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Lili Buzsaki

University of Kentucky, lili.buzsaki@uky.edu

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Lili Buzsaki, Student

Sarah Wackerbarth, PhD, Committee Chair

Dr. Corrine Williams, Director of Graduate Studies

Gabapentin Prescribing Practices Among Physicians: Clinical Indications and Reason- ing

CAPSTONE PROJECT PAPER

A paper submitted in partial fulfillment of the
Requirements for the degree of
Master of Public Health in the
University of Kentucky College of Public Health

By

Lili Buzsaki, MD

Lexington, KY

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Capstone Committee:

Sarah Wackerbarth, Ph.D. (Chair)

Moaz Abdelwadoud, MD, DrPH, MPH (Committee Member)

Terry Bunn, Ph.D. (Committee Member)

Tisha Johnson, MD, MPH (Committee Member)

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Abstract

Gabapentin is an anticonvulsant and nerve pain medication with a variety of off-label indications. There is at least some evidence that physicians have prescribed gabapentin to successfully treat several off-label conditions including alcohol dependence and withdrawal, brachioradial pruritus, chronic, refractory cough, diabetic neuropathy, fibromyalgia, hiccups (singultus), hot flashes, insomnia, neuropathic pain, adjunct therapy for postoperative pain, restless legs syndrome (RLS), anxiety disorders, and uremic pruritus.

An observational cross-sectional study was used to determine the various real-life off-label uses of gabapentin and physicians' perspectives with regard to particular advantages over other drugs and interventions, via an online survey. In addition, a secondary objective was to determine physicians' perspectives regarding whether gabapentin is being misused. The most common off-label indications for prescribing gabapentin for Family Medicine and most other physicians surveyed were neuropathic pain, diabetic neuropathy, and fibromyalgia. Psychiatrists most commonly prescribed gabapentin for anxiety disorders and insomnia. With respect to misuse and overdose, six Emergency Medicine physicians felt that gabapentin was not leading to increased overdoses and/or intoxications while three felt that it was.

Keywords: Gabapentin, Off-label Use, Off-label Indications, Prescribing practices, Misuse

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ABBREVIATIONS

AAPCC	American Association of Poison Control Centers
ACCM	American College of Critical Care Medicine
ACOG	American College of Obstetrics and Gynecology
ASHP	American Society of Health-System Pharmacists
COPD	Chronic Obstructive Pulmonary Disease
DOFSS	Kentucky Drug Overdose Fatality Surveillance System
EM	Emergency Medicine
ESRD	End Stage Renal Disease
EURLSSG	European Restless Legs Syndrome Study Group
FDA	Food and Drug Administration
FM	Family Medicine
GABA	<i>gamma</i> -aminobutyric acid
IM	Internal Medicine
IRLSSG	International Restless Legs Syndrome Study Group
NeuPSIG	Neuropathic Pain Special Interest Group
Neuro	Neurology
NICE	National Institute for Health and Care Excellence
OB/GYN	Obstetrician and Gynecologist
Occ Med	Occupational Medicine
OUD	Opioid Use Disorder
Peds	Pediatrics

Psych	Psychiatry
Pulm	Pulmonology
Rheum	Rheumatology
RLS	Restless legs syndrome
RLS-F	Restless legs syndrome Foundation
RLS/WED	Restless legs syndrome/Willis-Ekbom disease
SCCM	Society of Critical Care Medicine
SNRI	Serotonin–norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SUD	Substance Use Disorder
TCA	Tricyclic antidepressant
UK	United Kingdom

INTRODUCTION

Gabapentin is an anticonvulsant medication with a variety of off-label indications. The two FDA-approved indications for gabapentin are partial seizures and postherpetic neuralgia. There is at least some evidence that physicians have prescribed gabapentin to successfully treat several off-label conditions including alcohol dependence [4-6] and withdrawal [7], bipolar disorder [8], brachioradial pruritus [9-13], chronic, refractory cough [14, 15], diabetic neuropathy [16-20], fibromyalgia syndrome [21, 22], hiccups (singultus) [23-29], hot flashes [30-39], insomnia [8], neuropathic pain [20, 40-42], adjunct therapy for postoperative pain [43-45], restless legs syndrome (RLS) [46-51], anxiety disorders [8, 52], and uremic pruritus [53-56].

On July 1, 2017, gabapentin became a Schedule V controlled substance in Kentucky after several post-mortem toxicology reports in people with Opioid Use Disorder (OUD) revealed high levels of gabapentin in addition to opioids.

Gabapentin has previously been touted for its low side effect profile and low addiction potential. Therefore, the medication has been widely prescribed, especially as an effective drug to treat chronic, neuropathic pain. Physicians in Kentucky may have been discouraged from prescribing gabapentin for any other indications after adding it to the states' list of controlled substances. Although some studies have asserted that gabapentin is being abused as a way to increase the "high" experienced with opioids, it is unclear how prevalent this practice is, who is abusing the medication, and whether it was prescribed or obtained

illegally. Therefore, it would be important to learn more about the current uses of the medication and ensure that current laws and regulations support these indications in a way that protects all individuals' right to health and safety. Finally, this Capstone aimed to bridge the gap between the public health and clinical perspective on gabapentin.

Historical Background

The Food and Drug Administration (FDA) initially approved gabapentin in December of 1993 as an adjunctive therapy in the treatment of partial seizures in patients over twelve years of age with epilepsy. In October of 2000, the FDA approved gabapentin for use in anyone over three years of age for this indication. In May of 2004, it was also approved for postherpetic neuralgia in adults [1]. A precursor of gabapentin, called gabapentin enacarbil was approved in 2011 for the treatment of restless legs syndrome (RLS) [2]. In addition, pregabalin, a structural analog of gabapentin, is FDA approved to treat neuropathic pain, fibromyalgia, postherpetic neuralgia, diabetic peripheral neuropathy, and epilepsy[3].

Gabapentin has widely been prescribed for off-label indications. An off-label indication is the use of a medication for any population or disease for which the pharmaceutical company has not performed extensive randomized control trials to obtain FDA approval specifically for the indication. Reasons for not obtaining

FDA approval for a particular indication include lack of a financial incentive or not wanting to test the medication in certain populations such as pregnant women and children. Off-label indications for gabapentin include alcohol dependence [4-6] and withdrawal [7], bipolar disorder [8], brachioradial pruritus [9-13], chronic, refractory cough [14, 15], diabetic neuropathy [16-20], fibromyalgia syndrome [21, 22], hiccups (singultus) [23-29], hot flashes [30-39], insomnia [8], neuropathic pain [20, 40-42], adjunct therapy for postoperative pain [43-45], restless legs syndrome (RLS) [46-51], anxiety disorders [8, 52], and uremic pruritus [53-56].

The mechanism of action for gabapentin is still partially unclear leading to some uncertainty about gabapentin. It is thought to be structurally related to *gamma*-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system of mammals. Gabapentin does not appear to influence the synthesis or uptake of GABA, however, nor does it bind to GABA_A or GABA_B receptors. Gabapentin is thought to bind to the $\alpha_2\delta$ subunit of presynaptic voltage-gated calcium channels located throughout the brain. Further, it is believed that gabapentin modulates the release of excitatory neurotransmitters involved in epileptogenesis and nociception [57].

Pre- and post-approval clinical trials of gabapentin did not reveal significant signs of dependence, in addition to a fairly benign safety profile [58]. As a result of the safety profile and off-label indications, the medication has been widely prescribed.

In response to the opioid epidemic, Kentucky expanded the post-mortem toxicology panel performed on people dying as a result of an opioid overdose. After several post-mortem toxicology reports in people with Opioid Use Disorder revealed high levels of gabapentin in addition to opioids, gabapentin became a Schedule V controlled substance in Kentucky. This may affect the prescribing of gabapentin, especially for all its off-label indications.

LITERATURE REVIEW

The purpose of the literature review was to determine the various off-label indications for gabapentin and advantages over other drugs and interventions used for this indication. In addition, a secondary objective was to determine whether gabapentin is being misused and under what circumstances should the medication be used with more caution.

The following review of the literature is a summary of key concepts foundational to understanding the off-label indications and misuse potential of gabapentin. It represents theoretical and empirical knowledge gathered from the disciplines of medicine and public health. The works cited are collected from published journal articles published from January 2000 to February 2018. The National Library of Medicine database (PubMed) and Uptodate websites were used as the database for the literature review, as well as conference proceedings, papers, reports, bibliographies, and reference lists. Key words and phrases for the searches included “gabapentin off-label use,” “gabapentin off-label indications,” “gabapentin misuse,” and “gabapentin prescribing.” A secondary review of writings referenced in the bibliographies of key works and those recommended by experts, peers, and colleagues augmented the process.

Off-label uses of Gabapentin

Alcohol dependence and withdrawal

Three randomized control studies investigated the use of gabapentin to treat alcohol dependence and withdrawal. One study found that after seven days of detoxification treatment with diazepam and vitamins for acute alcohol withdrawal, a four-week course of gabapentin (300 mg twice daily) for four weeks reduces the number of drinks per day and number of heavy drinking days and increases percentage of days of abstinence, compared to placebo [5]. A second study found that a twelve-week course of gabapentin (1800 mg/day) effectively in treats alcohol dependence and relapse-related symptoms of insomnia, dysphoria, and craving [6]. The third study confirmed the latter, finding that even six weeks after treatment ended, gabapentin significantly delayed the onset to heavy drinking in patients with alcohol dependence and insomnia. Furthermore, these patients were less likely to feel tired and drowsy in the morning compared to alcohol-dependent patients treated with trazodone [4].

Brachioradial pruritus

Brachioradial pruritus is often refractory to treatment with topical or oral corticosteroids and antihistamines, capsaicin and cervical spine manipulation. However, brachioradial pruritus can be successfully treated with gabapentin at a dose of 100- 600 mg three times daily [9, 11-13].

Chronic, refractory cough

Out of the randomized control trials reviewed by the American College of Chest Physicians for the treatment of unexplained chronic cough, only gabapentin had sufficient, unbiased evidence to recommend its use. In particular, inhaled corticosteroids were affected by intervention fidelity bias, esomeprazole was only effective in patients with gastroesophageal acid reflux and morphine is not a viable long-term option in light of the opioid epidemic [14].

The recommended daily dose of gabapentin is between 300 to 1800 mg per day [15].

Diabetic neuropathy

Based on an extensive review of randomized control studies, the European Federation of Neurological Societies recommend tricyclic antidepressants (TCA), gabapentin, pregabalin and serotonin–norepinephrine reuptake inhibitors (SNRIs; duloxetine and venlafaxine) as first-line treatment for diabetic peripheral neuropathy (level A) [16].

The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation performed a systematic review of the literature from 1960 to August 2008 and recommends pregabalin as the treatment of choice for painful diabetic neuropathy (Level A). Second-line treatment for painful diabetic neu-

ropathy includes venlafaxine, duloxetine, amitriptyline, gabapentin (900-3600 mg per day), valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release), and capsaicin (Level B). [17]

The American Diabetes Association recommends pregabalin or duloxetine as the treatment of choice for diabetic neuropathy (Level A). After taking into account patients' socioeconomic status, comorbidities, and potential drug interactions, gabapentin was also recommended as a treatment of choice for diabetic neuropathy (Level B) [19].

Fibromyalgia

A 2017 Cochrane review concluded that there is insufficient evidence to support or refute the use of gabapentin for fibromyalgia as only one high-quality study has been performed. This does not mean that gabapentin does not effectively treat fibromyalgia; rather, there are not enough high-quality studies done to show its effect. Unfortunately, there are few other effective treatments for fibromyalgia. Often, this results in physicians treating patients with gabapentin when other treatments and interventions fail or are not a viable option [59]. The one high quality study that exists, a twelve-week, multi-center, double-blind randomized control trial, found that 91% of participants treated with gabapentin (1,200-2,400 mg/day) felt better and about half of the participants treated with gabapentin achieved a 30% or greater reduction in pain over baseline [21].

Hiccups (singultus)

A 2015 systemic review concluded that baclofen and gabapentin are the first-line therapy for persistent and intractable hiccups while metoclopramide and chlorpromazine are second-line agents [60]. Gabapentin effectively treats refractory hiccups in patients with co-morbidities including intention tremors, metastatic colon cancer, metastatic small cell lung cancer, pancreatic cancer, gastric cancer, coronary artery disease, COPD, diabetes mellitus, hiatal hernia, seminoma, lateral medullary infarct, and alcoholism [23, 24, 28, 29]. The effective dose ranges from 100 mg to 400 mg three times per day. [23, 24, 26] Patients continue to remain asymptomatic after three years. [27]

Hot flashes

The American College of Obstetrics and Gynecology as well as systemic reviews of the literature found good or consistent scientific evidence to conclude that gabapentin effectively treats hot flashes and vasomotor symptoms related to menopause and is a viable alternative to hormone therapy [30, 31, 38]. Specifically, a twelve-week course of gabapentin 900 mg per day led to a 50% reduction in the frequency and intensity of hot flashes from baseline [33]. Another study showed that gabapentin works just as well as estrogen in treating hot flashes, without the added risk of breast cancer [37]. Gabapentin (600 mg am/1,200 mg pm) showed similar effects in menopausal women with moderate to severe hot

flashes. In addition, the drug significantly reduced sleep interference [36].

