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ORIGINAL RESEARCH ARTICLE

Prevalence of Gabapentin Abuse: Comparison with Agents with Known Abuse Potential in a Commercially Insured US Population

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Abstract

Background Despite international calls to make gabapentin a controlled substance, studies of gabapentin use/abuse patterns are limited to small/high-risk samples and adverse event reports.

Objective The aim of this study was to conduct a systematic assessment of the abuse potential/prevalence of gabapentin in a large sample.

Data Source Truven Health MarketScan® Commercial Claims and Encounters database, years 2013–2015.

Eligibility Criteria Patients with two or more claims for one or more abusable drugs and ≥12 months' continuous enrollment were sampled for Lorenz curve analysis. Prevalence analysis was limited to those with ≥120 days of therapy.

Methods Abuse potential was measured as Lorenz-1 (consumption of drug supply by top 1% of users) of ≥15%. Dose thresholds were morphine milligram equivalent (MME) standards for opioids, and maximum labeled doses in milligrams (mg) for other drugs.

Results Lorenz-1 values were 37% opioids, 19% gabapentin, 15% pregabalin, 14% alprazolam, and 13% zolpidem. The top 1% gabapentin users filled prescriptions for a mean (median) 11,274 (9534) mg/day, more than three times the recommended maximum (3600 mg). Of these, one-quarter used or diverted ≥12,822 mg/day. The top 1% opioid and pregabalin users filled prescriptions for a mean (median) 180 (127) MMEs and 2474 (2219) mg/day, respectively. Of patients using opioids + gabapentin simultaneously, 24% had three or more claims exceeding the dose threshold within 12 months.

Limitations Established threshold criteria for gabapentinoid abuse are uncertain. Indications for gabapentinoid use (e.g. hot flashes, restless legs syndrome) were not measured.

Conclusion Gabapentin use patterns are similar to those of other abusable medications. High daily doses pose safety and/or diversion concerns, and investigation of the medical consequences of gabapentin abuse is needed.

Key Points

Several European and American studies of small/high-risk samples and adverse event databases have documented instances of gabapentin abuse, but no published work has systematically measured the prevalence of gabapentin abuse in a large sample.

In a large, commercially insured sample, gabapentin use patterns were similar to those of drugs with known abuse potential: use of a substantial proportion of drug supply by a small portion of users, high daily doses dispensed to patients in the top utilizing percentiles, and elevated rates of potential abuse in patients using both gabapentin and opioid medications.

The top 1% of gabapentin users consumed and/or diverted a mean (median) dosage of 11,274 (9534) mg/day, and 24% of those with concomitant use of opioids had three or more claims over labeled dose threshold in 12 months of follow-up.

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1 Introduction

Gabapentin, a structural analog of γ-aminobutryic acid (GABA), works primarily by binding to the α2δ subunit of voltage-gated calcium channels to decrease calcium influx [1]. Calcium influx has been known to facilitate neurotransmitter release, control neuronal excitability, and activate secondary messenger pathways [2]. In the presence of gabapentin, these properties are reduced [2], giving rise to its anticonvulsant and analgesic properties and indications approved by the US FDA for post-herpetic neuralgia and epilepsy [3]. While the full extent of the mechanism of gabapentin is unknown, it is likely multimodal, generating use in as many as 40 off-label indications. These indications primarily comprise psychiatric and pain conditions, along with treatment of muscle spasms, restless legs syndrome, tremor, hot flashes, nystagmus, and substance- and alcohol-related disorders [4].

Within the past decade, the idea that gabapentin poses abuse potential has risen, although gabapentin is a non-controlled substance in the US. The earliest assessments of gabapentin abuse prevalence were conducted in Europe. A brief report from the Tayside region of Scotland in 2009 identified 'exponential increases' in the quantity of gabapentin prescriptions [5]. In the region's substance misuse service, 5.2% of patients received gabapentin and were three times more likely than non-utilizers to report non-medical use of analgesics [5]. In 2011, approximately 20 cases of gabapentin addiction were reported to the European Monitoring Centre for Drugs and Drug Addiction [6]. Interestingly, one survey of 1500 individuals in the UK discerned a lifetime prevalence for gabapentin abuse to be 1.1%—higher than the 0.5% observed with pregabalin [7], a mechanistically similar Schedule-V gabapentinoid [8]. In an international study examining reports of gabapentin-related misuse, abuse, and dependence, researchers found 4301 cases of potential misuse, abuse, and dependence among 90,166 recipients of gabapentin over the period 2004–2015 [9]. Despite the generally low abuse prevalence rates suggested by these findings for the population overall, use of gabapentin without a prescription, or at a dose greater than prescribed, is more common among at-risk populations, such as incarcerated prisoners (16% lifetime prevalence) and those using other drugs nonmedically (15–26%) [10, 11].

A common trend among gabapentin abusers is to combine gabapentin with other drugs of known abuse, such as opioids, cocaine, and even quetiapine [12–18]. In surveys conducted in small samples, patients reported using gabapentin as a catalyst to potentiate the 'high' achieved from opioids [12, 13], while others reported replacing cocaine with gabapentin given its greater availability [16, 19]. On its own, gabapentin abuse effects have been described as euphoric, a marijuana-like 'high', relaxing, yielding a sense of calm, and overall enhanced sociability [5].

