Gabapentinoid Prescribing Practices at a Large Academic Medical Center

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Abstract

Objective: To evaluate indications for gabapentinoid prescription at an academic medical center.

Patients and Methods: We retrospectively reviewed patients aged 18 years or older who were prescribed gabapentinoids (gabapentin or pregabalin) during the 2019 calendar year at an academic medical center in the US Midwest. Patient demographic characteristics, indications for gabapentinoid prescription, and prescribing clinician specialities were abstracted from a random sample, and the findings were extrapolated to the overall cohort.

Results: A total of 6205 prescriptions for gabapentinoids were initially identified. In the random sample of prescriptions (n=721), 89.5% were for gabapentin and 10.5% were for pregabalin. More women than men were prescribed gabapentinoids, and the mean ± SD patient age was 58.6±16.9 years. The top 5 indications for gabapentinoid prescriptions were neuropathic pain, musculoskeletal pain, restless legs syndrome, anxiety, and headache. A majority (66.7%) of prescriptions had substantial-to-modest evidence, but 29.0% of prescriptions had conflicting or insufficient evidence.

Conclusion: To our knowledge, this study is one of the first to manually review clinical notes from multiple clinical specialities to ascertain indications for gabapentinoid prescriptions. Although most prescriptions had modest evidence to support their use, a high percentage of gabapentinoid prescriptions were issued for indications not supported by robust evidence. This suggests that prescribers are gravitating toward gabapentinoid use for reasons that are currently not fully understood. Clinician intent for off-label gabapentinoid prescriptions at the point of care should be further studied to understand the factors that lead to these clinical decisions.

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The number of prescriptions for gabapentinoids, which include gabapentin and pregabalin, has increased since 2003.[1-3] Many of these prescriptions were reportedly for off-label indications not supported by robust evidence.[1-3] The perception that gabapentinoids are safer than and an acceptable substitute for opioids as a consequence of the opioid crisis may be responsible for this increase.[4] A systematic review reported increased gabapentinoid misuse and abuse with increased patient harm, including increased hospitalization and overdoses with concurrent opioid use.[5] Concern for patient safety related to the increase in off-label gabapentinoid prescriptions has resulted in increased regulatory awareness, such as reclassifying gabapentinoids as controlled substances or including them in local prescription drug monitoring programs.[6]

Although their mechanism of action is unknown, gabapentinoids share structural similarity with the neurotransmitter γ-aminobutyric acid and bind to α_2-δ subunits of voltage-gated calcium channels in the central nervous system.[7] Gabapentin received US Food and Drug Administration (FDA) approval in 1993 as an adjunct agent for focal onset seizures in patients aged 3 years and older.[8] In 2002, it also received FDA approval for postherpetic neuralgia and became available as a generic medication in 2004.[7,8] Pregabalin received FDA approval in 2004 for neuropathic pain associated with diabetic neuropathy and postherpetic neuralgia and as an adjunctive modality for focal onset seizures.[9]

Although the indication of generalized anxiety disorder was submitted to the FDA in 2004, this indication did not receive FDA approval.[9] Pregabalin also received FDA approvals for fibromyalgia in 2007 and neuropathic pain associated with spinal cord injury in 2012. Since then, other forms of gabapentinoids, such as extended-release gabapentin and gabapentin enacarbil (gabapentin prodrug), have been introduced into the pharmaceutical marketplace and have received FDA approvals for indications of moderate to severe restless legs syndrome (RLS) and postherpetic neuralgia.[10,11] During this period of regulatory activity, brand-name gabapentin was marketed and promoted for many off-label uses.[12,13]

Previous studies evaluating off-label gabapentinoid prescriptions have mostly relied on pharmacy billing information or data generated from insurance claims.[1-3] However, this approach precludes the ability to provide insights into the rationale that clinicians document for prescribing gabapentinoids, whether for FDA-approved or off-label indications. Gabapentinoid prescribing indications can be best assessed by reviewing clinical documentation and are important to understand for informing evidence-based and safer gabapentinoid use. Here, we sought to evaluate indications for gabapentinoid prescriptions according to prescribing clinician specialty by retrospectively reviewing patient health records.

PATIENTS AND METHODS

Study Design
This study was approved by the Mayo Clinic Institutional Review Board. We retrospectively searched the electronic health records for all outpatients prescribed gabapentin or pregabalin at Mayo Clinic, Rochester, Minnesota, during the 2019 calendar year. We collected data only from patients who had documented consent for electronic health record review. If a patient had multiple prescriptions issued in 2019, only the first chronological instance was recorded.

After initially identifying all patients who were prescribed gabapentinoids, we performed random sampling of the patients by stratifying them according to prescribing clinician speciality. We randomly selected 100 patients per clinical speciality. In specialities with

fewer than 100 patients, all patients in that category were selected. Data within the relevant clinical notes for the first gabapentinoid prescription for the randomly sampled patients were manually reviewed and abstracted. The data collected included patient demographic characteristics, indications for gabapentinoid prescription (single or multiple), the specific gabapentinoid prescribed, dosage information, and the clinical speciality of the prescribing clinician. If a patient did not have a valid prescription or was tapering off gabapentinoid use while taking the first gabapentinoid prescription, the patient was excluded from the analysis.