Gabapentin also decreases hot flashes in men with androgen ablation-related vasomotor dysfunction [35].

Insomnia

At high doses, gabapentin may be associated with sedative effects [61]. Therefore, gabapentin is often prescribed to treat insomnia in patients with co-morbidities. In particular, using polysomnography, gabapentin has been shown to improve sleep, especially slow-wave sleep (important for memory consolidation), in healthy people, as well as in patients with epilepsy, restless legs syndrome, and alcohol dependence [4].

Neuropathic pain

After conducting a systematic review of randomized double-blind studies of oral and topical pharmacotherapy for neuropathic pain, the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain gave a strong recommendation for use of tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, pregabalin, and gabapentin (900–3600 mg/day) as first-line agents in treating neuropathic pain. [20]

After an extensive review of the literature performed by the National Institute for Health and Care Excellence (NICE), they concluded that capsaicin cream, gabapentin, morphine, nortriptyline and tramadol consistently reduced pain com-

pared with placebo. When cost is taken into account, it was determined that gabapentin has the highest net benefit and should be the treatment of choice for neuropathic pain [41]. The American College of Critical Care Medicine (ACCM) in conjunction with Society of Critical Care Medicine (SCCM) and American Society of Health-System Pharmacists (ASHP) recommend either enterally (orally) administered gabapentin or carbamazepine, in addition to intravenous opioids, be prescribed for treatment of neuropathic pain in the intensive care setting [40].

Adjunct Therapy for Postoperative pain

Two 2015 systematic reviews and meta-regression analyses of the use of gabapentin to prophylactically treat post-operative pain found that 300- 600 mg of oral gabapentin, one hour before surgery significantly decreased pain scores both within the first hour and the first day postoperatively, with the effect being the greatest in the first hour and gradually decreasing thereafter [43, 45]. One of the systematic reviews also looked at the effect of pregabalin in reducing the pain score and need for opiates in the first day. Although pregabalin also reduced both, gabapentin had a more profound effect than did pregabalin [45]. In addition, both the 2015 meta-analyses and a 2007 meta-analysis found a statistically and clinically significant decrease (by 35%) in 24-hour opiate consumption, post-operative nausea, vomiting, and pruritus [43, 44]. Furthermore, pain scores with movement were decreased during the first 24 hours at rest and at two, four, and twelve hours post-operatively [44].

Restless legs syndrome (RLS)

The International Restless Legs Syndrome Study Group (IRLSSG), European Restless Legs Syndrome Study Group (EURLSSG) and RLS Foundation (RLS-F) recommend $\alpha 2\delta$ ligands, such as gabapentin, for the prevention of dopaminergic-induced augmentation in restless legs syndrome/Willis-Ekbom disease (RLS/WED) after the correction of low iron levels and elimination of culprit antidepressants or antihistamines [51]. Gabapentin (300–1,200 mg) is similar in effectiveness and tolerability to ropinirole (0.25–1.50 mg), with respect to improvement of RLS, reduction of periodic leg movements and side effects [47].

Anxiety disorders

Gabapentin has anxiolytic effects at therapeutic doses [58]. Specifically, in a placebo-controlled study, gabapentin was superior in treating social phobia at 900 - 3,600 mg daily in three divided doses, over 14 weeks [52].

Misuse, Abuse, Dependence and Diversion of Gabapentin

Toxicity

Gabapentin is renally excreted and therefore must be used with caution in patients with poor renal function. One case series described two patients, both presenting with a three-day history of tremors involving their upper extremities. The first patient was a 78-year-old woman with a complex medical history requiring a cocktail of chronic medications¹ including gabapentin (900 mg/day). Physical examination confirmed bilateral upper extremity myoclonus without other associated symptoms. Labs revealed acute kidney injury secondary to a recently increased furosemide (total dose of 60 mg, daily) and lisinopril 5 mg daily, with hyperkalemia and azotemia. Gabapentin was discontinued and the myoclonus resolved after three days of hemodialysis.

The second case of bilateral upper extremity myoclonus involved a 55-year-old man with a complex medical history including ESRD on peritoneal dialysis and multiple chronic medications². The patient had been placed on a total daily dose of 600 mg of gabapentin for neuropathic pain three days prior to admission,

¹ Congestive heart failure, history of thromboembolism, hypertension, diabetes mellitus, hyperlipidemia, asthma, diabetic peripheral neuropathy, and depression treated with simvastatin, metformin, citalopram, fluticasone propionate inhaler, inhaled albuterol, lisinopril, furosemide, and metolazone.

² Anemia, diabetes mellitus, hypertension, neuropathic pain, hyperlipidemia, hepatitis C, peripheral vascular disease with recently amputated gangrenous toe and acute pain syndrome treated with clopidogrel, amlodipine, hydralazine, metoprolol, clonidine, atorvastatin, oxycodone, hydromorphone, long-term vancomycin and piperacillin/tazobactam, sevelamer, lanthanum, epoetin, and insulin glargine.

which precipitated the chief complaint along with altered mental status, hypotension, and worsening leg infection. After increasing the frequency of dialysis for four days and discontinuing gabapentin, the patient's acute symptoms resolved. The latter two cases show that gabapentin should be used with caution in patients with a severe, complex medical history, particularly poor renal function. Furthermore, there is a threshold effect for the development of myoclonus secondary to gabapentin; serum concentrations of gabapentin should be kept under 15 µg/mL to avoid symptomatic toxicity. Of note, metformin, citalopram, albuterol, amlodipine, oxycodone, and hydromorphone can also lead to myoclonus [62].

Overdose

In the event of a gabapentin overdose, it is extremely rare to have long-term sequelae. Adverse effects secondary to acute-on-chronic overdose usually develop within two to four hours and resolve within ten hours. Two overdoses illustrate this point: a 16-year-old female who ingested more than a one-and-a-half month supply of gabapentin (48.9 grams) developed diarrhea, dizziness, and lethargy that resolved within 18 hours, and a 32-year-old man who took about a three-month supply (91 grams) of gabapentin, in addition to valproic acid and alcohol developed drowsiness, dizziness, slurred speech, and nystagmus, which all resolved within 11 hours. Between 2000-2001, 4,837 gabapentin-only exposures were reported to the American Association of Poison Control Centers (AAPCC)

Toxic Exposure Surveillance System. Of these, no medical adverse effects were seen in 1,353 individuals, minor effects were seen in 913, moderate effects in 279, major effects in 25, and deaths were reported in three people. Doses associated with the three fatalities were 16.5 g, 48 g, and 59.4 g (about a 15-, 45- and 60-day dose, respectively) [63].

Fatalities associated with polysubstance use are more common. Mortality data from the Kentucky Drug Overdose Fatality Surveillance System (DOFSS) showed that of the decedents with postmortem toxicology studies, gabapentin was found in one third of overdose deaths and almost half of overdose deaths in decedents with a history of mental illness. It was more frequently found in female decedents over 44 years of age [64].

A 2017 systemic review called into question whether gabapentinoids (gabapentin, pregabalin and related derivatives) are the culprits in overdose deaths in people with opiate and polyvalent use disorder. Furthermore, fatalities were predominantly associated with pregabalin and not gabapentin [58].

Dependence

Dependence on a drug can either be physical or psychological and includes symptoms of withdrawal, tolerance and compulsion [65]. A 2017 systemic review by a German team looked at the risk of dependence on gabapentinoids. Of the

four individuals cited in the literature that met the criteria for behavioral dependence on gabapentinoids, not associated with other substance use disorders (other than nicotine), all had used pregabalin as opposed to gabapentin. The risks of behavioral and physical dependence on gabapentinoids were greater in pregabalin, compared to gabapentin, and the risk of harm and dependence on both medications were infrequent compared to other sedatives and stimulants. Having said this, the authors concluded that if possible, use of gabapentinoids should be prescribe cautiously and for a limited period of time in patients with current or prior substance use disorders [58].

The National Institute for Health and Care Excellence (NICE) did not find any evidence for dependence on gabapentin or pregabalin, in contrast to opioids. Furthermore, NICE was concerned that people with a history of substance use disorder may be denied treatment. Thus, they recommend that the risks and benefits of treatment be weighed on an individual basis [41].

Misuse

Misuse of a medication is when an individual takes the medication in a way other than how it was intended. For example, taking a higher dose than prescribed, a route of administration other than prescribed (e.g. inhalation instead of ingestion), or *diversion*—intentional or unintentional sharing of prescription medication with anyone other than the intended patient [65].

Two 2017 systemic reviews, one performed by a team at the University of Kentucky and another at the University of Texas, cited gabapentin misuse to be between 15-22%, among patients with a history of Opioid Use Disorder (OUD) living in the United States and United Kingdom (UK), with 40% claiming to use more than prescribed and 13% using nonprescribed gabapentin [65, 66]. In contrast, no gabapentin misuse was cited among individuals with a history of alcohol dependence, even among those who also had OUD [65]. With respect to the general population, 1.1% of a UK population-based sample of 1500 individuals between 16-59 years of age reported ever misusing gabapentin. In contrast, 28.1% and 9.1% reported using cannabis and cocaine, respectively [66].

Reports from Sweden indicate that pregabalin, but not gabapentin is being misused. Of the 198 reports of drug misuse or addiction in the Swedish database between 1980 and 2009, 16 reports of pregabalin misuse were identified but not a single report of gabapentin misuse. However, review of anecdotal online data did yield reports of recreational misuse of both drugs [61]. Diversion may also be taking place in the United States. Of 503 adults from Appalachian Kentucky with OUD, not currently in treatment, 15% claimed they used gabapentin “to get high” in the past six months. Most identified either providers or drug dealers as the source of the gabapentin [68]. Gabapentin reportably has a street value ranging from one to seven dollars per pill [66].

The University of Texas team concluded that the misuse of gabapentinoids occur predominantly in high-risk populations and are less common than that of other drugs. Furthermore, given their important role in treating several chronic diseases, the evidence does not support its restriction, but rather emphasizing the importance of identifying risk factors and signs of misuse [66].

The purpose of this study was to determine the various real-life off-label uses of gabapentin and physician perspectives with regard to particular advantages over other drugs and interventions. In addition, a secondary objective was to determine physicians' perspectives regarding whether gabapentin is being misused and should be more strictly regulated. By addressing these two objectives, the study helps physicians to optimize prescribing practices in order to enhance patient care, improve health outcomes and reduce costs.

METHODS

Study Design

An observational cross-sectional study was used to explore the clinical reasoning used by physicians when prescribing gabapentin for off-label indications, via an online survey tool.

Study Population and Sampling Strategy

The target population was any physician who prescribes gabapentin in the world. Since the purpose of the project was to identify factors being considered when prescribing gabapentin and not necessarily the prevalence of these factors, a convenience sample was used. Personal contacts that are physicians were sent an invitation e-mail including a link to an online survey (using secured University of Kentucky Qualtrics survey tools) and cover letter with a brief description of the purpose of the survey. Personal contacts were encouraged to invite their fellow physicians to take the survey as well. Less than 20 personal contacts were asked to participate. Some personal contacts sent the survey out to their entire department.

Physicians working both in and outside of Kentucky were asked to participate in order to obtain a large enough sample of physicians. The ages of the physicians are presumable between 24 to 90 years. Both men and women, of any ethnic background that are healthy enough to practice medicine were welcome to take

the survey. The proposed sample composition of physicians was about 15 Primary Care Physicians/Psychiatrists and 5 Emergency Medicine/Urgent Care physicians. Inclusion criteria included being a physician practicing medicine that prescribes gabapentin or treats patients prescribed gabapentin by another physician.

Study Measures

Physicians that provide continuity of care (all physicians except Emergency Medicine physicians) were asked whether they prescribe gabapentin, if so, how often and for what indications. For off-label indications, they were asked to discuss the advantages of gabapentin over other medications and interventions for the indication. To determine physicians' thoughts and attitudes regarding its misuse and overdose potential, Emergency Medicine physicians were asked about their experiences with misuses and overdoses associated with gabapentin, as they are most often the ones treating acute adverse events. Survey questions are included in Appendix A.

Data Collection Tools and Analytic Strategy

The secured University of Kentucky Qualtrics survey tools were used to create an online survey to explore the clinical reasoning used by physicians when prescribing gabapentin for off-label indications. Enrollment began on February 7th,

2018 after the study was approved by the IRB committee and ended on April 2nd, 2018. Once surveys were received, the responses to each question were examined to look for an overall consensus and any sort of unique patient profile. For example, women in their twenties with diagnosis X that have co-morbidities Y, are also on medication Z, and have not responded to medications A, B, and C. The responses were examined according to specialty. All analyses were conducted using Microsoft Excel software.