Despite concern about abuse potential, gabapentin has been described as relatively safe, even when ingested in quantities as high as 50,000 mg and up to 90,000 mg [20, 21], both of which far exceed the FDA-recommended maximum dose of 3600 mg/day [1]. The clinical manifestations of most reported overdoses were limited to mild sedation, nausea, somnolence, dizziness, and loose stooling, all of which required only mild symptomatic support. In addition, a study examining gabapentin overdoses across three poison control centers from 1998 to 2000 reported just 20 instances of gabapentin overdose wherein gabapentin was the sole agent involved [22]. Of these overdoses, no patients were admitted to hospital for medical care, and no fatalities resulted. However, there have been at least two gabapentin overdose fatalities reported, where one individual was estimated to have taken 15,600 mg via pill count [23], and another individual's post-mortem serum gabapentin level was 88 μg/mL [24], which is seven times the median blood concentration observed in a post-mortem toxicology study of gabapentin abusers [25]. Lastly, an international study determined that gabapentin was the sole agent identified in 3 of 86 overdose fatalities, whereas the other 83 fatalities involved multiple agents [9].

While evidence regarding the safety of gabapentin in abuse and/or overdose is mixed, there is general consensus that prolonged gabapentin misuse followed by abrupt discontinuation may provoke withdrawal requiring hospitalization. Numerous instances of gabapentin withdrawal syndrome have been reported as it mimics a benzodiazepine withdrawal-like state consisting of symptoms such as disorientation, anxiety, insomnia, palpitations, diaphoresis, and abdominal cramping [26–32]. In addition, there are case reports of more clinically serious symptoms, such as dystonic reactions [33], catatonia [34], akathisia [35], and status epilepticus [36]. One such study reported that more than 50% of the study population who abused gabapentinoids required hospitalization to manage withdrawal symptoms [6]. The potential for overdose resulting in death poses particular concern because no gabapentin antidote exists.

The aforementioned literature examining the prevalence of gabapentin abuse has been limited in scope to small samples, self-reports, high-risk populations, and poison control databases [10, 11]. A more systematic, large-sample assessment of gabapentin utilization is needed given the growing recognition of the potential for abuse, its potential societal impact, and recent suggestions to consider making gabapentin a controlled substance in the US [37, 38]. To address this unmet need, we report the prevalence and

characteristics of patients with evidence of gabapentin abuse in a large sample of commercially insured enrollees, and compare patterns of gabapentin use with those of several commonly abused controlled substances.

2 Methods

2.1 Study Overview

This study was a retrospective cohort analysis of data obtained from the Truven Health MarketScan® Commercial Claims and Encounters database. The MarketScan database is a fully de-identified, Health Insurance Portability and Accountability Act (HIPAA)-compliant dataset comprising claims for all healthcare (medical and pharmacy) services provided to approximately 50 million commercially insured enrollees each year. Data are obtained by Truven Health from employers and health insurance plans, cleaned for quality and accuracy, and de-identified using encrypted case numbers for research purposes. The study was deemed exempt from Institutional Review Board (IRB) review by the Midwestern University IRB committee.

Study subjects were aged 16 through 64 years and had two or more pharmacy claims for one or more of the following commonly used abusable medications: alprazolam, gabapentin, pregabalin, zolpidem, or any opioid medication, including opioid-only products (e.g. oxycontin, oxycodone), pain-relief combinations (e.g. hydrocodone-acetaminophen), and cough/cold combinations.

2.2 Outcomes

Two outcomes were studied. For both outcomes, drug supply was calculated as milligrams for all drugs except opioids, for which supply was calculated as morphine milligram equivalents (MME) using a standard formula provided by the US Centers for Disease Control and Prevention (CDC) [39, 40]. Throughout this article, the term 'supply' refers to these units of measure.

2.2.1 Abuse Potential

To assess abuse potential for gabapentin compared with other drugs, Lorenz curves were calculated. Lorenz curves assess cumulative percentage of supply consumed as a function of utilization frequency at a population level and are considered a standard measure of abuse potential [41–43]. The primary Lorenz curve measure is Lorenz-1, which represents the percentage of total drug supply consumed by the top 1% of users. A Lorenz-1 of 15% or more (i.e. the top 1% of users consume $\geq$15% of the drug supply) is considered to indicate high potential for abuse [42]. Consistent with previous work, the curves were calculated for 12 months of utilization, beginning with each subject's first observed claim, and all study subjects were continuously eligible from the first observed claim date through the subsequent 12 months [43].

2.2.2 Abuse Prevalence

To assess abuse prevalence, gabapentin, pregabalin, and opioids were studied. These drugs were chosen because of reports of concomitant opioid-gabapentin abuse [10–12, 14, 15] and in order to compare gabapentin with pregabalin, which is considered to have greater abuse potential than gabapentin and is a Schedule-V controlled substance [8]. Additionally, opioids were chosen as a comparator for gabapentin because they represent a 'worst-case scenario' for patient safety concerns and abuse potential [39, 43]. As such, they represent a conservative benchmark in testing the hypothesized gabapentin abuse.

Prevalence calculations were based on 12- and 24-month time periods, beginning on the first observed claim date for cohorts of subjects who were continuously eligible throughout those follow-up periods. Daily dose thresholds used to define potential abuse were based on CDC guidance for opioids (50 MMEs) [40] and on FDA product labels for gabapentin (3600 mg) [1] and pregabalin (600 mg) [8]. Two measures of potential abuse were calculated and reported for the sample overall (for Lorenz-1 and Lorenz-5 users), and for those in the bottom 95% of use (i.e. less than Lorenz-5). Both measures were intended to identify ongoing abuse, rather than one or two aberrant claims that could represent keying errors or unconsumed supply (e.g. for a single surgery).