Categorization of Indications
We reviewed previously published studies to determine common uses of gabapentinoids.[2,4,12] On the basis of this review and our clinical experience, we selected specific indications for gabapentinoid prescriptions for our analysis. These specific indications were then grouped into larger clinically relevant categories: (1) pain, including neuropathic pain, musculoskeletal pain, cancer-related pain, headache, fibromyalgia, and other chronic pain (eg, leg cramps and nonspecific pain disorder); (2) neurologic, consisting of seizures and tremors; (3) sleep, comprising RLS, periodic limb movement disorder (PLMD), and insomnia; (4) psychiatric, including anxiety, mood disorders (depression, bipolar, and posttraumatic stress disorder), and substance use disorder; and (5) miscellaneous, denoted by perioperative indications (ie, preoperative orders by a surgical specialist), gastrointestinal indications (abdominal pain, irritable bowel syndrome, and general gastrointestinal symptoms), hot flashes, cough, pruritus, and other indications. The other indications contained in the miscellaneous category consisted of diagnoses that did not fit into any other category and did not have enough prescriptions issued to warrant a separate indication category.

Categorization of Clinical Specialties
The following clinical specialties were classified according to the prescribing clinician profiles listed in our electronic health record: (1) hematology/oncology (including palliative care and hospice), (2) internal medicine (including primary care internal medicine,

family medicine, general internal medicine, and women's health), (3) medical subspecialities (including allergy and immunology, breast clinic, cardiology, dermatology, endocrinology, gastroenterology, genetics, infectious diseases, nephrology, pulmonology, rheumatology, transplant medicine, and vascular medicine), (4) neurology, (5) physical medicine and rehabilitation/pain medicine (including physical medicine and rehabilitation, sports medicine, fibromyalgia clinic, pain clinic, and pain rehabilitation program), (6) psychiatry (including nicotine dependence clinic), (7) sleep medicine, and (8) surgical subspecialities (including general surgery, cardiovascular surgery, colorectal surgery, dental surgery, otorhinolaryngology, neurosurgery, obstetrics and gynecology, ophthalmology, orthopedics, thoracic surgery, urology, urogynecology, and vascular interventional radiology).

Formation of an Evidence Table for Gabapentinoid Prescription Indications

All FDA-approved indications for pregabalin and gabapentin were first reviewed. We then informally reviewed available guidelines from academic/clinical societies and organizations for the prescribed indications that were not FDA-approved. If these guidelines did not provide clear direction, the previously published studies were reviewed to determine whether evidence supported the prescription indication. The studies we reviewed included systematic reviews and meta-analyses, and randomized clinical trials in some instances. Three study personnel (L.L.H., J.A.W., A.V.) assessed the amount of available evidence for the indications and categorized them as substantial, modest, insufficient, conflicting, or none.

Statistical Analyses

Patient demographic characteristics were summarized as frequency (%) for categorical variables and mean ± SD for continuous variables. A random sample of patients equally stratified by prescribing clinician specialty was collected from the overall cohort. Indications were calculated as percentages by specialty and then extrapolated to the larger data set. Because the number of prescriptions issued differed among the specialties, the extrapolated percentages were calculated by weighting the specialities for the categories of each indication and the individual indications within each medication group (pregabalin or gabapentin). Weights were determined for each indication by multiplying the percentage of indications for each specialty from the random sample by the number of overall patients in the specialty. This product was then added to the number of patients from every specialty, divided by the total number of indications for each medication group, and multiplied by 100. A patient could have more than 1 indication for a prescription. All data analyses were performed with SAS software (v9.4, SAS Institute Inc).

RESULTS

A total of 6205 prescriptions for gabapentinoids were issued in 2019 at our center. We selected a random sample of 721 prescriptions for further analysis and extrapolation to the initial cohort. Most of the overall prescriptions were for gabapentin (89.5%), whereas 10.5% were for pregabalin (Table 1). Slightly more prescriptions were issued for women (58.4%) than for men (41.6%), and the mean ± SD patient age was 58.6±16.9 years. The prescribing clinician specialties in which most overall gabapentinoid prescriptions were issued were internal medicine (49.3%), followed by neurology (18.2%) and surgical subspecialties (11.5%) (Table 1). Only 4 prescriptions for gabapentin enacarbil were present in our random sample.

The prevalence of each indication within each speciality is highlighted in Table 2. The most common indication for gabapentinoid prescription was neuropathic pain. Neuropathic pain indications accounted for at least one-third of overall gabapentinoid prescriptions for all specialties, except psychiatry and sleep. Musculoskeletal pain was the second most common indication for gabapentinoid prescriptions. The 3 specialties that issued the highest percentage of gabapentinoid prescriptions for musculoskeletal pain were physical medicine and rehabilitation/pain medicine, internal medicine, and surgical subspecialties. Notably, 9.8% of gabapentinoid prescriptions for musculoskeletal pain were issued by psychiatry specialists, which was similar to those prescribed by hematology/oncology specialists.