Ethical Considerations

The study was reviewed and approved by the University of Kentucky Internal Review Board (protocol #43376).

RESULTS

Sample Description

The study participants who responded to the Qualtrics survey included 17 Family Medicine physicians, 12 Psychiatrists, 9 Emergency Medicine physicians, two Neurologists, two Internists, two Other physicians (one of which was an Addiction Medicine specialist), one Intensivist physician, one Occupational Medicine physician, Pediatrician, Pulmonologist, Rheumatologist, and Surgeon (Table 1), of which 39 out of 41 prescribe gabapentin (the Intensivist and one Internist did not; Table 2 and Figure 2). Emergency Medicine physicians were not asked whether or not they prescribed gabapentin because they do not provide continuity of care and do not regularly initiate medications for chronic conditions.

Table 1. Frequency and Percentage of Participants by Clinical Specialty

Specialty	FM	EM	Psych	IM	Neuro	Other	Intensive Care	Occ Med	Peds	Pulm	Rheum	Surgery
Number	17	9	12	2	2	2	1	1	1	1	1	1
Percentage	34%	18%	24%	4%	4%	4%	2%	2%	2%	2%	2%	2%

FM= Family Medicine, EM= Emergency Medicine, Psych= Psychiatry, IM= Internal Medicine, Neuro= Neurology, Occ Med= Occupational Medicine, Peds= Pediatrics, Pulm= Pulmonology, Rheum= Rheumatology

Table 2. Frequency and Percentage of Gabapentin Prescriptions by Clinical Specialty

Specialty	FM	Psych	IM	Neuro	Other	Intensive Care	Occ Med	Peds	Pulm	Rheum	Surgery
Number	17	12	2	2	2	1	1	1	1	1	1
Percentage	100%	100%	50%	100%	100%	0%	100%	100%	100%	100%	100%

FM= Family Medicine, EM= Emergency Medicine, Psych= Psychiatry, IM= Internal Medicine, Neuro= Neurology, Occ Med= Occupational Medicine, Peds= Pediatrics, Pulm= Pulmonology, Rheum= Rheumatology

Have you ever prescribed gabapentin?

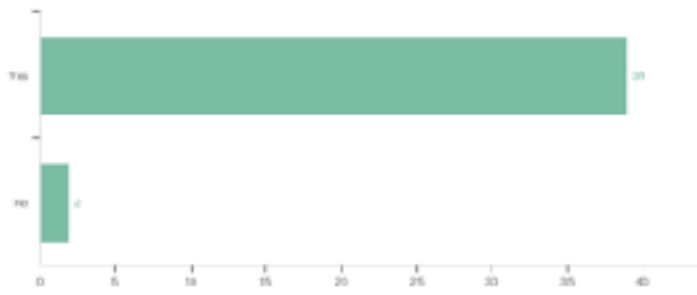


Figure 2. Frequency Distribution of Physicians Prescribing Gabapentin

The majority (21 out of 39 physicians) reported that ten percent or fewer of their patients were taking gabapentin (Figure 3). Less than one third reported that 11-20% of their patients were taking gabapentin (12 out of 39) and six physicians reported 21-50% of their patients were taking the medication. No physician reported a number over 50%.

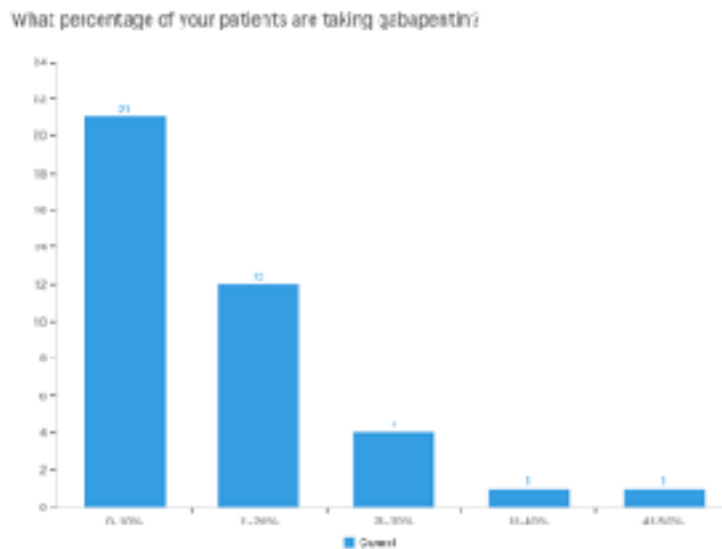


Figure 3 Distribution of Gabapentin Prescriptions

The Surgeon had the highest proportion of patients on the medication (41-50%), followed by Family Medicine physicians and then Psychiatrists (Table 3 and Figure 4). The “Other” physician wrote that prior to gabapentin becoming a scheduled medication, 50-60% of his or her patients were on the medication. Now it is between zero to ten percent.

Table 3 Percentage of Patients taking Gabapentin by Clinical Specialty

Specialty	FM	Psych	Neuro	Other	Occ Med	Peds	Pulm	Rheum	Surgery
0-10%	59%	33%	100%	100%	100%	100%	0%	0%	50%
11-20%	18%	58%	0%	0%	0%	0%	100%	100%	0%
21-30%	18%	8%	0%	0%	0%	0%	0%	0%	0%
31-40%	6%	0%	0%	0%	0%	0%	0%	0%	0%
41-50%	0%	0%	0%	0%	0%	0%	0%	0%	50%

FM= Family Medicine, EM= Emergency Medicine, Psych= Psychiatry, IM= Internal Medicine, Neuro= Neurology, Occ Med= Occupational Medicine, Peds= Pediatrics, Pulm= Pulmonology, Rheum= Rheumatology

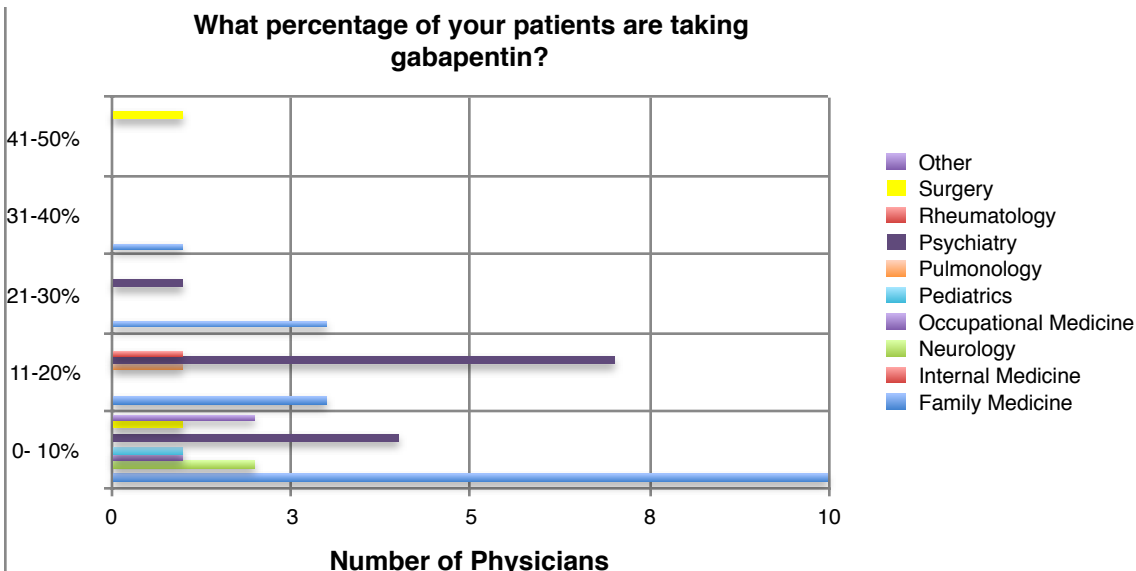


Figure 4 Percentage of Patients taking Gabapentin by Clinical Specialty

About half of the physicians with patients on gabapentin initiated the medication (Figure 5). Psychiatrists reported to placing a higher proportion of their patients on gabapentin than other physicians, with one of the Psychiatrists reporting to have initiated the prescription for 81-90% of his or her patients that are currently on gabapentin (Table 4). Family Medicine physicians were the second most likely to initiate the prescription, whereas the others surveyed rarely initiated the prescription.

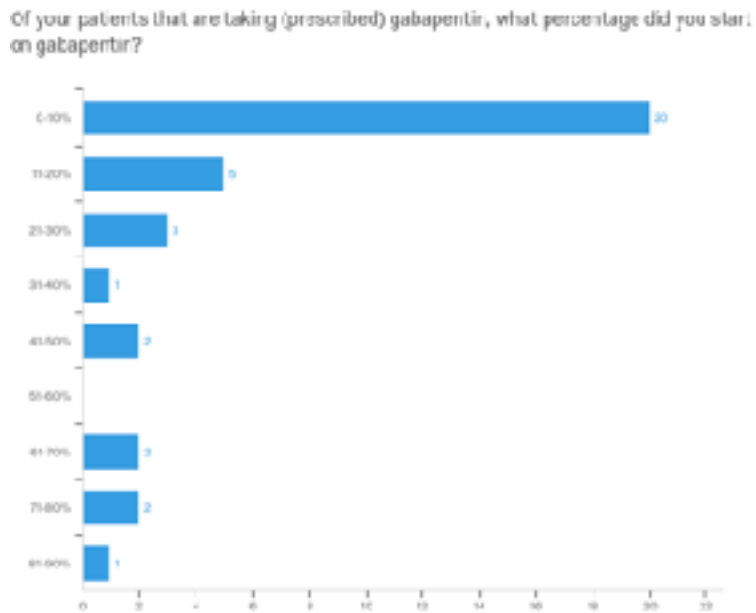


Figure 5 Percentage and Frequency Distribution of Patients Started on Gabapentin

Table 4 Percentage of Patients started on Gabapentin by Clinical Specialty

Specialty	FM	Psych	Neuro	Other	Occ Med	Peds	Pulm	Rheum	Surgery
0-10%	47%	33%	100%	100%	100%	100%	100%	100%	100%
11-20%	20%	17%	0%	0%	0%	0%	0%	0%	0%
21-30%	13%	8%	0%	0%	0%	0%	0%	0%	0%
31-40%	0%	8%	0%	0%	0%	0%	0%	0%	0%
41-50%	7%	8%	0%	0%	0%	0%	0%	0%	0%
51-60%	0%	0%	0%	0%	0%	0%	0%	0%	0%
61-70%	7%	8%	0%	0%	0%	0%	0%	0%	0%
71-80%	7%	8%	0%	0%	0%	0%	0%	0%	0%
81-90%	0%	8%	0%	0%	0%	0%	0%	0%	0%

FM= Family Medicine, EM= Emergency Medicine, Psych= Psychiatry, IM= Internal Medicine, Neuro= Neurology, Occ Med= Occupational Medicine, Peds= Pediatrics, Pulm= Pulmonology, Rheum= Rheumatology

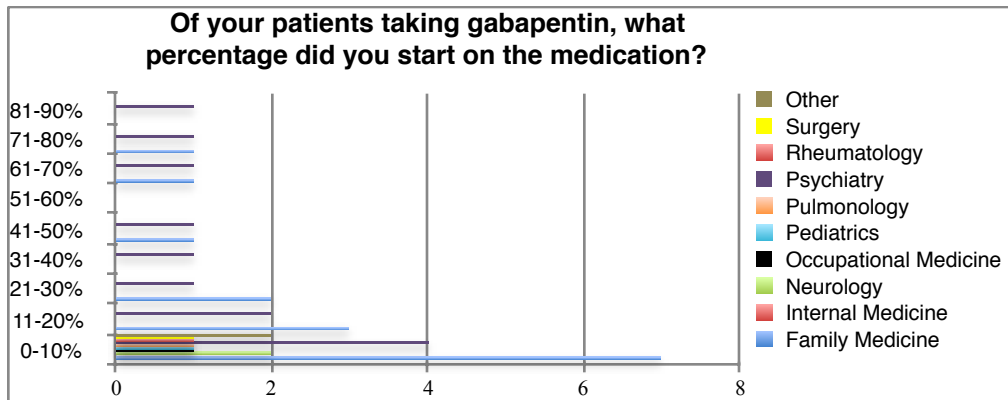


Figure 6 Percentages and Frequency Distribution of Patients Started on Gabapentin by Clinical Specialty

Conditions For Which Gabapentin is Prescribed

Among respondents to the survey, neuropathic pain was the most common indication for prescribing gabapentin, followed by diabetic neuropathy, fibromyalgia and postherpetic neuralgia (Appendix B). Alcohol dependence or withdrawal and anxiety disorders were the most common indication for which the FDA has yet to approve a gabapentinoid, followed by insomnia. All 17 of the Family Medicine physicians had prescribed gabapentin for neuropathic pain, 16 of the 17 had prescribed it for diabetic neuropathy, approximately half for fibromyalgia, and ten out of 17 for postherpetic neuralgia (Table 5 and Figure 7). Psychiatrists most commonly prescribed gabapentin for anxiety disorders, followed by insomnia. The same number of Psychiatrists prescribed gabapentin for neuropathic pain as for alcohol dependence. Interestingly, neither of the Neurologists prescribed gabapentin for partial seizures, although one Family Medicine physician and the Pediatrician prescribed gabapentin for partial seizures. None of the Psychiatrists prescribed gabapentin for cocaine withdrawal, although one of the Family Medicine physicians had prescribed the medication for cocaine withdrawal. As expected, the Pulmonologist had prescribed gabapentin for chronic cough. Two of the Psychiatrists and one of the Family Medicine physicians prescribed gabapentin for bipolar disorder. In addition to the eight Family Medicine physicians, five of the Psychiatrists and the Rheumatologist had prescribed gabapentin for fibromyalgia. Two Family Medicine physicians, a Psychiatrist and the Surgeon, also prescribed the medication for cancer-related hot flashes and brachioradial pruritus. One Family Medicine physician prescribed gabapentin for

postoperative pain and another Family Medicine physician prescribed it for menopause-related hot flashes. Gabapentin is the drug of choice for one of the Psychiatrists for insomnia in patients with alcoholism; otherwise the Psychiatrist prescribes it as a second-line agent for insomnia. Another Psychiatrist prescribed gabapentin second-line for anxiety in patients that did not respond to selective serotonin reuptake inhibitors (SSRIs), in order to avoid the use of a benzodiazepine. The Psychiatrist also prescribed gabapentin in patients developing anxiety secondary to cannabis use discontinuation.