1. The first method assessed dose per dispensed day, measured at a claim level as total supply dispensed divided by the 'days supply' value recorded on the claim. For example, if a quantity of 30 gabapentin tablets, 400 mg strength, was dispensed with a 'days supply' of 28, the claim's dose per dispensed day was calculated as 12,000 mg/28 days = 429 mg per dispensed day. Potential abuse was defined as three or more claims exceeding the daily dose thresholds.
2. The second method measured supply on an ongoing basis and was calculated per calendar day instead of per pharmacist-recorded dispensed day. This calculation was used to address the possibility that patients fill multiple 30-day prescriptions during a given month on a regular basis, visiting multiple prescribers or pharmacies and receiving 30-day supplies from each to avoid detection of abuse [44].

For this second measure, total supply dispensed was calculated on a rolling-quarterly basis at each month of treatment. For example, for the month of March, total supply was calculated from January through March; for the month of April, total supply was calculated from February through April; and so on through all months of follow-up. For each consecutive rolling quarter, total supply dispensed was divided by 90, yielding a measure of total dispensed supply per calendar day. Abuse was defined as three or more rolling quarters in which the dispensed supply per calendar day exceeded the threshold, counting only consecutive quarters. The calculation was done on consecutive quarters to avoid defining normal refill timing (e.g. filling a 90-day supply of medication in 1 month and consuming it over a 3-month period) as abuse. Results of the two methods were compared.

2.3 Cohort Inclusion/Exclusion Criteria

Figures 1 and 2 show the sample selection flowcharts for the Lorenz curve and abuse rate calculations. In addition to the aforementioned age and continuous eligibility criteria for the follow-up period, subjects with at least one claim for any patch or for any form of fentanyl were excluded from analyses to include oral formulations only, and because fentanyl is often prescribed to patients who are considered opioid-tolerant and likely require doses that exceed 50 MMEs daily [45].

Additional criteria were applied to the abuse prevalence analyses, consistent with previous work on this topic [43, 46]. Patients included in these analyses had two or more claims and ≥120 days of treatment (final fill date minus initial observed fill date) for one or more study drug, and were continuously eligible for ≥6 months preceding the first study drug claim (to allow for measurement of baseline diagnoses and medical utilization). Patients with chronic kidney disease or cancer (diagnosis codes reported in electronic supplementary Table 1) were excluded because these conditions affect drug pharmacokinetics and drug consumption, respectively.

2.4 Statistical Analyses

Although the primary analytic approach for the potential abuse prevalence analysis was descriptive, consistent with the exploratory nature of the work, bivariate statistics were used to compare the rates of potential abuse by drug. Bivariate statistics were also used to assess the significance of baseline differences, which were measured from 6 months prior through 7 days after the first study drug claim date, among cohorts defined by abuse types: no abuse, opioid abuse only, gabapentin abuse only, pregabalin abuse only, and combinations (i.e. abuse of more than one drug during follow-up) consisting of ≥20 patients. The 7-day window after study drug start was used to account for minor errors in recorded date of service.

Baseline diagnoses and medical services use were measured using claims from facilities, including both general acute care and psychiatric hospitals. These facility claims, which are included in the Truven Health database

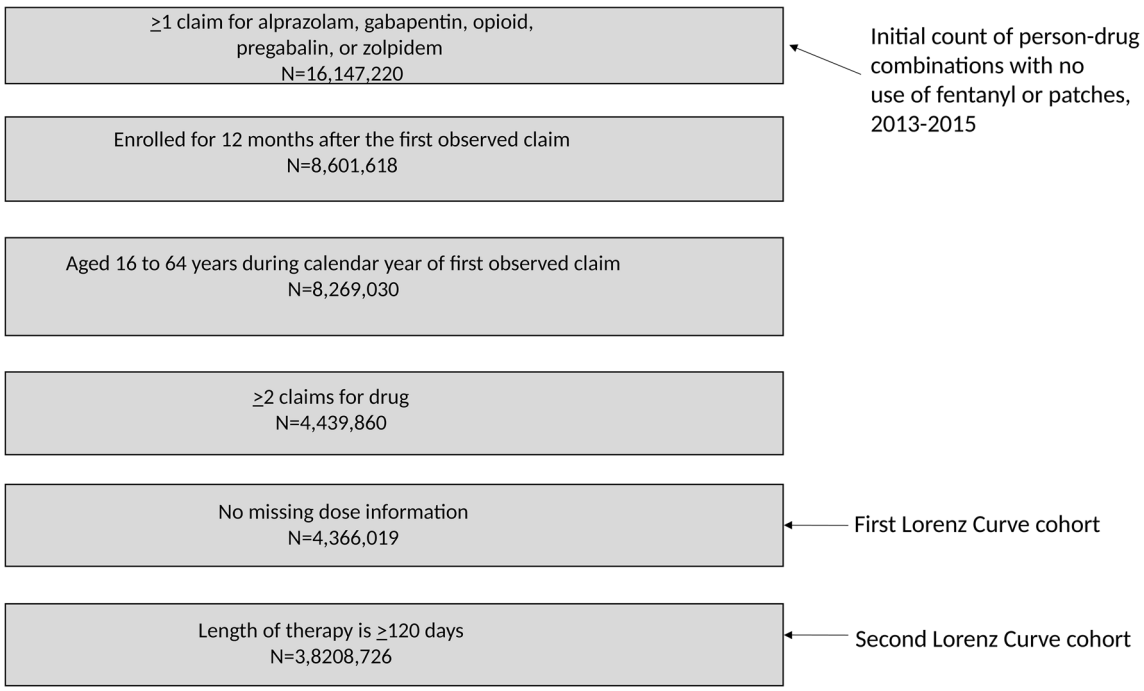

Fig. 1 Sample selection flowchart for Lorenz curve calculation of abuse potential