TABLE 1. Overall Population Demographic Characteristics[a]		
Characteristic	Overall cohort (N=6205)	Random sample (n=721)
Age (y)	58.6±16.9	57.2±16.9
Sex		
Female	3621 (58.4)	406 (56.3)
Male	2584 (41.6)	315 (43.7)
Gabapentinoid		
Gabapentin	5554 (89.5)	645 (89.5)
Pregabalin	651 (10.5)	76 (10.5)
Clinical specialty		
Hematology/oncology	312 (5.0)	92 (12.8)
Internal medicine	3058 (49.3)	100 (13.9)
Medical subspecialties	445 (7.2)	91 (12.6)
Neurology	1131 (18.2)	94 (13.0)
Physical medicine/fibromyalgia/pain clinic	352 (5.7)	92 (12.8)
Psychiatry	99 (1.6)	82 (11.4)
Sleep	96 (1.5)	74 (10.3)
Surgical subspecialties	712 (11.5)	96 (13.3)

[a]Data are summarized as mean ± SD for patient age and as number (%) of patients for all other variables.

Within the sleep medicine specialty, 8.1% of prescriptions in the random sample were for neuropathic pain, whereas 6.8% were for insomnia (Table 2). Within psychiatry, 73.2% of prescriptions were for anxiety, 26.8% for insomnia, 24.4% for mood disorders, and 12.2% for substance use disorders. Headaches were the fifth most common indication overall (9.3%), and most of these prescriptions were issued by neurology specialists. Gabapentinoid prescriptions were issued as part of the perioperative order set for 6.9% of prescriptions, and many of these were issued by surgical specialists (31.3%). The least common indication was for seizures (0.8%). More than 1 indication was documented for 188 (26.1%) prescriptions in the random sample; therefore, the percentage of prescriptions exceeded 100% for each clinical specialty.

Table 3 summarizes the level of evidence supporting (or not supporting) the indications for gabapentinoid prescriptions in the overall cohort.[14-54] Gabapentinoid prescriptions for pain-related indications, such as neuropathic pain, headaches, and musculoskeletal pain, were the most common (82.1%). Although neuropathic pain and fibromyalgia indications had substantial evidence for treatment with gabapentinoids, evidence supporting their use for pain indications such as headache, osteoarthritis, and chronic abdominal pain was insufficient.

As expected, most prescriptions for sleep indications were for RLS and PLMD symptoms, which were the third most common indication for gabapentinoid prescriptions. However, only gabapentin enacarbil, and not immediate-release gabapentin, has FDA approval for the management of RLS.[7,10,11] The difference between these formulations is important because their pharmacokinetic profiles are distinct.[11] Additionally, evidence supporting gabapentinoid prescriptions for insomnia was insufficient. With regard to anxiety, pregabalin is approved for this use in Europe but has not received approval in the United States.[55] Our findings from 2 systematic reviews indicate that moderate evidence supports this practice.[39,40] In contrast, less than 5% of prescriptions were issued for mood indications, but evidence supporting gabapentinoid prescriptions for depression and bipolar disorder indications was insufficient.[37,38] Additionally, guidelines from the US Department of Veterans Affairs recommend against the use of gabapentinoids for treating posttraumatic stress disorder.[41] A small percentage of prescriptions were issued for miscellaneous indications, such as burning mouth syndrome, cramp fasciculation syndrome, dysesthesias without pain, dystonia, hand-foot syndrome, hypnic jerks, leprosy, motor restlessness, opsoclonus, acute pain associated with penile implant procedure, sweating, and tongue sensitivity. We also categorized the indications in the random sample by levels of evidence for any indication. For the prescriptions (26.1%) that had more

Indication	Hematology/oncology	Internal medicine	Medical subspecialities	Neurology	Physical/pain medicine	Psychiatry	Sleep	Surgical subspecialities	Total
Neuropathic pain	64.1	38.0	33.0	41.5	46.7	8.5	8.1	52.1	37.7
Musculoskeletal pain	9.8	33.0	14.3	12.8	47.8	9.8	1.4	25.0	20.0
RLS/PLMD	1.1	3.0	3.3	3.2	0.0	9.8	91.9	1.0	12.1
Anxiety	1.1	8.0	2.2	1.1	1.1	73.2	5.4	0.0	10.7
Headache	3.3	10.0	6.6	41.5	1.1	8.5	1.4	0.0	9.3
Perioperative indications	1.1	3.0	0.0	1.1	16.3	0.0	0.0	31.3	6.9
Insomnia	0.0	4.0	2.2	3.2	4.3	26.8	6.8	0.0	5.5
Other chronic pains	8.7	5.0	9.9	2.1	3.3	8.5	5.4	5.2	6.0
Mood disorders	0.0	4.0	1.1	0.0	1.1	24.4	1.4	0.0	3.6
Gastrointestinal indications	0.0	1.0	18.7	0.0	0.0	1.2	0.0	0.0	2.6
Cancer-related pain	16.3	0.0	0.0	3.2	0.0	0.0	0.0	2.1	2.8
Hot flashes	12.0	5.0	1.1	0.0	0.0	2.4	0.0	0.0	2.6
Other indications	4.3	0.0	4.4	4.3	1.1	2.4	1.4	2.1	2.5
Cough	0.0	0.0	17.6	0.0	0.0	0.0	0.0	0.0	2.2
Fibromyalgia	0.0	6.0	2.2	2.1	0.0	4.9	0.0	0.0	1.9
Pruritis	3.3	0.0	6.6	0.0	1.1	0.0	0.0	0.0	1.4
Substance use disorder	0.0	0.0	0.0	0.0	0.0	12.2	0.0	0.0	1.4
Tremors	1.1	1.0	0.0	6.4	0.0	3.7	0.0	0.0	1.5
Seizures	1.1	0.0	0.0	5.3	0.0	0.0	0.0	0.0	0.8