Table 5 Percentage of Physicians in Specialty prescribing Gabapentin for each Clinical Indication

	FM (n=17)	Psych (n=12)	IM (n=2)	Neuro (n=2)	Other (n=2)	Occ Med (n=1)	Peds (n=1)	Pulm (n=1)	Rheum (n=1)	Surgery (n=1)
Partial Seizures	7%	0%	0%	0%	0%	0%	100%	0%	0%	0%
Postherpetic Neuralgia	59%	8%	50%	50%	0%	0%	0%	0%	0%	0%
Restless Legs Syndrome	41%	25%	0%	0%	50%	0%	0%	0%	0%	0%
Cocaine withdrawal	6%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Insomnia	12%	67%	0%	0%	0%	0%	0%	0%	0%	0%
Diabetic neuropathy	94%	8%	50%	50%	0%	0%	0%	0%	0%	0%
Cancer related hot-flashes	6%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Anxiety disorder	6%	83%	0%	0%	0%	0%	0%	0%	0%	0%
Bipolar disorder	6%	17%	0%	0%	0%	0%	0%	0%	0%	0%
Alcohol dependence	24%	50%	0%	0%	50%	0%	0%	0%	0%	0%
Brachioradial pruritus	6%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Chronic cough	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%
Fibromyalgia	47%	42%	0%	0%	0%	0%	0%	0%	100%	0%
Postoperative pain	12%	8%	0%	0%	0%	0%	0%	0%	0%	100%
Neuropathic pain	100%	50%	50%	100%	0%	100%	0%	0%	100%	0%

FM= Family Medicine, EM= Emergency Medicine, Psych= Psychiatry, IM= Internal Medicine, Neuro= Neurology, Occ Med= Occupational Medicine, Peds= Pediatrics, Pulm= Pulmonology, Rheum= Rheumatology

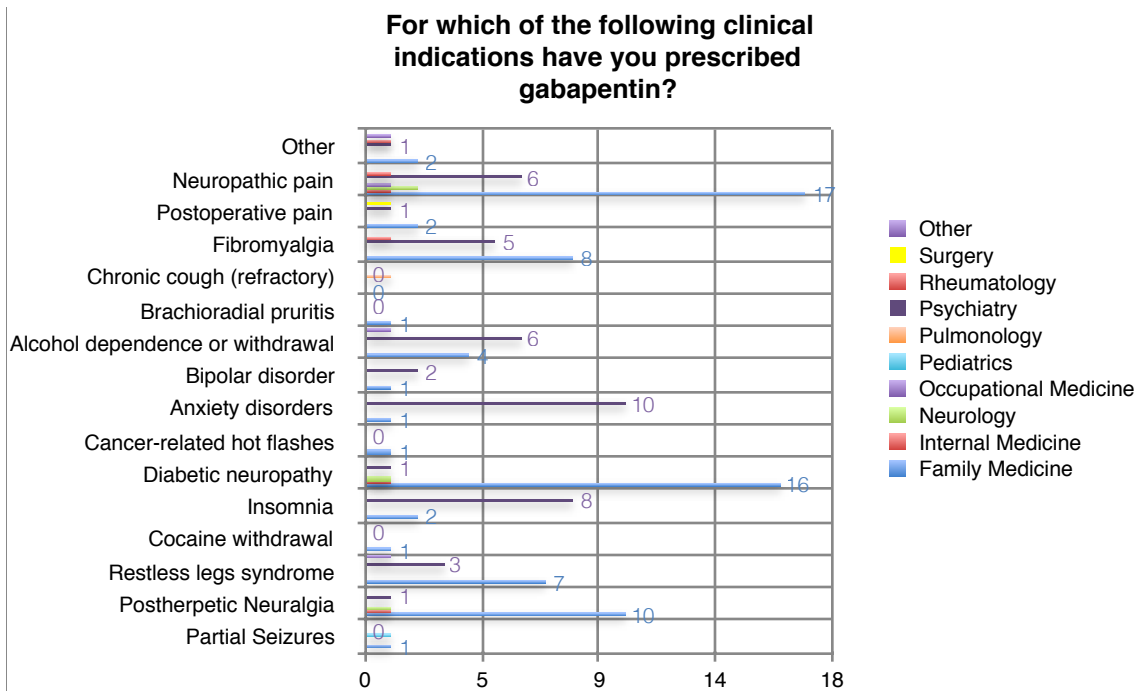


Figure 7 Frequency Distribution of Physicians in Clinical Specialty prescribing Gabapentin for each Clinical Indication

Restless Legs Syndrome (RLS)

Eleven physicians (seven Family Medicine physicians, three Psychiatrists, and one “other” physician) prescribed gabapentin for RLS (Figure 7). Ropinirole was the most common drug of choice, followed by pramipexole, prescribed by five and four Family Medicine physicians, respectively (One Family Medicine physician had written the two medications in as a comment as opposed to selecting the box; Figure 8 and Table 6). One of the Psychiatrists also prescribed

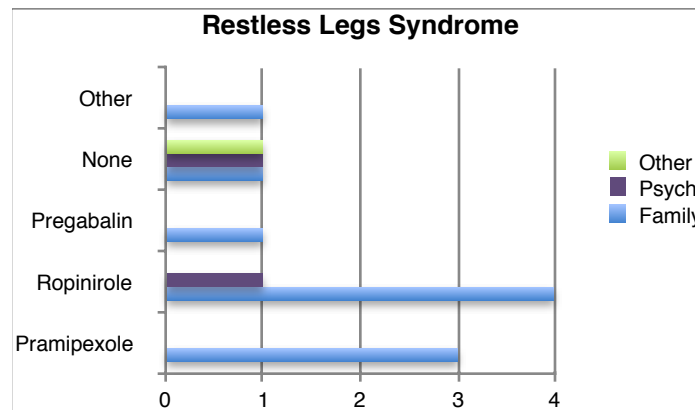


Figure 8 Frequency Distribution of Medications prescribed for Restless Legs Syndrome by Physicians Who Also Prescribe Gabapentin

ropinirole prior to gabapentin. One Family Medicine physician, Psychiatrist, and “other” physician prescribed gabapentin as the drug of choice. One Family Med-

icine physician preferred pregabalin, while another reported that most of his or her patients with RLS were inherited and therefore already on a medication. However, he or she commented that pregabalin is not always paid for by insurance and is a controlled substance, making gabapentin more appealing. Another Family Medicine physician stated that gabapentin is prescribed when there is a contraindication to the other medications. One of the Psychiatrists had commented that he or she does not usually treat RLS but that if the patient has a co-morbidity such as anxiety or insomnia, gabapentin is the drug of choice for treating the co-morbidity in a patient with RLS.

Table 6 Percentage of Physicians in Clinical Specialty Prescribing Alternative Treatment or Intervention Prior and/or In Addition to Gabapentin for the Treatment of Restless Legs Syndrome

	FM (n=17)	Psych (n=12)	Other (n=2)
Pramipexole	18%	0%	0%
Ropinirole	24%	8%	0%
Pregabalin	6%	0%	0%
None	6%	8%	50%
Other	6%	0%	0%

FM= Family Medicine, Psych= Psychiatry

Cocaine Withdrawal

One Family Medicine physician prescribed gabapentin for cocaine withdrawal. He or she also prescribed benzodiazepines, doxepin, clonidine, and modafinil in addition or prior to gabapentin.

Insomnia

Ten physicians (eight Psychiatrists and two Family Medicine physicians) prescribed gabapentin for insomnia (Figure 7). Melatonin was the drug of choice for Psychiatrists (Figure 9 and Table 7). Second-line therapy included zolpidem, lorazepam, and behavioral therapy, followed by doxepin and diphenhydramine, then eszopiclone and diazepam. Psychiatrists also tried zaleplon, suvorexant, ramelteon, melatonin agonists, and flurazepam. One Psychiatrist would use mirzapine and quetiapine only if the patient had co-morbidities such as mood disorders. Another Psychiatrist would only use gabapentin for insomnia in patients with refractory insomnia such as patients with primary depression. The Psychiatrist prescribed gabapentin in addition to benzodiazepines or hypnotics if the latter are insufficient. Trazodone was another medication prescribed by the Psychiatrist. Family Medicine physicians tried behavioral therapy, melatonin, zolpidem, lorazepam, doxepin, diphenhydramine, eszopiclone, zaleplon, melatonin agonist and triazolam. One Family Medicine physician added that he or she starts with non-pharmaceutical approaches, followed by melatonin, antihistamines, TCAs, and trazodone.

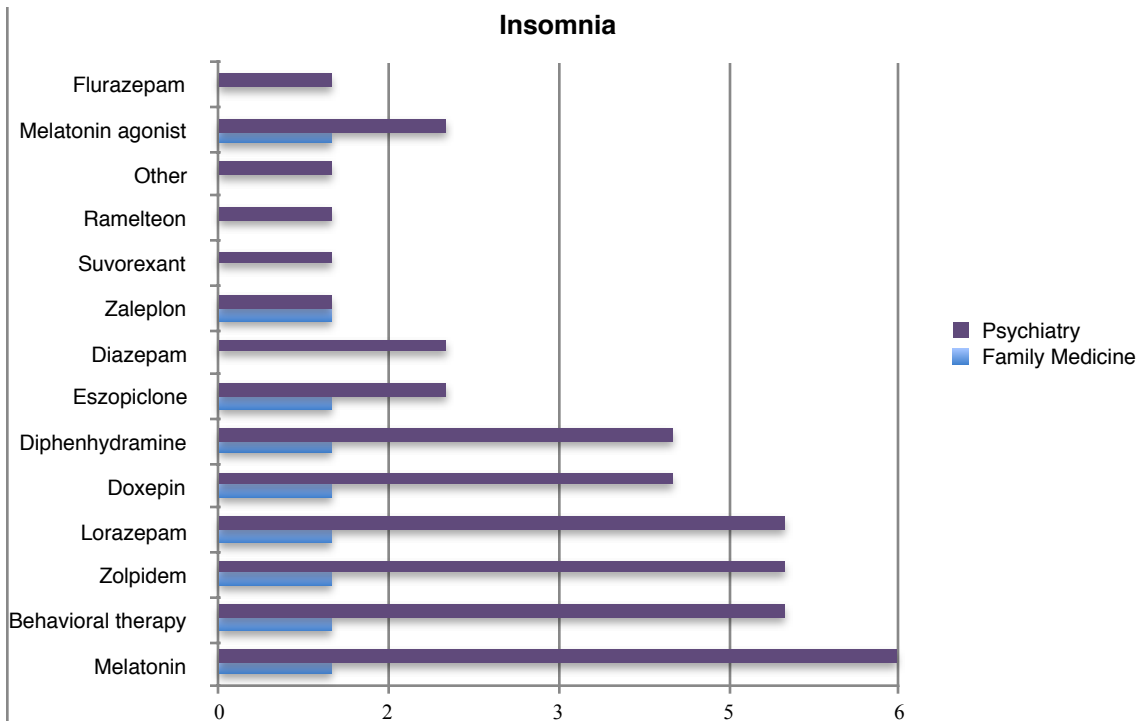


Figure 9 Frequency Distribution of Medications prescribed for Insomnia by Physicians Who Also Prescribe Gabapentin for the Indication