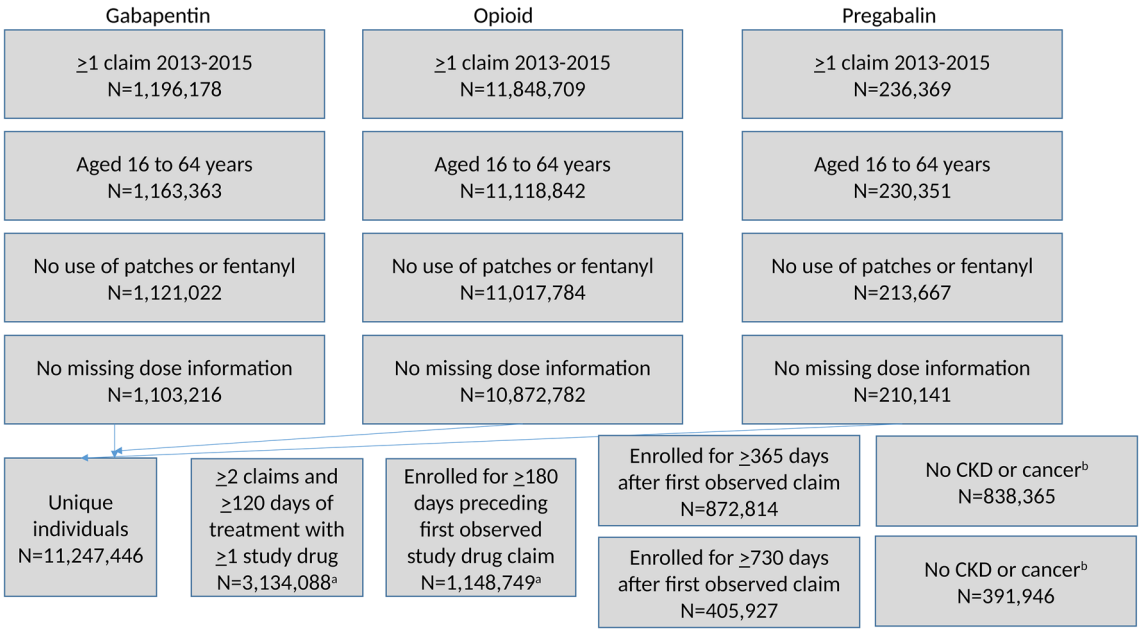

Fig. 2 Sample selection flowchart for calculation of abuse rates. [a]In the 24-month analysis, counts at these two stages were slightly lower because of exclusions based on patch and/or fentanyl use during the 24-month (instead of 12-month) follow-up period. [b]Diagnosis codes are shown in electronic supplementary Table 2. *CKD* chronic kidney disease

of medical services, comprise inpatient hospital stays, outpatient hospital visits, and emergency department visits. These services were examined because they are high in cost and are commonly used by patients who abuse opioids [47, 48].

Pearson's Chi-square tests were used for binomial measures, and analysis of variance (ANOVA) tests were used for interval-scale variables. An α (critical *P*) value of 0.001 was used because of the large sample size. All analyses were performed using SPSS version 23.0 (IBM SPSS, Armonk, NY, USA).

3 Results

3.1 Lorenz Curves: Percentage of Supply Consumed by Top Users

Lorenz curves indicated moderate to high abuse potential for all study medications among all users with two or more claims (Fig. 3a, b). As expected, abuse potential was particularly high for opioids, with the top 1% of users consuming 37% of supply. The top 1% of users of gabapentin and pregabalin consumed 19 and 15% of supply, respectively, with slightly lower Lorenz-1 percentages for alprazolam (14%) and zolpidem (13%). Among users with two or more claims and ≥120 days of treatment, results were similar for all users, new users (i.e. ≥6 months of eligibility prior to the first study drug claim), and 24 months of follow-up (Table 1; electronic supplementary Fig. 1).

3.2 Patterns of Use

The study sample for the prevalence analyses comprised 838,365 unique patients followed for 12 months (n = 72,477 for gabapentin, 786,655 for opioids, and 11,655 for pregabalin), and 391,946 unique patients followed for 24 months (n = 25,560 for gabapentin, 378,304 for opioids, and 4163 for pregabalin), after the initially observed study drug claim (Table 1). Among patients treated with gabapentin or pregabalin for 120 days or more, substantial proportions (22 and 26%, respectively) also used opioids for at least 120 days concomitantly during the 12-month follow-up period. These patterns of use continued throughout 24-month follow-up; 40% of gabapentin users and 39% of pregabalin users also took one or more opioids concomitantly for 120 days or longer.