TABLE 2. Highlight Table of Gabapentinoid Prescription Indications According to Prescribing Clinician Specialty in the Random Sample[a,b]

[a]PLMD, periodic limb movement disorder; RLS, restless legs syndrome.

[b]Data shown are the percentage of patients/prescriptions in the random sample (n=721). Some prescriptions had more than 1 indication documented. Color scale represents darker green shading for each 10-percentage point increment.

than 1 indication, we chose the highest level of evidence. Overall, 44.0% of prescriptions had at least 1 indication with a substantial level of evidence for gabapentinoid use, whereas 22.7% of prescriptions had modest evidence, 7.2% had conflicting evidence, 21.8% had insufficient evidence, and 4.3% were too heterogeneous to characterize.

DISCUSSION

Our study focused on data collected from current clinical practices in a large academic institution in the US Midwest. We recognize the regulatory limitations for on-label or FDA-approved indications for gabapentinoid use, but we chose to characterize the indications in this study according to the amount of evidence supporting their use. Our findings indicate that more than one-third of prescriptions for gabapentinoids in our sample had at least substantial evidence supporting their use;

however, a small but considerable percentage of gabapentinoid prescriptions were issued for indications not supported by robust evidence.

Most of the prescriptions issued in our study were for pain-related indications. This is consistent with the findings of previous studies that examined gabapentin prescribing trends in the US population.[1] Although gabapentinoids have substantial evidence for treating neuropathic pain (including cancer-related neuropathic pain) and fibromyalgia, evidence for their use for other pain indications is insufficient. A possible reason for gabapentinoid use for multiple pain indications is the assumption that gabapentinoids are beneficial for all chronic pain disorders because of their efficacy in treating neuropathic pain. This assumption may be exacerbated by the lack of alternative analgesic options in the context of the opioid crisis and by potential

TABLE 3. Evidence Table of Gabapentinoid Prescription Indications in Overall Cohort[a]

Indication category	Gabapentin (n=5554)			Pregabalin (n=651)		
	No. (%)	Supportive evidence	Comments	No. (%)	Supportive evidence	Comments
Pain indications	4565 (82.2)			530 (81.4)		
Headache disorder	796 (14.3)	Conflicting	Strongly recommended for migraine prophylaxis by 2012 Canadian Headache Society Guidelines[14] Insufficient evidence in 2012 AAN guidelines[15] Insufficient evidence in 2 systematic reviews[16,17] and 1 randomized clinical trial[18]	9 (1.4)	Insufficient	Use not evaluated by the Canadian Headache Society[15] or AAN[15] or in controlled clinical trials (systematic review)[16]
Neuropathic pain	2266 (40.8)	Substantial	FDA-approved for postherpetic neuralgia First-line therapy in 2010 EFNS, 2013 NICE, 2014 CPS, and 2015 NeuPSIG guidelines for all types of neuropathic pain, except trigeminal neuralgia[19,20]	262 (40.2)	Substantial	FDA-approved for postherpetic neuralgia, diabetic peripheral neuropathy, and spinal cord injury First-line therapy in 2010 EFNS, 2013 NICE, 2014 CPS, and 2015 NeuPSIG guidelines for all types of neuropathic pain, except trigeminal neuralgia[19,20]
Fibromyalgia	154 (2.8)	Substantial	Option for management in ACR guidelines[21] Recommended by CPS EULAR recommends use for research only[22] No comments on use from AWMF[23]	73 (11.2)	Substantial	FDA-approved for fibromyalgia Option for management in ACR and EULAR guidelines[21,22] Recommended by CPS and AWMF as the second-line agent[23]
Musculoskeletal pain	1504 (27.1)	Insufficient	Lack of evidence in 2019 ACR guidelines and cohort study for osteoarthritis[24,25]	95 (14.6)	Insufficient	Lack of evidence in 2019 ACR guidelines and cohort study for osteoarthritis[24,25]
Cancer-related pain	85 (1.5)	Substantial	First-line therapy for cancer-related neuropathic pain by NCI, ESMO, and SEOM[26-28] Permitted for clinical trial testing for chemotherapy-induced peripheral neuropathy by NCI[26]	26 (4.0)	Modest	First-line therapy for cancer-related neuropathic pain by NCI[26]
Other chronic pain[b]	207 (3.7)			103 (15.8)		
Neurologic indications	153 (2.8)			21 (3.2)		
Seizure	50 (0.9)	Substantial	FDA-approved as adjunct for focal seizures	21 (3.2)	Substantial	FDA-approved as adjunct for focal seizures
Tremor	107 (1.9)	Modest		0 (0)	Insufficient	Low evidence in systematic review[31]