	FM (n=17)	Psych (n=12)
Flurazepam	0%	8%
Melatonin Agonist	6%	17%
Other	0%	8%
Ramelteon	0%	8%
Suvorexant	0%	8%
Zaleplon	6%	8%
Diazepam	0%	17%
Eszopiclone	6%	17%
Diphenhydramine	6%	33%
Doxepin	6%	33%
Lorazepam	6%	42%
Zolpidem	6%	42%
Behavioral therapy	6%	42%
Melatonin	6%	50%

Table 7 Percentage of Physicians in Clinical Specialty Prescribing Alternative Treatment or Intervention Prior and/or In Addition to Gabapentin for the Treatment of Insomnia

FM= Family Medicine, Psych= Psychiatry

Diabetic Neuropathy

Sixteen Family Medicine physicians and one Psychiatrist, Neurologist, and Internist prescribed gabapentin for diabetic neuropathy (Figure 7). Amitriptyline was the most popular medication, selected by ten Family Medicine physicians, the Internist and one of the Neurologists (Figure 10). The second most common medication was duloxetine, which was prescribed by seven Family Medicine physicians, one Psychiatrist and Neurologist, followed by venlafaxine, prescribed by five Family Medicine physicians. Pregabalin was prescribed by five Family Medicine physicians and one Neurologist. Nortriptyline was prescribed by four Family Medicine physicians and one Neurologist. Three Family Medicine physicians and one Neurologist prescribed carbamazepine and a lidocaine patch. However, one of the Family Medicine physicians commented that although carbamazepine has been prescribed, it was prescribed as an alternative treatment when all else failed. Five Family Medicine physicians also prescribed venlafaxine, four prescribed capsaicin and three prescribed tramadol. Two Family Medicine physicians and one Neurologist prescribed Transcutaneous Electrical Nerve Stimulation (TENS), three Family Medicine physicians prescribed gabapentin as the drug of choice for diabetic neuropathy (one Family Medicine physician wrote it in as a comment), two Family Medicine physicians prescribed ibuprofen, and one prescribed acetyl-L-carnitine, valproate and doxepin. One Family Medicine physician had stated that getting the patients' blood glucose levels under control is done prior to prescribing any medications. One of the nine Family Medicine

physicians that prescribed amitriptyline first-line said that the medication did not work in 50-80% of patients so gabapentin is prescribed second-line. Another Family Medicine physician used non-controlled medications prior to trying controlled medications.

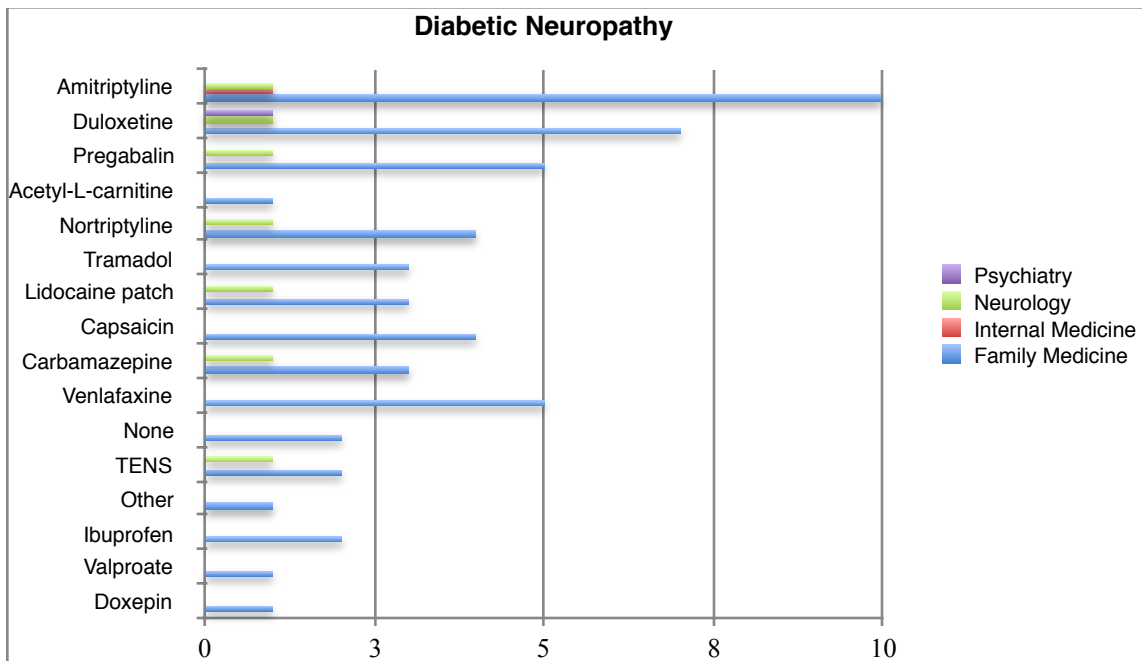


Figure 10 Frequency Distribution of Medications prescribed for Diabetic Neuropathy by Physicians Who Also Prescribe Gabapentin for the Indication

Hot Flashes

Two physicians, both Family Medicine physicians, prescribed gabapentin for hot flashes, one for cancer-related hot flashes and the other for menopause-related hot flashes (Figure 7). The physician that prescribed gabapentin for cancer-related hot flashes also tried venlafaxine and paroxetine (Figure 11). The physician that prescribed gabapentin for menopause-related hot flashes also tried estrogen replacement therapy and paroxetine.

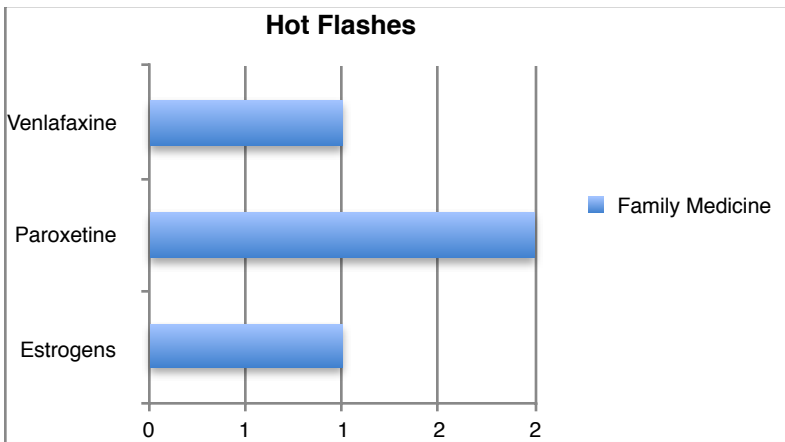


Figure 11 Frequency Distribution of Medications prescribed for Hot Flashes by Physicians Who Also Prescribe Gabapentin for the Indication

Anxiety Disorders

Ten Psychiatrists and one Family Medicine physician prescribed gabapentin to treat anxiety disorders (Figure 7). SSRIs (sertraline, citalopram and escitalopram) were the drugs of choice, followed by the benzodiazepines clonazepam and lorazepam, then SNRIs venlafaxine and duloxetine (Figure 12). Three Psychiatrists also prescribed fluoxetine, buspirone, paroxetine and mirtazepine; two prescribed quetiapine and hydroxyzine, while one tried cognitive behavioral therapy, fluvoxamine, alprazolam, and diazepam. One Family Medicine physician also tried pregabalin, oxazepam, chlordiazepoxide, and chlorazepate. Two of the Psychiatrists used gabapentin as the treatment of choice for patients with substance use disorders that also have anxiety. Two Psychiatrists prescribed gabapentin second-line in place of benzodiazepines, which, one of the Psychiatrists added “*are more addictive and ‘much, much more’ dangerous.*” The same physician remarked that antidepressants cannot be prescribed on an as needed basis, as they take about 6 weeks to work. One Psychiatrist commented “*Antipsychotics should not be prescribed for anxiety if a medication with fewer side effects (gabapentin), is available.*” Another Psychiatrist used gabapentin in patients with either cannabis use disorder or neuropathic pain, in addition to anxiety. Finally, a fourth psychiatrist commented that he or she used gabapentin only for treatment-refractory depression as a last resort.

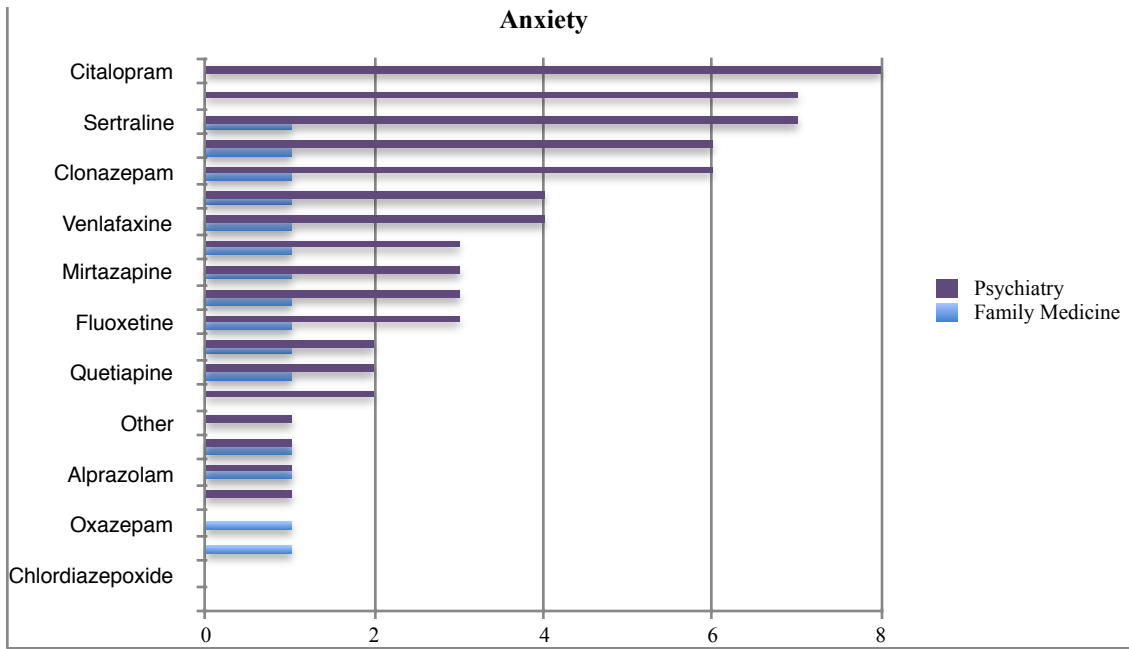


Figure 12 Frequency Distribution of Medications prescribed for Anxiety by Physicians Who Also Prescribe Gabapentin for the Indication

Bipolar Disorder

Two Psychiatrists and one Family Medicine physician used gabapentin for bipolar disorder (Figure 7). Both Psychiatrists used lithium as first-line therapy (Figure 13). One Psychiatrist and one Family Medicine physician used psychotherapy, lamotrigine, valproate, divalproex, risperidone, olanzapine and aripiprazole. One Psychiatrist used ziprasidone and one Family Medicine physician used carbamazepine, quetiapine, and asenapine (Figures 13 and 14).