The results indicate a strong association between Lorenz measures and the study metrics of potential abuse. Measured for the sample overall, rates of abuse calculated using either metric were low: 3–8% based on claims, and 2–3% based on rolling quarters. In contrast, of patients in the top 1% of users, virtually all (98–100%) met the claims-based standard for potential abuse, and the vast majority (79–91%) met the more stringent rolling-quarter-based standard. Among those not in the top 5% (i.e. bottom 95%), potential abuse was rare, ≤5% for all measures and drugs.

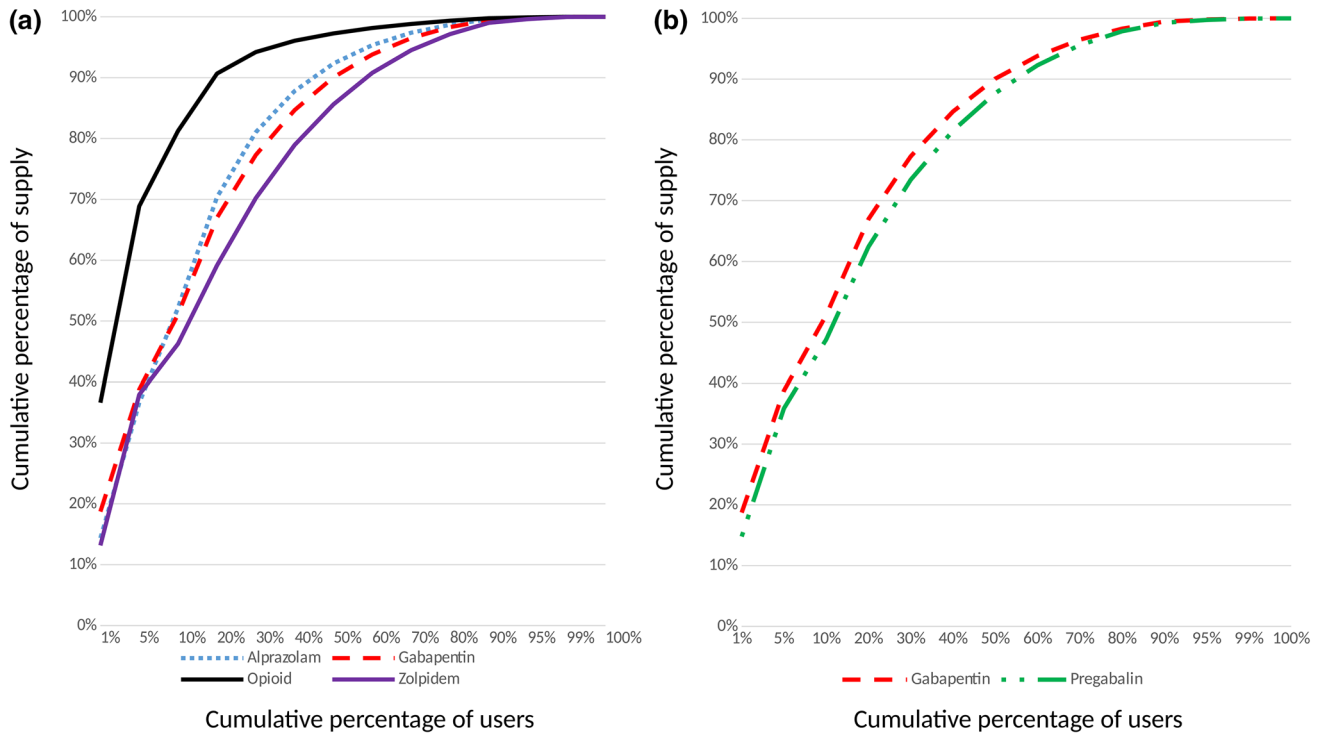

Fig. 3 Lorenz curves for all continuously enrolled users with two or more claims (first Lorenz curve cohort): **a** alprazolam, gabapentin, opioid, and zolpidem; **b** gabapentin and pregabalin

Almost no users in the bottom 95% met the rolling-quarter definition for sustained abuse.

3.3 Supply Per Day for Top 1% and 5% of Utilizers

Among users in the top 1%, the average supply per calendar day far exceeded dosing thresholds for all drugs, during both 12 and 24 months of follow-up (Table 1). Gabapentin users in the top-utilizing 1% filled prescriptions for a mean (median) of 11,274 (9534) mg/calendar day, a result similar to that for the top 1% of opioid users, with an MME of 180 (127) per day, and top 1% of pregabalin users, with 2474 (2219) mg/day. The 75th percentile values for supply per calendar day indicate that among the top 1% of users, one-quarter exceeded daily doses of gabapentin 12,822 mg, 187 MME opioids, and pregabalin 2943 mg, all of which were >3.5-fold the labeled maximum daily dose. Results were similar when use was measured per treatment day, although doses measured per treatment day were higher for all study drugs and for the 24-month follow-up.

For the top 5% of users, supply per calendar day was generally lower but still reflected considerable use in excess of the dosing thresholds. For example, the 75th percentile values indicate that one-quarter exceeded daily doses of gabapentin 5425 mg, 58 MME opioids, and pregabalin 1479 mg.