TABLE 3. Continued						
	Gabapentin (n=5554)			Pregabalin (n=651)		
Indication category	No. (%)	Supportive evidence	Comments	No. (%)	Supportive evidence	Comments
			Level B evidence by AAN[29] Low evidence in systematic review[30]			
Sleep indications	421 (7.6)			43 (6.6)		
Insomnia	211 (3.8)	Insufficient	2017 AASM guidelines state not enough evidence[32] Systematic review suggests potential efficacy when used in patients with other medical illnesses[33]	3 (0.5)	Insufficient	Not evaluated in AASM guidelines[32]
RLS/PLMD	216 (3.9)	Modest/conflicting	FDA approved the use of gabapentin enacarbil for RLS AASM states low evidence for the use of immediate-release gabapentin for RLS and PLMD[34] No conclusions from AAN for immediate-release gabapentin use for RLS[35]	41 (6.3)	Modest	AASM states low evidence for RLS and PLMD[34] AAN states moderate evidence for RLS[35]
Psychiatric indications	327 (5.9)			105 (16.1)		
Anxiety	284 (5.1)	Modest	Permitted for clinical trial testing as an adjunct after failing other therapies for panic disorder by APA[36] Moderate evidence for use in systematic reviews[37,38]	71 (10.9)	Modest	Moderate evidence for use in systematic reviews[39,40]
Mood disorder	121 (2.2)	Insufficient	Lack of clear evidence for benefit in depression, bipolar, or obsessive-compulsive disorders[39] Recommend against use for PTSD by Veterans Affairs guidelines[41]	34 (5.2)	Insufficient	Recommend against use for PTSD by Veterans Affairs guidelines[41]
Substance use disorder	12 (0.2)	Modest	Can be used for alcohol withdrawal by APA,[42] ASAM,[43] and Veterans Affairs guidelines[44] Systematic review reports potential benefits for alcohol and opioid abuse[38]	0 (0)	Insufficient	No data

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TABLE 3. Continued

Indication category	Gabapentin (n=5554)			Pregabalin (n=651)		
	No. (%)	Supportive evidence	Comments	No. (%)	Supportive evidence	Comments
Miscellaneous indications	757 (13.6)			67 (10.3)		
Gastrointestinal	52 (0.9)	Insufficient	Limited evidence for neuropathic abdominal pain or IBS[45]	68 (10.4)	Insufficient	Low evidence as an adjunct for pancreatitis pain[46] Limited evidence for IBS[45]
Hot flash	197 (3.5)	Substantial	Appropriate for use in NAMS and ACOG guidelines[47,48]	0 (0)	Modest	Appropriate for use in NAMS guidelines[47]
Perioperative	387 (7.0)	Insufficient	Conflicting recommendations for use in the perioperative period by AAPM and ESRA guidelines Systematic review results do not support use for postoperative pain management[49]	21 (3.2)	Insufficient	Conflicting recommendations for use in the perioperative period by AAPM and ESRA guidelines Systematic review results do not support use for postoperative pain management[49]
Pruritus	39 (0.7)	Modest	Recommended for general pruritus of unknown origin by the British Association of Dermatologists[50] Recommended for neuropathic itch and hemodialysis-related itch by European chronic pruritus guidelines[51] Cochrane review states evidence for use with CKD-related itching[52]	2 (0.3)	Modest	Recommended for general pruritus of unknown origin by the British Association of Dermatologists[50] Recommended for neuropathic itch and hemodialysis-related itch by European chronic pruritus guidelines[51] Cochrane review states evidence for use with CKD-related itching[52]
Cough	43 (0.8)	Modest	Low evidence for chronic refractory cough by ERS guidelines[53] Recommended for clinical trial testing by CHEST for unexplained chronic cough[54]	39 (6.0)	Insufficient	CHEST states that further research is needed for unexplained chronic cough[54]
Other indications[b]	95 (1.7)			5 (0.8)		

[a]AAN, American Academy of Neurology; AAPM, American Pain Society; AASM, American Academy of Sleep Medicine; ACOG, American College of Obstetricians and Gynecologists; ACR, American College of Rheumatology; APA, American Psychological Association; ASAM, American Society of Addiction Medicine; AWMF, Association of the Scientific Medical Societies in Germany; CHEST, American College of Chest Physicians; CKD, chronic kidney disease; CPS, Canadian Pain Society; EFNS, European Federation of Neurological Societies; ERS, European Respiratory Society; ESMO, European Society for Medical Oncology; ESRA, European Society of Regional Anaesthesia and Pain Therapy; EULAR, European League Against Rheumatism; FDA, US Food and Drug Administration; IBS, irritable bowel syndrome; NAMS, National Addiction Management Service; NCI, National Cancer Institute; NeuPSIG, International Association for the Study of Pain; NICE, National Institute for Health and Care Excellence; PLMD, periodic limb movement disorder; PTSD, posttraumatic stress disorder; RLS, restless legs syndrome; SEOM, Spanish Society of Medical Oncology.