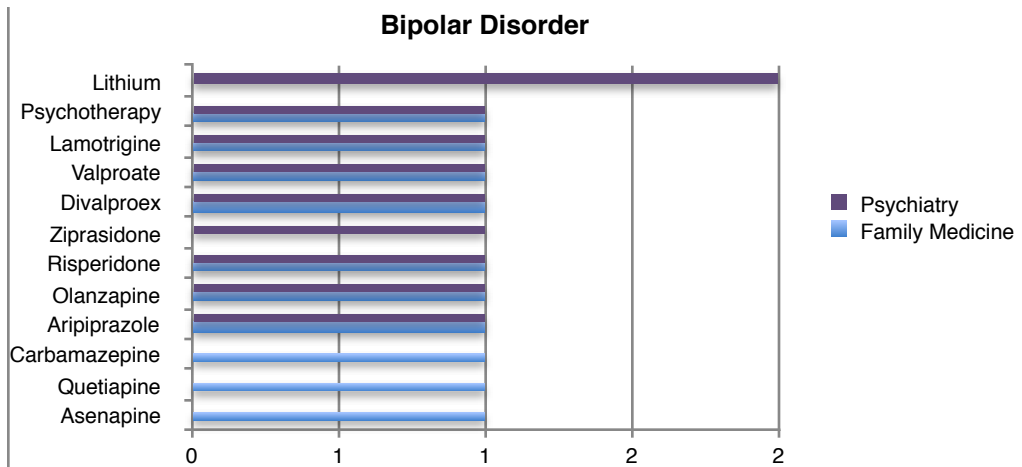


Figure 13 Frequency Distribution of Medications prescribed for Bipolar Disorder by Physicians Who Also Prescribe Gabapentin for the Indication According to Clinical Specialty

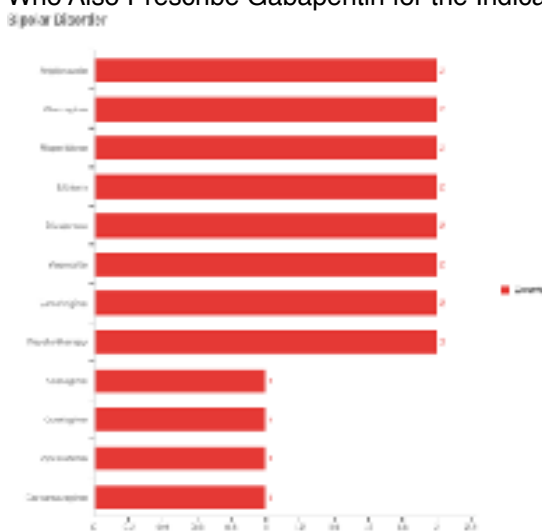


Figure 14 Frequency Distribution of Medications prescribed for Bipolar Disorder by Physicians Who Also Prescribe Gabapentin for the Indication

Alcohol Withdrawal and Dependence

Eleven physicians (six Psychiatrists, four Family Medicine physicians, and the Addiction Medicine specialist) prescribed gabapentin for alcohol withdrawal or dependence (Figure 7). The most common drug among the three specialties was lorazepam, with all four Family Medicine physicians, half of the Psychiatrists, and the Addiction Medicine specialist prescribing it (Figure 15). The second most common drug among Psychiatrists was phenobarbital with two of the six Psychiatrist, one of the Family Medicine physicians and the Addiction Medicine specialist prescribing it. Among the Family Medicine physicians, diazepam, folate, and thiamine were the second most common medications prescribed. The Addiction Medicine specialist prescribed all three; one of the Psychiatrists prescribed folate and thiamine. Two Family Medicine physicians prescribed clonidine, oxazepam, and isotonic saline with 5% dextrose. One of the Psychiatrists and the Addiction Medicine specialist also prescribed clonidine. One Psychiatrist and one Family Medicine physician prescribed a multivitamin and one Family Medicine physician had prescribed carbamazepine. One of the Family Medicine physicians commented that he or she also uses naltrexone, acamprosate, and disulfiram for alcohol-dependent patients pursuing abstinence. Another Family Medicine physician added that he or she individualizes the treatment for each patient and gabapentin may be preferred over some of the other medications, depending on the patient. One of the Psychiatrists added that gabapentin is the drug of choice, especially for patients in whom ongoing benzodiazepines are a “*bad idea*.”

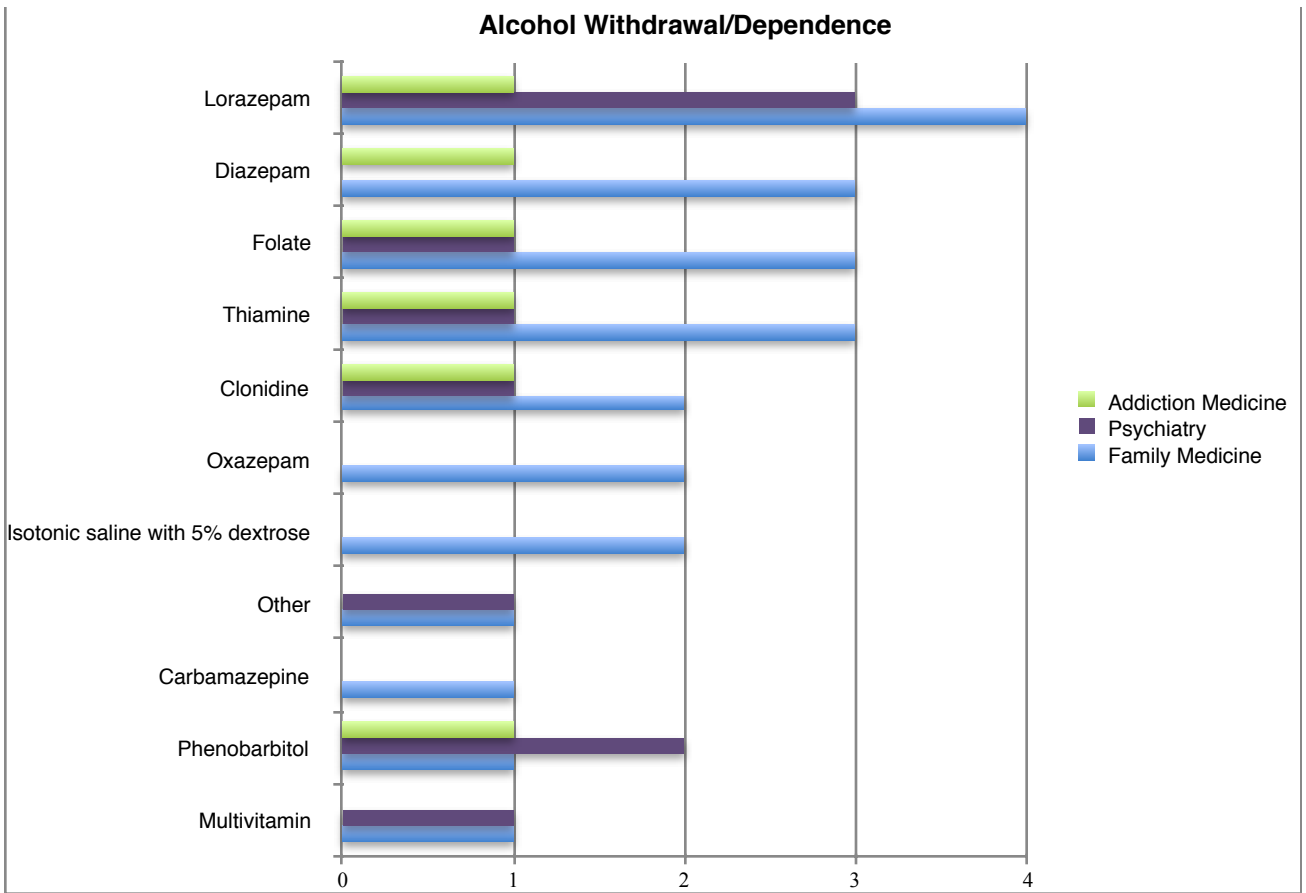


Figure 15 Frequency Distribution of Medications prescribed for Alcohol Withdrawal/Dependence by Physicians Who Also Prescribe Gabapentin for the Indication

Brachioradial Pruritus

One of the Family Medicine physicians prescribed gabapentin for brachioradial pruritus. Lidocaine and amitriptyline were also tried (Figure 16).

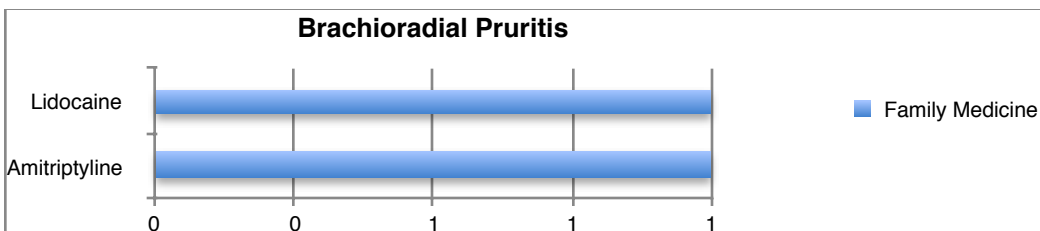


Figure 16 Frequency Distribution of Medications prescribed for Brachioradial Pruritus by Physicians Who Also Prescribe Gabapentin for the Indication

Chronic Cough

The Pulmonologist prescribed gabapentin for chronic cough. Cough suppression techniques, breathing exercises, guaifenesin, inhaled budesonide, and chlorpheniramine were also tried (Figure 17).

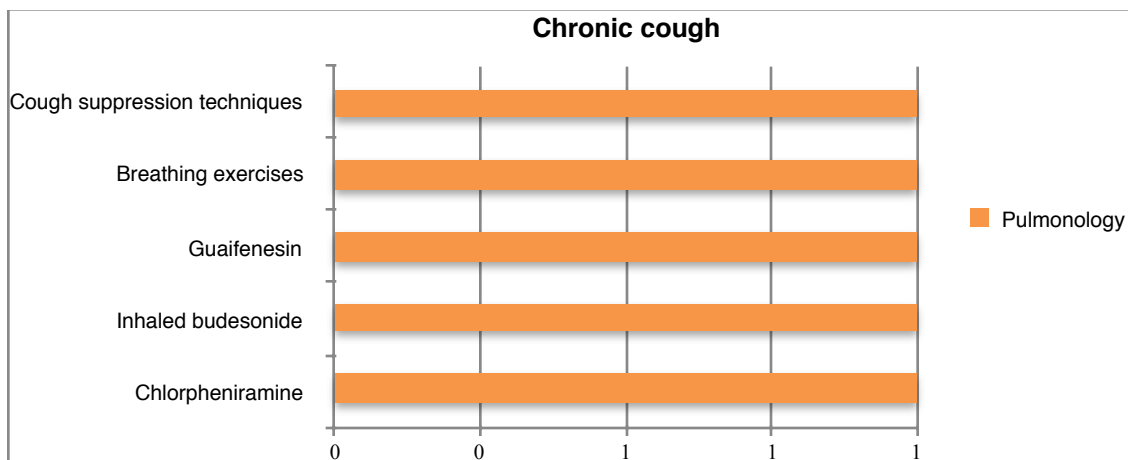


Figure 17 Frequency Distribution of Medications prescribed for Chronic Cough by Physicians Who Also Prescribe Gabapentin for the Indication

Fibromyalgia

Fourteen physicians (eight Family Medicine physicians, five Psychiatrists, and the Rheumatologist) prescribed gabapentin for fibromyalgia (Figure 7). All eight of the Family Medicine physicians, two of the Psychiatrists, and the Rheumatologist recommended exercise (Figure 18). Seven Family Medicine physicians, one of the Psychiatrists and the Rheumatologist recommended physical therapy. The most common answer choice among the Psychiatrists was duloxetine (three Psychiatrists); five of the Family Medicine physicians and the Rheumatologist also prescribed this medication. Five Family Medicine physicians also prescribed amitriptyline and pregabalin. The second most common answer choices among

the Psychiatrists were Cognitive Behavioral Therapy and yoga (two psychiatrists); the Rheumatologist also prescribed both of these interventions along with four and three Family Medicine physicians, respectively. Four Family Medicine physicians and one Psychiatrist prescribed Venlafaxine. Three Family Medicine physicians and one Psychiatrist recommended Tai Chi. Three Family Medicine physicians prescribed cyclobenzaprine. One physician had commented that he or she prefers muscle relaxers and uses tramadol and opioids in addition to another medication if the patient has other co-morbidities. One Family Medicine physician prescribed milnacipran and Osteopathic Manipulation Therapy, each.

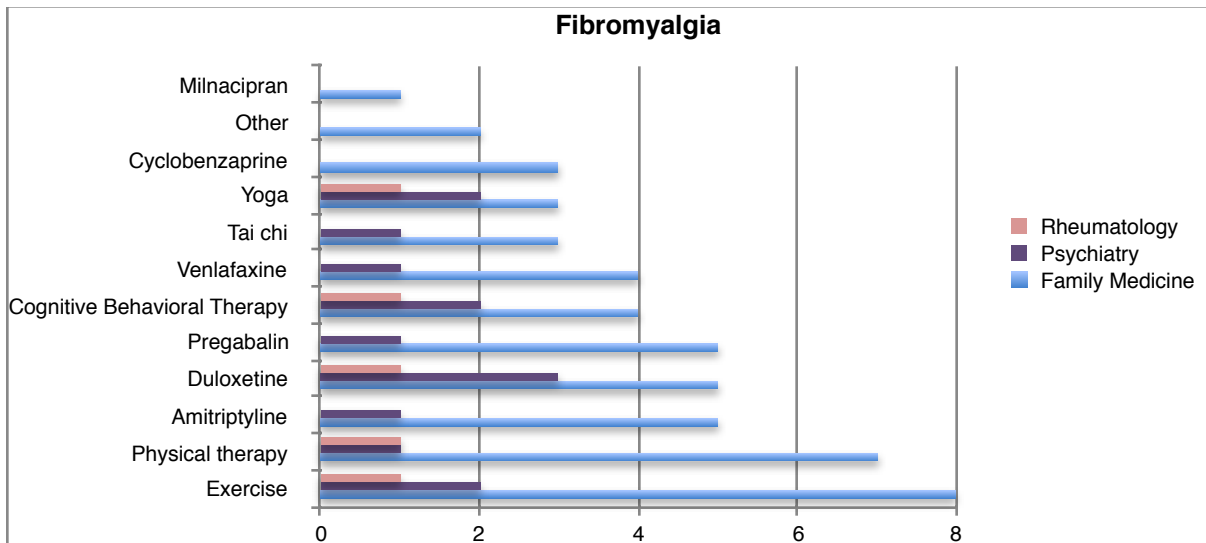


Figure 18 Frequency Distribution of Medications prescribed for Fibromyalgia by Physicians Who Also Prescribe Gabapentin for the Indication

Post-operative Pain

Two of the Family Medicine physicians, one of the Psychiatrists and the Surgeon prescribed gabapentin for post-operative pain (Figure 7). In addition, one of the Family Medicine physicians prescribed tramadol, diclofenac, morphine, celecoxib, ketorolac, intravenous acetaminophen, lidocaine, meperidine, fentanyl and hydromorphone (Figure 19). The Surgeon also prescribed tramadol, diclofenac, ibuprofen, and morphine. One of the Psychiatrists prescribed ibuprofen.