3.4 Characteristics Associated with Potential Abuse

Table 2 shows the percentages of patients with potential abuse of at least one study drug, characterized by patterns of use for 120 days or more. Among those using only one drug for ≥120 days, the percentages with three or more claims exceeding the dose threshold were 3.2% for gabapentin, 4.9% for pregabalin, and 7.5% for opioids. Rates were much higher among patients using both opioids and either pregabalin or gabapentin concomitantly for ≥120 days: 24% of patients using both an opioid and gabapentin ($n = 15{,}848$), 28% of those using both an opioid and pregabalin ($n = 2823$), and 42% of patients using all three study drugs ($n = 170$), had at least three claims over the dose threshold in the 12-month follow-up period.

Of patients identified as a potential abuser of at least one drug using the rolling-quarter-based method, 95% were also identified as potential abusers using the claim-based method (not shown in Table 2). Potential abuse rates measured using rolling quarters were generally lower but were, like the claims-based measures, elevated for patients using more than one study drug during follow-up. Of patients using both an opioid and gabapentin concomitantly for at least 120 days, 11% had three or more rolling calendar quarters exceeding the maximum labeled doses.

Table 1 Drug utilization metrics: users of gabapentin, opioids, and/or pregabalin with two or more claims and ≥120 days of therapy

	12-month follow-up[a]			24-month follow-up[a]		
	Gabapentin	Opioids	Pregabalin	Gabapentin	Opioids	Pregabalin
Use patterns						
No. of users	72,477	786,655	11,655	25,560	378,304	4163
Additional study drugs used, any therapy length [*N* (%)]						
Gabapentin	–	74,069 (9.4)	3942 (33.8)	–	36,061 (9.5)	1642 (39.4)
Opioids	51,101 (70.5)	–	8552 (73.4)	20,255 (79.2)	–	3318 (79.7)
Pregabalin	5056 (7.0)	14,121 (1.8)	–	2247 (8.8)	6875 (1.8)	–
Additional study drugs used concomitantly for ≥120 days [*N* (%)]						
Gabapentin	–	16,018 (2.0)	440 (3.8)	–	10,247 (2.7)	276 (6.6)
Opioids	16,018 (22.1)	–	2993 (25.7)	10,247 (40.1)	–	1642 (39.4)
Pregabalin	440 (0.6)	2993 (0.4)		276 (1.1)	1642 (0.4)	–
Percentage of users with three or more claims exceeding the labeled dose thresholds (%)[b]						
All users	2.5	8.0	4.0	2.9	9.7	4.2
Top 1%	97.9	98.8	100.0	99.2	94.8	100.0
Top 5%	46.6	66.3	65.3	46.4	67.8	59.4
Bottom 95%	0.2	5.0	0.8	0.6	6.6	1.3
Percentage of users with three or more rolling calendar quarters exceeding the common dose thresholds (%)[b,c]						
All users	1.9	1.6	3.2	2.1	1.2	3.7
Top 1%	79.1	90.5	90.5	81.2	83.7	100.0
Top 5%	36.9	32.8	58.2	37.5	24.8	58.9
Bottom 95%	0.0	0.0	0.3	0.2	0.0	0.8
Supply per calendar day, top 1% of users[d]						
No. of cases	723	7783	116	255	3822	41
Mean (SD)	11,274 (5309)	180 (208)	2474 (791)	9757 (5768)	102 (147)	1946 (544)
Median (IQR)	9534 (7397–12,822)	127 (90–187)	2219 (1832–2943)	7693 (5918–11,466)	64 (45–108)	1726 (1469–2450)
Supply per treatment day, top 1% of users[d]						
No. of cases	723	7783	116	255	3822	41
Mean (SD)	13,378 (6461)	199 (222)	2823 (919)	12,665 (7802)	121 (163)	2368 (744)
Median (IQR)	11,225 (8876–16,256)	144 (101–209)	2595 (2120–3143)	9758 (7132–15,574))	77 (52–133)	2227 (1696–2911)
Supply per calendar day, top 5% of users[d]						
No. of cases	3606	38,236	582	1279	18,773	207
Mean (SD)	4806 (4121)	60 (112)	1153 (798)	3895 (3954)	33 (75)	859 (629)
Median (IQR)	3132 (2466–5425)	30 (20–58)	814 (592–1479)	2441 (1923–3945)	16 (11–29)	555 (444–1110)
Supply per treatment day, top 5% of users[d]						
No. of cases	3606	38,236	582	1279	18,773	207
Mean (SD)	5823 (5058)	70 (121)	1401 (971)	5302 (5553)	42 (85)	1280 (959)
Median (IQR)	3707 (2804–6923)	37 (24–70)	1020 (646–1857)	2962 (2141–6321)	21 (13–41)	860 (497–1796)
Percentage of total sample supply, top users (%)[d]						
Top 1%, all users[e]	17.1	32.2	13.1	16.8	35.5	13.1
Top 5%, all users[e]	37.0	64.4	34.4	36.2	69.4	32.9
Top 1%, new users	13.6	33.5	10.4	15.9	34.6	11.5
Top 5%, new users	28.9	55.0	24.2	31.9	54.9	25.6

CKD chronic kidney disease, *IQR* interquartile range (25th–75th percentile), *MMEs* morphine milligram equivalents, *SD* standard deviation

[a] With continuous enrollment during follow-up periods shown in column headers

[b] Thresholds based on labeled indications: 3600 mg for gabapentin, 600 mg for pregabalin, and 50 MMEs for opioids (e.g. labeled dose for hydrocodone 10 mg/300 mg is one tablet every 4–6 h)