[b]Evidence was not identified because of heterogeneity in category.

off-label marketing practices.[4,12,13] Another possible reason for nonevidence-based use of gabapentinoids is that clinicians frequently receive positive feedback from patients about the efficacy of gabapentinoids for chronic pain indications, but this information has not been formally evaluated or reported in published studies. This real-world clinical experience with gabapentinoids indicates a clear need for additional education on appropriate gabapentinoid use for chronic pain indications and/or an increased body of evidence to support their current off-label use for pain.

Sleep-related indications, such as RLS and PLMD, were also common in our study. RLS and PLMD had a modest level of evidence for both gabapentin and pregabalin use, despite not having FDA approval for the management of RLS.[7,10,11] Additionally, evidence supporting the use of gabapentinoids for insomnia is insufficient. The use of gabapentinoids for this indication may result from clinicians exploiting the somnolence side effect of gabapentinoids for patients prescribed the medication for additional indications. A few prescriptions were issued for indications that lack standard treatment options, which suggests that clinicians may be inclined to prescribe gabapentinoids as a safe therapeutic option for conditions with few therapies or treatment options.

As with all retrospective reviews of real-world clinical data, our study has several limitations. Although we identified more than 6000 gabapentinoid prescriptions issued during the 2019 calendar year at our center, the time and effort to manually review all of the associated health records were not feasible. Therefore, we randomly selected a smaller sample that was representative of the cohort for analysis. Our sampling and extrapolation method had limitations and could have led to a more accurate representation of the specialties with fewer gabapentinoid prescriptions. In doing so, we may have missed additional information that could have yielded further insight into gabapentinoid prescribing patterns and practices. Because of the challenges with documentation during clinical visits, the prescribing clinicians may not have fully documented their reasons for prescribing gabapentinoids. Patients who were prescribed gabapentinoids for indications with less evidence to support their use could have had treatment failure with first-line medications with more evidence. However, collecting such information was beyond the scope of our study, and we acknowledge this as an additional limitation. We also did not identify the intentions clinicians had for prescribing gabapentinoids. This information could be gathered in a future targeted study of clinician prescribing practices. The starting doses of gabapentinoids varied among the prescriptions, many of which included tapering instructions. Therefore, accurately characterizing the target gabapentin dose administered to patients was unfeasible, which was an additional limitation of our study. We also observed that clinicians would occasionally document different off-label indications than what the original prescribing clinician had intended. This may have contributed to a small percentage of the off-label use we observed.

Despite these limitations, our study is, to our knowledge, one of the first to manually review clinical notes from multiple clinical specialities to ascertain and evaluate indications for gabapentinoid prescriptions. Our study is distinguished from previous studies reporting off-label gabapentinoid use by our analysis of the evidence and guidelines for non−FDA-approved indications and our manual examination of health records. Knowledge that gabapentinoids are considered for the treatment of certain indications, although many are not supported by robust evidence, is of value to the medical community. Highlighting real-world clinical practice could lead to future investigations to characterize the appropriateness for these indications.

CONCLUSION

Our findings show that more than 25% of gabapentinoid prescriptions do not have robust supporting evidence. Although the top indication for prescribing gabapentinoids was neuropathic pain, which had substantial evidence and guideline support, the second most common indication was musculoskeletal pain, which had insufficient evidence. By specifically determining prescriber specialties and patient conditions with a high prescribing frequency and low level of supporting evidence, our study lays the foundation for future research. Clear documentation of the intentions underlying off-label gabapentinoid

prescriptions at the point of care by primary care practitioners and specialists could further this body of research.

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REFERENCES

1. Pauly NJ, Delcher C, Slavova S, Lindahl E, Talbert J, Freeman PR. Trends in gabapentin prescribing in a commercially insured U.S. adult population, 2009-2016. *J Manag Care Spec Pharm.* 2020;26(3):246-252. https://doi.org/10.18553/jmcp.2020.26.3.246.

2. Costales B, Goodin AJ. Outpatient off-label gabapentin use for psychiatric indications among U.S. adults, 2011-2016. *Psychiatr Serv.* 2021;72(11):1246-1253. https://doi.org/10.1176/appi.ps.202000338.

3. Zhou L, Bhattacharjee S, Kwoh CK, et al. Dual-trajectories of opioid and gabapentinoid use and risk of subsequent drug overdose among Medicare beneficiaries in the United States: a retrospective cohort study. *Addiction.* 2021;116(4):819-830. https://doi.org/10.1111/add.15189.

4. Goodman CW, Brett AS. A clinical overview of off-label use of gabapentinoid drugs. *JAMA Intern Med.* 2019;179(5):695-701. https://doi.org/10.1001/jamainternmed.2019.0086.