Gabapentin was prescribed by one of the Family Medicine physicians, as adjunct therapy in patients that did not respond to initial pain control.

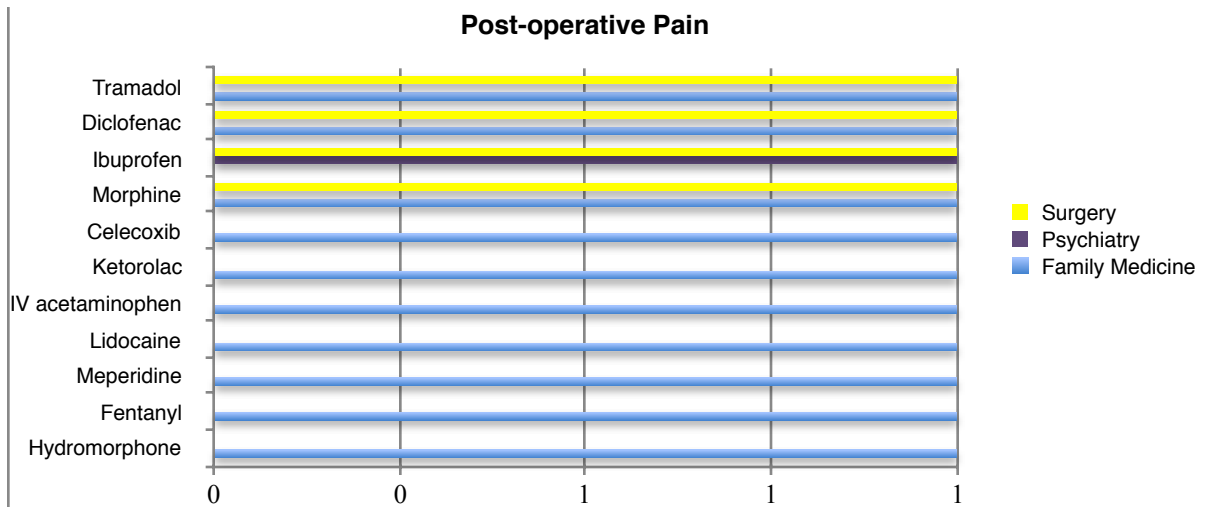


Figure 19 Frequency Distribution of Medications prescribed for Post-operative Pain by Physicians Who Also Prescribe Gabapentin for the Indication

Neuropathic Pain

Twenty-eight physicians (17 Family Medicine physicians, six Psychiatrists, two Neurologists, one Rheumatologist, Occupational Medicine physician, and Internist) prescribed gabapentin for neuropathic pain (Figure 7). The most popular

medications were duloxetine followed by amitriptyline (Figure 20). Nine Family Medicine physicians, a Psychiatrist, a Neurologist, the Occupational Medicine physician, and the Rheumatologist prescribed amitriptyline. Ten Family Medicine physicians, two Psychiatrists, and a Neurologist prescribed duloxetine. Six Family Medicine physicians, a Neurologist and the Rheumatologist prescribed pregabalin. Five Family Medicine physicians, the Occupational Medicine physician and Internist prescribed capsaicin and venlafaxine. One of the Family Medicine physicians also used nerve stimulation and Osteopathic Manipulation Therapy.

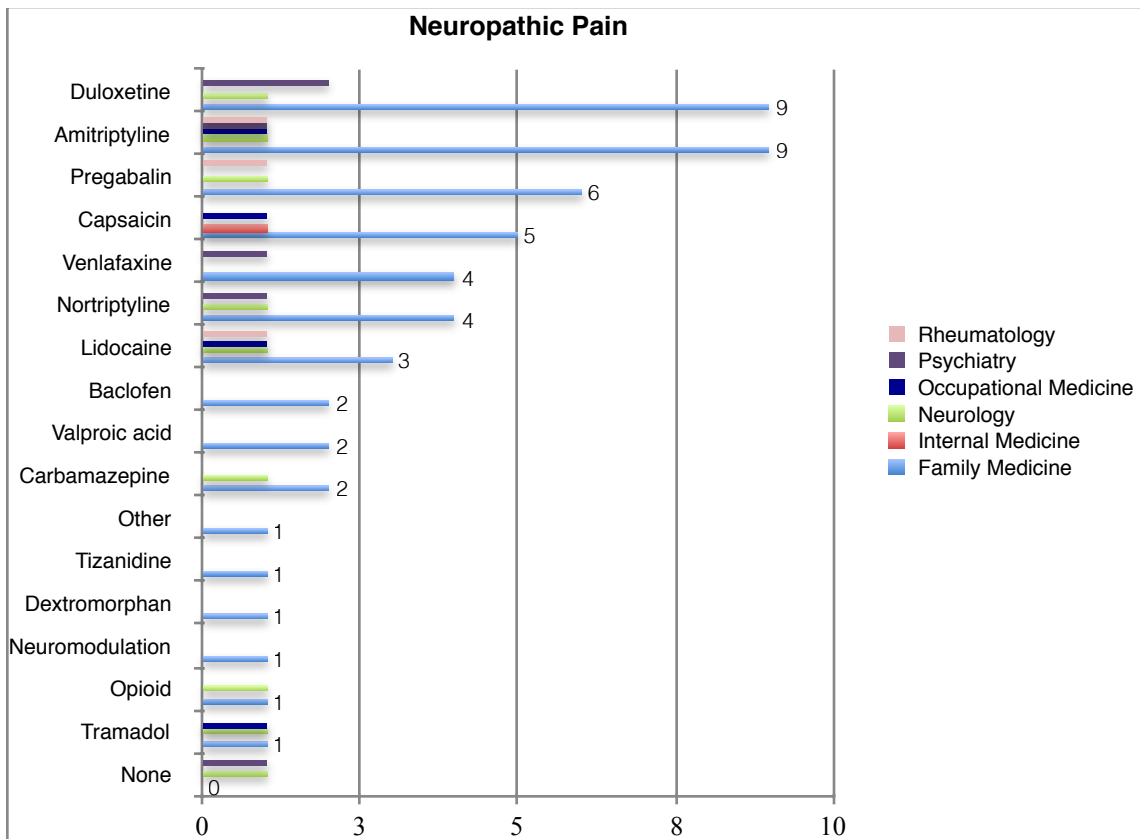


Figure 20 Frequency Distribution of Medications prescribed for Neuropathic Pain by Physicians Who Also Prescribe Gabapentin for the Indication

Summary

For the majority of conditions, gabapentin was not the drug of choice but was prescribed as a second or third-line agent when other medications had either failed or when a patient had co-morbidities that responded to gabapentin. First-line agents included benzodiazepines, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors.

Some of the reasons for prescribing gabapentin included that the medication had the potential to help with more than one indication, it is generic, well-tolerated, safe, inexpensive, great response was seen in the past, has few side effects, not metabolized in the liver, the benefits outweighed the risks with respect to pain relief, moderate evidence of efficacy from patient studies, failure to respond to non-controlled medications, and/or all other medications and modalities. As one physician put it, *“For [off-label] indications you're usually going through a host of meds, none of which works completely, so gabapentin is a trial and you have to see the effects vs. risks for each patient vs. other meds.”* Several physicians mentioned that gabapentin is *“far less addictive and toxic than other medications,”* particularly benzodiazepines and tricyclic antidepressants, prescribed for the same indication (See Appendix C and Influence of Substance Use Disorder, Opioid Use Disorder, and Opioid Prescription on Physician Prescribing of Gabapentin).

Experiences Discontinuing Gabapentin

The majority of physicians reported having successfully weaned patients off of gabapentin (Figure 21). One of the Family Medicine physicians, who had responded “no,” said he or she has never tried to wean a patient off. Two of the Psychiatrists added that they never had any issues with weaning. Common reasons for weaning included inconvenience now that it became a controlled medication in Kentucky, poor kidney function, side effects such as sedation, word-finding, and sleep ataxia, medication switch, failure of a random drug screen, concerns for misuse and overdose, and the inciting factor was resolved.

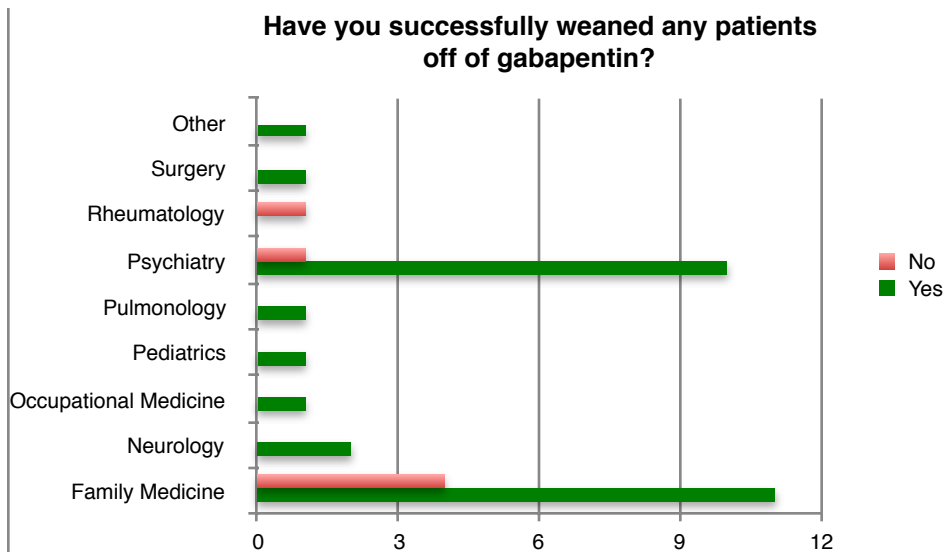


Figure 21 Frequency Distribution of Physicians that have Successfully Weaned Patients Off Gabapentin by Medical Specialty

Influence of Substance Use Disorder, Opioid Use Disorder and Opioid Prescription on Physician Prescribing of Gabapentin

Most of the Psychiatrists would be more likely to prescribe gabapentin to a patient with a history of Substance Use Disorder (SUD), whereas most of the Family Medicine physicians would be less likely (Figure 22). One of the Family Medicine physicians commented that he or she would try not to prescribe it to people with SUD now that it is a controlled substance in Kentucky. Another Family Medicine physician said he or she would be more likely to use gabapentin in a patient with alcohol dependence but that there is a “*small real abuse or diversion potential*” in patients with Opioid Use Disorder (OUD). Another Family Medicine physician echoed this remark. A fourth Family Medicine physician also mentioned heroin and opioid misuse as the reason to be less likely to prescribe gabapentin to a patient with SUD. Finally, one of the Family Medicine physicians who would be more likely to prescribe gabapentin to a patient with SUD mentioned that if the patient had an appropriate indication, “*gabapentin is far less risky than benzodiazepine or opioids and is a great substitute with good results in many cases.*” Many of the Psychiatrists had echoed the latter Family Medicine physicians’ remarks, adding that they preferred gabapentin to benzodiazepines for the treatment of anxiety. Another Psychiatrists agreed that gabapentin is often a great alternative to benzodiazepines and has never seen a patient have the same withdrawal symptoms as seen with benzodiazepines. A third Psychiatrist said his or her decision depends on the substance the patient was addicted to and the

patient's response to alternative medicines. A fourth Psychiatrist refers patients with SUD to specialists.