[c] Rolling calendar quarters measured monthly; metric counts the number of times that both the current and the previous rolling quarter exceeded the threshold, based on the total supply dispensed in previous 90 days, divided by 90

[d] Rank ordered by total supply used during the follow-up period

[e] No requirement for 6 months of pretreatment eligibility; includes patients with CKD or cancer (corresponds to the Lorenz curves shown in electronic supplementary Fig. 1)

Table 2 Percentage with use exceeding the dose thresholds, by patterns of use (≥120 days), 12-month follow-up

	Opioid only	Gabapentin only	Pregabalin only	Opioid + gabapentin[a]	Gabapentin + pregabalin[a]	Opioid + pregabalin[a]	All three study drugs[a]
No. of cases	765,354	47,480	6420	15,848	270	2823	170
Three or more claims exceeding the labeled dose thresholds (%)[b]	7.5	3.2	4.9	24.2	8.9	28.0	41.8
Three or more rolling calendar quarters exceeding the common dose thresholds (%)[b,c]	1.4	2.0	3.3	11.4	6.3	17.1	28.2

MMEs morphine milligram equivalents

[a] Indicates concomitant use of the drugs shown in the column header for ≥120 days. Patients using more than one drug without ≥120 days overlap were classified based on the chronologically first medication

[b] All comparisons were statistically significant at $p < 0.001$ using Pearson's Chi-square test. Metric indicates whether any drug used by the patient exceeded thresholds shown. Dose thresholds based on labeled indications: 3600 mg for gabapentin, 600 mg for pregabalin, and 50 MMEs for opioids (e.g. labeled dose for hydrocodone 10 mg/300 mg is one tablet every 4–6 h)

[c] Rolling calendar quarters measured monthly; metric counts the number of times that both the current and the previous rolling quarter exceeded the threshold, based on the total supply dispensed in the previous 90 days, divided by 90

Analyses of baseline facility utilization and diagnoses for the top 1% indicate a strong association between high utilization of opioids and a diagnosis of alcohol/drug abuse/addiction (Table 3). Among opioid users in the top 1%, 49% were diagnosed with abuse/addiction in a facility (hospital inpatient, emergency department, or outpatient hospital) during the 6 months prior to the first study drug claim. Results also indicated a strong association between pain, particularly musculoskeletal pain, and top 1% use of opioids with the other study drugs, particularly pregabalin. Of the top 1% users of both opioids and gabapentin, or pregabalin alone, 54% were diagnosed with pain in a facility during the baseline period. More than 59% of opioid + pregabalin top 1% users had a pain diagnosis. Results were similar in analyses of the top 5% of users (Electronic Supplementary Table 2).

4 Discussion

This study, which, as far as the authors are aware, is the first to examine gabapentin abuse in a large US population, found that gabapentin use patterns display several characteristics that have been associated with abuse of opioids in previous work, although to a lesser degree. These include the use of a substantial proportion of drug supply by a small proportion of users, high average daily doses dispensed to patients in the top utilizing percentiles, and elevated rates of potential gabapentin abuse in patients using both gabapentin and opioid medications. Of the top 1% of gabapentin users, 79–98% displayed evidence of sustained use above the common dose thresholds, whereas almost no users (0–0.2%) in the bottom 95% displayed the same use pattern.

Results are consistent with previous work suggesting that gabapentin abuse, although rare at a population level, may pose serious concerns for patient safety, diversion, or both [10]. The top 1% of gabapentin users filled prescriptions for an average of 11,274 mg/calendar day, and, of those, the top 25% either consumed or diverted more than 12,822 mg/day, which is more than 3.5-fold the labeled maximum dose. If consumed, doses this high may cause overdose or withdrawal, with potential implications for both economic and humanistic cost [49]. Moreover, abuse prevalence rates were elevated among those using more than one study drug for ≥120 days; 24% of patients with simultaneous opioid and gabapentin use, and 42% of patients with simultaneous use of opioids and both gabapentinoids, had at least three claims exceeding the dose threshold in 12 months of follow-up. These findings provide systematic evidence of a linkage between gabapentinoid abuse and opioid abuse, which has been reported in previous work conducted in small and/or high-risk samples [10–12, 14, 15].

Table 3 Baseline facility utilization metrics, all-cause and disease-specific, cohort groups with ≥120 days of treatment, by percentile groups, top 1%[a]