5. Evoy KE, Sadrameli S, Contreras J, Covvey JR, Peckham AM, Morrison MD. Abuse and misuse of pregabalin and gabapentin: a systematic review update. *Drugs.* 2021;81(1):125-156. https://doi.org/10.1007/s40265-020-01432-7.

6. Karavolis ZA, Su AB, Peckham AM. State-level response to gabapentin misuse in the United States: implications and future direction. *Am J Health Syst Pharm.* 2022;79(9):e143-e148. https://doi.org/10.1093/ajhp/zxab486.

7. Neurontin (Gabapentin). *Prescribing information.* Incorp: Parke-Davis Division of Pfizer; 2020. Accessed February 7, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020235s036,020882s022,021129s022lbl.pdf.

8. Yasaei R, Katta S, Saadabadi A. Gabapentin. StatPearls [Internet]; 2022.

9. Lyrica FDA approval history. Drugs.com. Accessed May 23, 2022. https://www.drugs.com/history/lyrica.html

10. gabapentin Gralise. *Prescribing information.* Depomed; 2017. Accessed February 7, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022544s012lbl.pdf.

11. Horizant (gabapentin enacarbil). Prescribing information. Arbor Pharmaceuticals. LLC; 2020. Accessed February 7, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022399s010lbl.pdf.

12. Peckham AM, Evoy KE, Ochs L, Covvey JR. Gabapentin for off-label use: evidence-based or cause for concern? *Subst Abuse.* 2018;12:1178221818801311. https://doi.org/10.1177/1178221818801311.

13. Krautkramer CJ. Neurontin and off-label marketing. *Virtual Mentor.* 2006;8(6):397-402. https://doi.org/10.1001/virtualmentor.2006.8.6.hlaw1-0606.

14. Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci.* 2012;39(2):S1-S59.

15. Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache.* 2012;52(6):930-945. https://doi.org/10.1111/j.1526-4610.2012.02185.x.

16. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev.* 2013;6:CD010609. https://doi.org/10.1002/14651858.CD010609.

17. Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: an updated Cochrane review. *Cephalalgia.* 2015;35(1):51-62. https://doi.org/10.1177/0333102414534325.

18. Silberstein S, Goode-Sellers S, Twomey C, Saiers J, Ascher J. Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. *Cephalalgia.* 2013;33(2):101-111. https://doi.org/10.1177/0333102412466968.

19. Cruccu G, Truini A. A review of Neuropathic Pain: from Guidelines to Clinical Practice. *Pain Ther.* 2017;6(suppl 1):35-42. https://doi.org/10.1007/s40122-017-0087-0.

20. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol.* 2010;17(9):1113. e88. https://doi.org/10.1111/j.1468-1331.2010.02999.x.

21. American College of Rheumatology. Fibromyalgia. Accessed May 23, 2022. https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Fibromyalgia.

22. Macfarlane GJ, Kronisch C, Atzeni F, et al. EULAR recommendations for management of fibromyalgia. *Ann Rheum Dis.* 2017;76(12):e54. https://doi.org/10.1136/annrheumdis-2017-211587.

23. Kia S, Choy E. Update on treatment guideline in fibromyalgia syndrome with focus on pharmacology. *Biomedicines.* 2017;5(2). https://doi.org/10.3390/biomedicines5020020.

24. Appleyard T, Ashworth J, Bedson J, Yu D, Peat G. Trends in gabapentinoid prescribing in patients with osteoarthritis: a United Kingdom national cohort study in primary care. *Osteoarthr Cartil.* 2019;27(10):1437-1444. https://doi.org/10.1016/j.joca.2019.06.008.

25. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and knee. *Arthritis Care Res (Hoboken).* American College of Rheumatology. 2020;72(2):149-162. https://doi.org/10.1002/acr.24131.

26. National Cancer Institute. Cancer pain (PDQ®): health professional version. Accessed February 7, 2022. https://www.cancer.gov/about-cancer/treatment/side-effects/pain/pain-hp-pdq

27. Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2018;29(suppl 4):iv166-iv191. https://doi.org/10.1093/annonc/mdy152.

28. Jara C, Del Barco S, Grávalos C, et al. SEOM clinical guideline for treatment of cancer pain (2017). *Clin Transl Oncol*. 2018; 20(1):97-107. https://doi.org/10.1007/s12094-017-1791-2.

29. Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. *Neurology*. 2011;77(19):1752-1755. https://doi.org/10.1212/WNL.0b013e318236f0fd.

30. Zappia M, Albanese A, Bruno E, et al. Treatment of essential tremor: a systematic review of evidence and recommendations from the Italian Movement Disorders Association. *J Neurol*. 2013; 260(3):714-740. https://doi.org/10.1007/s00415-012-6628-x.

31. Bruno E, Nicoletti A, Quattrocchi G, Filippini G, Colosimo C, Zappia M. Pregabalin for essential tremor. *Cochrane Database Syst Rev*. 2016;10(10):CD009682. https://doi.org/10.1002/14651858.CD009682.pub2.

32. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017; 13(2):307-349. https://doi.org/10.5664/jcsm.6470.

33. Liu GJ, Karim MR, Xu LL, et al. Efficacy and tolerability of gabapentin in adults with sleep disturbance in medical illness: a systematic review and meta-analysis. *Front Neurol*. 2017;8:316. https://doi.org/10.3389/fneur.2017.00316.

34. Aurora RN, Kristo DA, Bista SR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. *Sleep*. 2012;35(8):1039-1062. https://doi.org/10.5665/sleep.1988.

35. Winkelman JW, Armstrong MJ, Allen RP, et al. Practice guideline summary: treatment of restless legs syndrome in adults: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2016;87(24):2585-2593. https://doi.org/10.1212/WNL.0000000000003388.

36. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Panic Disorder*. 1st ed. American Psychiatric Association; 1998:86.

37. Ahmed S, Bachu R, Kotapati P, et al. Use of gabapentin in the treatment of substance use and psychiatric disorders: a systematic review. *Front Psychiatry*. 2019;10:228. https://doi.org/10.3389/fpsyt.2019.00228.

38. Berlin RK, Butler PM, Perloff MD. Gabapentin therapy in psychiatric disorders: a systematic review. *Prim Care Companion CNS Disord*. 2015;17(5). https://doi.org/10.4088/PCC.15r01821.

39. Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. *BMJ*. 2011;342:d1199. https://doi.org/10.1136/bmj.d1199.

40. Generoso MB, Trevizol AP, Kasper S, Cho HJ, Cordeiro Q, Shiozawa P. Pregabalin for generalized anxiety disorder: an updated systematic review and meta-analysis. *Int Clin Psychopharmacol*. 2017;32(1):49-55. https://doi.org/10.1097/YIC.0000000000000147.

41. VA/DOD clinical practice guideline for the management of posttraumatic stress disorder and acute stress disorder. Department of Veterans Affairs, Department of Defense. Accessed February 7, 2022. https://healthquality.va.gov/HEALTHQUALITY/guidelines/MH/ptsd/VADoDPTSDCPGPocketCardFinal508-082918b.pdf

42. American Psychiatric Association. The American Psychiatric Association practice guideline for the pharmacological treatment of patients with alcohol use disorder. Accessed February 7, 2022. https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9781615371969

43. The ASAM clinical practice guideline on alcohol withdrawal management. *J Addict Med*. 2020;14(3S suppl 1):1-72. https://doi.org/10.1097/ADM.0000000000000668.

44. US Department of Veterans Affairs. VA/DOD clinical practice guidelines. Management of substance use disorder. Accessed May 23, 2022. https://www.healthquality.va.gov/guidelines/MH/sud/.

45. Lambarth A, Zarate-Lopez N, Fayaz A. Oral and parenteral anti-neuropathic agents for the management of pain and discomfort in irritable bowel syndrome: a systematic review and meta-analysis. *Neurogastroenterol Motil*. 2022;34(1): e14289. https://doi.org/10.1111/nmo.14289.

46. Gurusamy KS, Lusuku C, Davidson BR. Pregabalin for decreasing pancreatic pain in chronic pancreatitis. *Cochrane Database Syst Rev*. 2016;2(2):CD011522. https://doi.org/10.1002/14651858.CD011522.pub2.

47. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of the North American Menopause Society. *Menopause*. 2015;22(11):1155-1172. https://doi.org/10.1097/GME.0000000000000546. quiz 1173-1174.

48. ACOG Practice Bulletin No. 141. ACOG Practice Bulletin No. 141: management of menopausal symptoms. *Obstet Gynecol*. 2014;123(1):202-216. https://doi.org/10.1097/01.AOG.0000441353.20693.78.

49. Verret M, Lauzier F, Zarychanski R, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain: a systematic review and meta-analysis. *Anesthesiology*. 2020;133(2):265-279. https://doi.org/10.1097/ALN.0000000000003428.

50. Millington GWM, Collins A, Lovell CR, et al. British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis, 2018. *Br J Dermatol*. 2018;178(1):34-60. https://doi.org/10.1111/bjd.16117.

51. Weisshaar E, Szepietowski JC, Darsow U, et al. European guideline on chronic pruritus. *Acta Derm Venereol*. 2012;92(5):563-581. https://doi.org/10.2340/00015555-1400.

52. Hercz D, Jiang SH, Webster AC. Interventions for itch in people with advanced chronic kidney disease. *Cochrane Database Syst Rev*. 2020;12(12):CD011393. https://doi.org/10.1002/14651858.CD011393.pub2.

53. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J*. 2020;55(1). https://doi.org/10.1183/13993003.01136-2019.

54. Gibson P, Wang G, McGarvey L, et al. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. *Chest*. 2016;149(1):27-44. https://doi.org/10.1378/chest.15-149.

55. Greenblatt HK, Greenblatt DJ. Gabapentin and pregabalin for the treatment of anxiety disorders. *Clin Pharmacol Drug Dev*. 2018;7(3):228-232. https://doi.org/10.1002/cpdd.446.