prescribing, and some states have implemented regulatory changes to decrease access.[30]

Though the federal government has not moved to reclassify gabapentin as a controlled substance, several states including Virginia,[31] Michigan,[32] West Virginia,[33] Tennessee,[34] and Kentucky[35] have passed legislation to label this medication as a Schedule V medication. Minnesota, Ohio, Wyoming, Massachusetts, North Dakota, Nebraska, and New Jersey require that gabapentin dispensing be reported to the state's Prescription Drug Monitoring Program (PDMP).[15,30]

The purpose of this study was to describe gabapentin dispensing patterns and to assess misuse among individuals prescribed gabapentin. We hypothesized that gabapentin misuse rarely occurs among individuals dispensed gabapentin alone and that individuals with an opioid use disorder (OUD) would have more misuse in comparison to individuals without OUD. As state-level regulations and policies are rapidly evolving to monitor gabapentin prescriptions and misuse, it is critical to determine whether universal or targeted strategies are warranted.

Methods

A secondary analysis of existing data from Ohio's PDMP was conducted. The study period was restricted to prescriptions dispensed from December 1, 2016 to March 31, 2017 because gabapentin was mandated to be reported to Ohio's PDMP as of December 1, 2016. The sample was restricted to adult residents (age $\geq$ 18 years) of Ohio who had filled at least one gabapentin prescription during the study period. Patients with terminal illnesses, as determined by prescribers that were in palliative medicine or hospice, were excluded from the study. Gabapentin prescriptions were identified by therapeutic class description, which included gabapentin and Neurotin®. Any medications dispensed in the 4-month study period were considered co-dispensed with gabapentin. Individuals who were dispensed FDA-approved MOUDs reported to the Ohio PDMP during the study period were categorized as individuals with an OUD. FDA-approved MOUDs reported to the Ohio PDMP included buprenorphine. The buprenorphine transdermal patch (Butrans®), solution for injection (Buprenex®), and film (Belbuca®) were not categorized as MOUD because these formulations are indicated for the treatment of pain. Methadone solution was categorized as MOUD per Ohio regulations. Finally, methadone tablets were not categorized as MOUD as they are indicated in the treatment of pain. Pharmacy keying errors were addressed by a strategy developed and reviewed by the Ohio Board of Pharmacy. A statistical cut point of the top and bottom 0.01% was used to identify values that were highly unlikely to be observed.[36,37]

Measures

Gabapentin's daily dose was calculated by *Quantity* × *Strength (mg)/Days Supply* for tablets and capsules and by *Quantity* × *Strength (mg/ml)/Days Supply* for solutions. The dose was categorized as low (<900 mg daily), moderate (900–1799 mg daily), or high (≥1800 mg daily)[27]. Supratherapeutic dosing for each individual was defined at the prescription level and potential misuse was defined at the rolling 3-month windows to avoid potentially overly-sensitive measures of supratherapeutic prescriptions and to account for potential keying errors.[15] Individuals were identified as having supratherapeutic dosing if they were dispensed 2 or more gabapentin prescriptions with a daily dose exceeding 3600 mg during the study period. Meanwhile, the rolling 3-month window was able to identify individuals who received multiple prescriptions to obtain a high dose of gabapentin. The first rolling 3-month window was from December 2016 to February 2017, and the second was from January 2017 to March 2017. Potential misuse was defined as a daily dose exceeding 3600 mg for both windows.

Misuse potential was measured by Lorenz-1, which has been used to estimate the misuse potential of prescription drugs and to estimate misuse potential of gabapentin using claims data.[15,38] Lorenz-1 shows the percentage of drug consumption by the top 1% of all individuals. A value exceeding 15% is considered a strong indicator of misuse.[15,39] The Lorenz-curve analysis was based on the total quantity of gabapentin dispensed per individual. Multiple provider episodes (MPE), reflecting non-medical use of prescription opioids within administrative data,[40] occurs when an individual has five or more prescribers and uses five or more pharmacies within 6 months.[41] As it is unknown whether existing MPE thresholds can be applied to gabapentin and that gabapentin misuse is more likely to occur among individuals with a history of OUD, we compared the mean number of prescribers and pharmacies by OUD status.

Analysis

Stata/MP 14.0 was the statistical software package used to conduct the analysis.[42] Descriptive statistics were used to summarize individual characteristics, drugs co-dispensed with gabapentin, the quantity and daily dose of gabapentin dispensed. The Chi-square test was used to identify statistically significant differences in gabapentin's supratherapeutic dosing by OUD. Wilcoxon rank-sum test was used to determine whether there were statistically significant differences in the number of prescribers and the number of pharmacies used by individuals who were dispensed MOUD versus those who were not. Lorenz-1 values were also estimated by OUD status. This study was reviewed by the West Virginia University Institutional Review Board (IRB) and was determined not to be human subjects research.