	No. of drugs in top 1% use	Top 1% use				
		Opioid only	Gabapentin only	Pregabalin only	Gabapentin + opioid	Pregabalin + opioid
No. of cases	829,877	7654	616	84	102	27
Mean age (SD), years[b]	44 (13)	43 (13)	50 (11)	49 (9)	52 (9)	49 (12)
Female (%)[b]	60.0	41.2	59.3	63.1	53.9	74.1
Diagnoses (%)[b]						
Addiction[c]	7.3	49.3	12.8	16.7	17.6	25.9
Anxiety	2.3	5.0	7.1	2.4	3.9	18.5
Depression	2.2	5.0	7.1	6.0	5.9	18.5
Detoxification services	0.1	2.4	0.3	0.0	0.0	0.0
Injury	10.6	9.7	7.5	10.7	8.8	29.6
Pain, any	23.8	31.4	37.7	53.6	53.9	59.3
Pain, chronic	1.1	5.6	4.9	4.8	4.9	7.4
Pain, musculoskeletal	22.5	29.2	34.7	46.4	50.0	59.3
Pain, vascular	0.4	0.6	1.0	1.2	1.0	3.7
Pain, neuropathic	1.6	2.0	5.5	6.0	9.8	7.4
Schizophrenia	0.0	0.1	0.3	0.0	1.0	0.0
Inpatient hospital (%)[d]						
All-cause	7.8	10.8	11.4	10.7	11.8	25.9
Addiction	0.9	5.2	2.6	0.0	2.0	0.0
Injury	0.7	1.9	1.1	1.2	2.0	14.8
Pain	2.2	5.2	6.5	8.3	5.9	22.2
Emergency department (%)[d]						
All-cause	19.3	18.2	18.0	13.1	29.4	37.0
Addiction	2.3	5.8	3.7	3.6	3.9	3.7
Injury	5.3	4.4	3.1	4.8	2.9	3.7
Pain	4.3	5.1	5.5	7.1	14.7	22.2
Outpatient hospital (%)[d]						
All-cause	46.3	41.5	56.2	66.7	64.7	66.7
Addiction	3.3	9.0	5.8	7.1	3.9	11.1
Injury	6.4	5.1	4.2	3.6	2.0	11.1
Pain	14.8	18.6	24.8	35.7	40.2	29.6

[a] 12-month follow-up cohort. Percentiles based on rank ordering by total supply used during the follow-up period. Baseline was measured 183 days preceding through 7 days following the first claim for any study drug. Facility claims include inpatient stays, emergency department visits, and outpatient hospital visits at acute care hospitals, including psychiatric facilities. Excludes patients with top 1% use of both gabapentin and pregabalin ($n = 5$)

[b] All comparisons were significant at $p < 0.001$, except for emergency department use overall ($p = 0.001$) and injury ($p = 0.002$)

[c] In addition to facility services as shown, includes patients with at least one claim for methadone, buprenorphine, or naloxone

[d] All-cause measures based on place-of-service codes

The present study also extends previous work on administrative claims-based measures of prescription drug abuse [41–43, 50], and responds to calls for population-level algorithms suitable for surveillance and targeted interventions [43]. In addition to Lorenz curve analysis, which has been used in previous work to measure abuse of opioids and other controlled substances, the present study employed counts of rolling calendar quarters and claims exceeding the labeled dose thresholds, which have not been used previously to our knowledge. An advantage of the present study metrics is that they do not require information on the number of prescribers or pharmacies (i.e. 'provider shopping') as some claims-based algorithms do [50]. The strong concordance between Lorenz curve results and these count measures provides a preliminary indication, but not

definitive proof, of their validity as indicators of abuse at levels that merit intervention.

In that regard, while the present study findings provide support for recommendations to make gabapentin a controlled substance, they do not provide definitive evidence of harm. The present study findings suggest a need for additional research into the predictive validity of the study metrics for medical sequelae of abuse, such as emergency department visits or hospitalizations during and after periods of non-medical drug use. Whether the degree of abuse (e.g. number of claims or quarters) is associated with increasing medical service use should be addressed as part of that effort. Finally, the possibility that medication supply is being diverted rather than consumed at the highest daily dose, points to the need for research into markers of abuse versus diversion.

4.1 Limitations

Several study limitations should be noted. First, the authors are not aware of any established dose threshold criteria to constitute abuse of pregabalin or gabapentin, as there are for MME. Maximum labeled doses in other countries may be greater or less than those used in the US, and it is possible that the use of different thresholds would have resulted in changes to the prevalence rates identified in the present study. However, findings of the Lorenz curve analysis, which did not depend on specific dose thresholds, were similar to those of the threshold-based abuse prevalence analysis. Second, 'days supply' information, which was used to calculate the claims-based measure of potential abuse, is subject to keying errors made by the dispensing pharmacy. However, neither the rolling-quarter metric nor the calculation of supply per calendar day were affected by this limitation, and these measures produced similar results. Third, because the study focused on facility services in profiling baseline utilization history, several indications for use of the study drugs, such as hot flashes and restless legs syndrome, were not included in the profiles. Future research should explore a wider range of patient characteristics, including indications for use of abused medications. In addition, the present study was limited to a relatively brief time span and therefore did not assess time trends in abuse prevalence rates. Further research over longer periods of time is needed given the growing attention to the problem of prescription drug abuse [51], particularly since a tightening of the opioid supply has the potential to lead to a search for more readily available alternatives.

5 Conclusions

Use patterns for gabapentin are similar to those of other medications with known abuse potential. On average, the top 1% of gabapentin users consumes more than three times the maximum FDA-labeled daily dose, providing support for recent calls to make gabapentin a controlled substance. Further investigation of the medical consequences of gabapentin abuse, with or without concomitant opioid abuse, is warranted.

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Author contributions All three authors contributed to the study concept and design. KAF analyzed the data, and results were interpreted by all three authors. AMP and KAF drafted the manuscript, and all three authors reviewed and revised it critically for intellectual content. All three authors approved the final version to be published.

Compliance with Ethical Standards

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Conflict of interest Alyssa M. Peckham, Kathleen A. Fairman, and David A. Sclar have no relationships (financial, employment, or other) relevant to the topic of this article and have no conflicts of interest to report.

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