Results

More than two million (2,256,859) individuals were dispensed a controlled medication during the study period, and 379,372 individuals (16.8%) who were dispensed at least one gabapentin prescription were included in the study. Sixty-

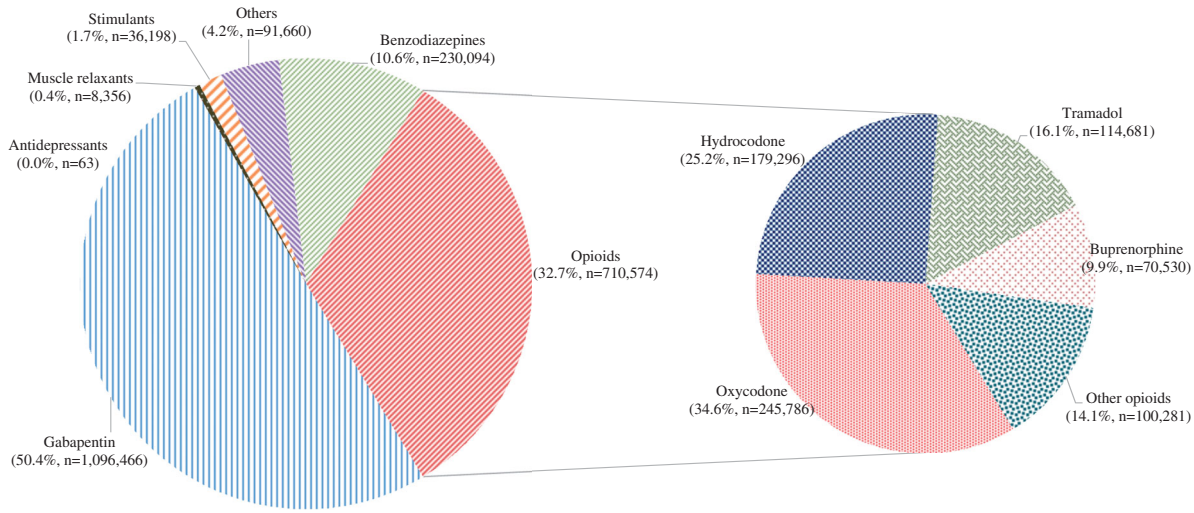

Figure 1. Numbers and percentages of prescriptions for controlled substances among individuals dispensed gabapentin ($N = 379,372$), Ohio Automated Rx Reporting System, December 1, 2016 to March 31, 2017.

two percent of the individuals dispensed gabapentin were female, and the mean age (±SD) was 58.1 (±15.5). Slightly more than one-third (38.9%) only filled prescriptions for gabapentin and were not dispensed other medications required to be reported to the PDMP. Half of the individuals (50.9%) filled prescriptions for gabapentin and opioids, while only 10.2% of the individuals filled prescriptions for gabapentin and non-opioids.

The numbers and percentages of prescriptions for controlled substances are shown in Figure 1. Sixty-eight percent of gabapentin prescriptions and 50.5% of opioid prescriptions dispensed with gabapentin were from primary care physicians (PCPs). Only 6.5% of the total gabapentin prescriptions were from prescribers specialized in neurology or psychiatry.

Gabapentin daily doses per prescription ranged from 25 mg to 7000 mg. The mean gabapentin daily dose (±SD) was 1103.8 (±865.9) mg. Forty-three percent of gabapentin prescriptions ($N = 1,096,141$) were low dose, 30.1% were moderate dose, and 27.1% were high dose. Few prescriptions (0.32%) were supratherapeutic. Overall, 0.39% of individuals ($N = 379,372$) were identified as having been dispensed two or more supratherapeutic gabapentin prescriptions, and 0.64% met the criterion for gabapentin misuse during the study period. The Lorenz-1 value of gabapentin was 5.5%, which does not exceed the threshold for misuse potential (15%), and the Lorenz-1 value for individuals with an OUD was lower compared to individuals without OUD (3.9% versus 5.5%). Individuals with an OUD were significantly more likely to have been dispensed prescriptions classified as supratherapeutic ($p < 0.001$), had more prescribers (median 3 versus 1, $p < 0.001$), and used more pharmacies (median 2 versus 1, $p < 0.001$) (see Table 1).

Discussion

This is the first study to investigate gabapentin dispensing patterns and misuse using PDMP data. Lorenz-1 value suggests a lack of misuse potential for gabapentin among Ohio residents dispensed gabapentin from prescribed sources. Regulators and policymakers may need to consider alternative measurements when monitor gabapentin misuse. Contrary to this finding, Peckham and colleagues[15] reported a Lorenz-1 value of 19% for gabapentin using national commercial claims data from 2013 to 2015. State-level requirements to check the PDMP before prescribing opioids has demonstrated to reduce the quantity of opioids and benzodiazepines dispensed in Ohio.[36] It is unknown, but possible, that gabapentin dispensing patterns have recently changed because of increased monitoring of opioid prescribing practices and due to prescriber's anticipation of mandatory reporting to the PDMP. Future studies are needed to explore the impact of PDMP's implementation on gabapentin dispensing.

The overall prevalence of supratherapeutic dosing was very low (0.32%), and while individuals with OUD were associated with having supratherapeutic prescriptions, the clinical significance is unclear. This result is consistent with findings observed in another published study that gabapentin overuse was associated with a history of addiction.[43] Due to the increased risk of opioid-related death, clinical practices suggest that a low dose of gabapentin be used in combination with opioids.[44,45] There is a need to monitor for safety among individuals who receive supratherapeutic prescriptions and who are at risk of misuse. Reasons why clinicians prescribe supratherapeutic doses of gabapentin among individuals with OUD is unknown. Additional research is needed to understand patterns of co-dispensing gabapentin and opioids, as well as reasons for supratherapeutic dosing.

The mean number of prescribers and pharmacies used by individuals with OUD was only marginally higher compared to individuals without OUD. Individuals co-prescribed MOUD may have a higher number of prescribers because their PCP may not be waivered to prescribe buprenorphine (The Drug Addiction Treatment Act of 2000 waiver) or they are receiving addiction treatment in a specialty setting. Though the results we observed in our study are statistically

Table 1. Measurement of gabapentin misuse by co-dispensed MOUD among individuals dispensed gabapentin, Ohio Automated Rx Reporting System, December 1, 2016 to March 31, 2017.

Measurement of Misuse	Individual receiving MOUD ($n = 9016$)	Individual not receiving MOUD ($n = 370,356$)	p-Value
Number of prescribers*	Median = 3 2.92 (SD = 1.53)	Median =1 1.75 (SD = 1.07)	<0.001
Number of pharmacies*	Median =2 2.25 (SD = 1.23)	Median =1 1.33 (SD = 0.66)	<0.001
Supratherapeutic dosing (measured by 2 or more gabapentin Rx > 3600 mg/day)**			
Yes	0.45% ($n = 41$)	0.22% ($n = 799$)	<0.001
No	99.50% ($n = 8971$)	99.77% ($n = 369,488$)	
Potential misuse (measured by both rolling 3-month windows > 3600 mg/day)**			
Yes	1.13% ($n = 102$)	0.32% ($n = 1179$)	<0.001
No	98.87% ($n = 8914$)	99.68% ($n = 369,177$)	

Note. Numbers may not add up due to missing values in supratherapeutic dosing (measured by 2 or more gabapentin Rx > 3600 mg/day).
*Number of prescribers and pharmacies were tested using Wilcoxon rank-sum test.
**Supratherapeutic dosing was tested using Chi-square test.

significant, the effect size is too low to draw any definite conclusions on "doctor shopping" among patients receiving MOUD versus patients not receiving MOUD. The results suggest that focusing on OUD status to identify "doctor shopping" among individuals using gabapentin may not be useful and hence different strategies may need to be developed to identify gabapentin misuse. In studies measuring gabapentin misuse in populations with risky drug use or a history of SUDs, it may be important to determine the source of gabapentin to better understand whether gabapentin prescriptions are being diverted or whether it is obtained through illicit drug markets.

There are several study limitations worth noting. PDMP data captures only controlled medications and hence does not capture all medications or drugs that are used in combination with gabapentin. Second, this study identified drugs that were co-dispensed with gabapentin during the study period and co-dispensing may not accurately capture concurrent use. Third, we developed a strategy to address keying errors and had it reviewed by the Ohio Board of Pharmacy, yet it is still unknown whether the observed extremely high gabapentin doses were accurate or reflected keying errors. Fourth, the Ohio PDMP has established interstate data sharing with neighboring states. However, due to the difference in state mandates on gabapentin reporting, our data may not capture all Ohio residents who receive gabapentin across state borders. Receipt of MOUD, as a proxy for OUD, is a conservative approach that underestimates the number of individuals with an OUD given that 19.7% of those with an opioid use disorder receive specialty substance use treatment[46] and that methadone from opioid treatment program is not reported to the PDMP. Finally, a study period of 4 months may not be long enough to represent the gabapentin prescribing pattern. Despite these limitations, two measurements were used to ensure the robustness of identifying misuse. Besides, Lorenz-curve analysis has demonstrated high sensitivity (99.5–99.9%) and high negative predictive value (100%) to predict future misuse,[47] which added strength to our conclusion.

Conclusions

Among Ohio residents dispensed gabapentin, there was no evidence of misuse using PDMP data based on the Lorenz-1 value, yet supratherapeutic dosing of gabapentin was observed and was associated with OUD. New strategies may be needed to identify the non-medical use of gabapentin. As states struggle to address gabapentin misuse through regulations and legislation, there is a significant need for empirical research on gabapentin abuse liability, diversion sources, motivations for misuse, and universal or targeted interventions to reduce adverse events.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

YZ designed this study, managed the preparation of the data, performed the statistical analyses, and prepared the original draft. ARC developed, reviewed, and contributed to the code to accurately categorize medications based on indication and formulation. ELW conceptualized this study, contributed to the design of this study, curated the study data, contributed to the analytic approach, and supervised this study. All authors contributed to the interpretation of the results and the revision of this manuscript.

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