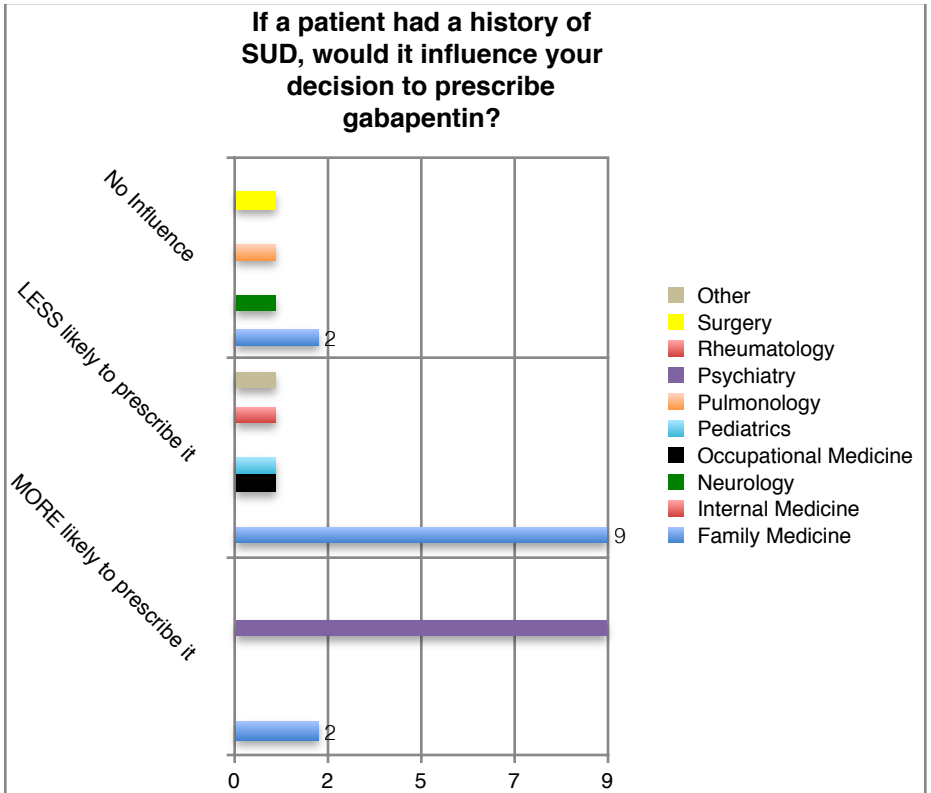


Figure 22 Frequency Distribution Of Physicians Who's Decision To Prescribe Gabapentin Would Be Influenced By Patient History of Substance Use Disorder (SUD)

With respect to the physicians who would be more likely to prescribe gabapentin to a patient with SUD, the Psychiatrists would either also be more likely to prescribe gabapentin to a patient with OUD or the OUD would not influence their decision, whereas one Family Medicine physician would be less likely to prescribe gabapentin to this patient (Figure 23). Another Family Medicine physician commented that it would depend on the reason—if the patient had a solid indication for an opioid, but did not want to prescribe the patient an opioid, gabapentin would be a good alternative. One of the Psychiatrists had mentioned that

gabapentin is a great alternative for other more addicting substances and another Psychiatrist would use gabapentin to treat a patient with OUD and anxiety.

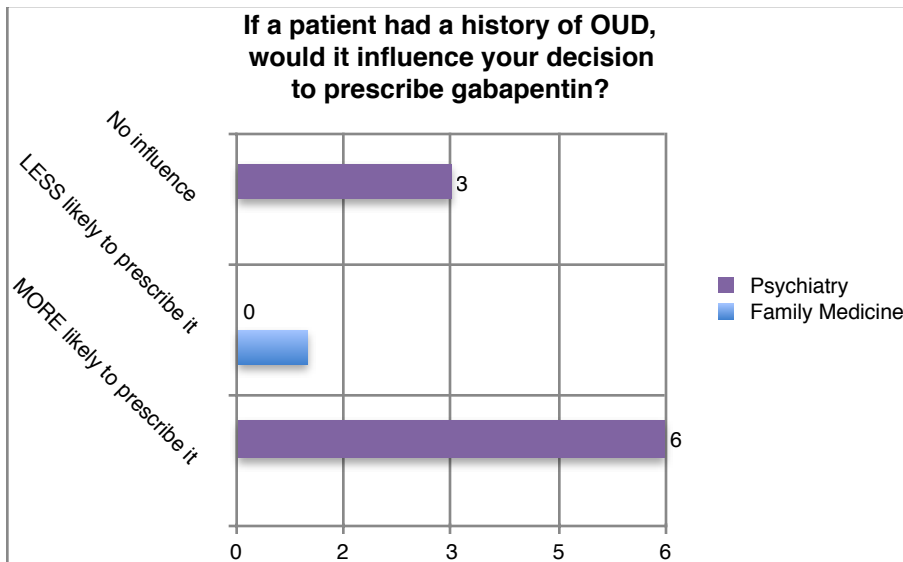


Figure 23 Frequency Distribution Of Physicians Who's Decision To Prescribe Gabapentin Would Be Influenced By Patient History of Opioid Use Disorder (OUD)

A patient's use of opioids would make all but two Family Medicine physicians less likely to prescribe gabapentin (Figure 24). One Family Physician would be more likely to prescribe gabapentin whereas the other Family Physician's decision would be unaffected by having a patient on opioids. The Family Medicine physician that would be more likely to prescribe gabapentin would use gabapentin to reduce a patient's use of opioids. Five Psychiatrists would be more likely to prescribe gabapentin, one Psychiatrist would be less likely and four Psychiatrists' decisions would not be influenced by the legitimate use of opioids. The two Neurologists appeared to agree with the consensus among the Psychiatrists—one would be more likely to prescribe gabapentin whereas the other's decision would be unaffected, as would the Pulmonologist and Surgeon's decisions. The Occu-

ational Medicine Physician, Pediatrician, Rheumatologist, and other physician would be less likely to prescribe gabapentin.

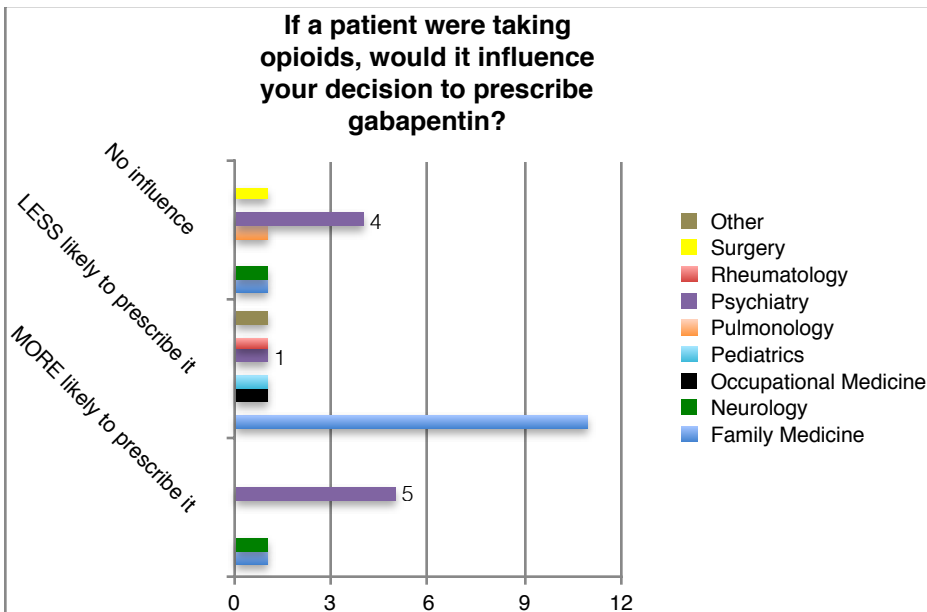


Figure 24 Frequency Distribution Of Physicians Who's Decision To Prescribe Gabapentin Would Be Influenced By Patient Co-Treatment With Opioids

Impact of Gabapentin Becoming a Controlled Substance

The majority of physicians agreed that gabapentin becoming a controlled substance would affect their prescribing practices of the medication. The one Family Physician that chose “other” wrote *“it would likely affect the ability of some patients to get their medication.”* In other words, gabapentin becoming a controlled substance would affect the prescribing practices of ten out of 16 Family Medicine physicians, ten out of eleven Psychiatrists, the Addiction Medicine specialist, the Rheumatologist, the Pulmonologist, and the Adult Neurologist. It would not affect the prescribing practices of the Surgeon, who does not practice in the US, the Pediatrician, the Occupational Medicine physician, and the Pediatric Neurologist. Of the two Family Medicine physicians who commented on their decision, one

mentioned that this leads to additional administrative tasks—a signed controlled substance contract, a six-month limit on the medication, and paper scripts. Another wrote *“Controlled substances are monitored aggressively, sometimes to a ridiculous degree. It would jeopardize my ability to prescribe if I am seen in any way as an over prescriber.”*

Of the two Psychiatrists that commented on their decision, one wrote that he or she would avoid prescribing gabapentin, if possible, as he or she is averse to prescribing controlled medications. The other Psychiatrist wrote that he or she would use it more sparingly, but would protest the decision to the state board because the Psychiatrist did not think it is appropriate to consider gabapentin a controlled substance. The Neurologist whose prescribing practices would be unaffected by the decision to make gabapentin a controlled substance wrote that most epilepsy medications are already controlled substances. Therefore, adding gabapentin to the list would not be a barrier since the essential support with administrative tasks is already in place.

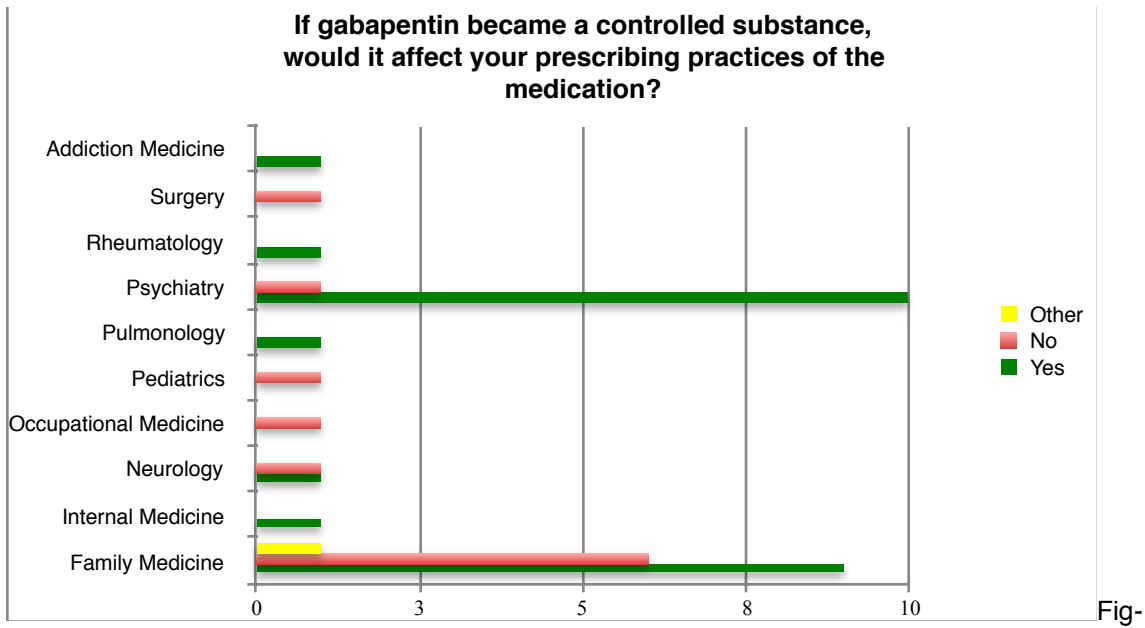


Figure 25 Frequency Distribution Of Physicians Who's Decision To Prescribe Gabapentin Would Be Influenced By Controlled Substance Status Of The Medication

Experience of Emergency Medicine Physicians with Gabapentin

In the past three months, the Emergency Medicine physicians that answered the survey saw between five and 50 patients for an overdose or intoxication (Figure

26). Emergency Medicine physician D did not give a number but wrote that about one percent of his or her patients came in for an overdose in the past three

months. Physician E and H also gave percentages—

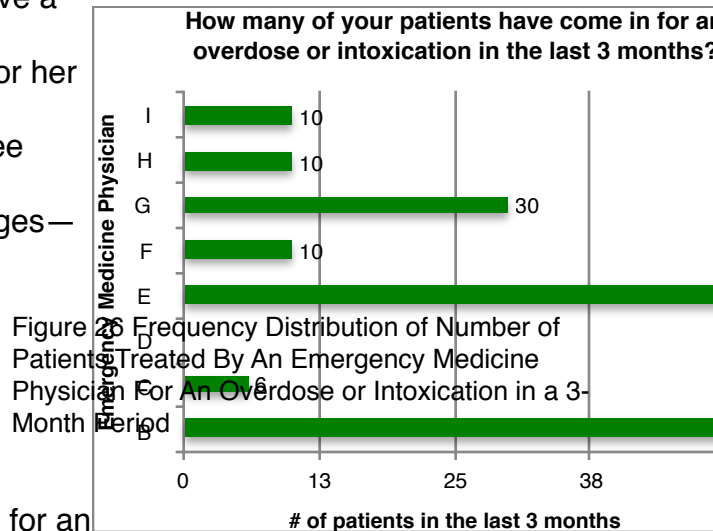
50 and ten patients represent five and one

percent of their patients, respectively. There-

fore, we can estimate that Emergency Medi-

cine physician D had about ten patients come in for an

overdose or intoxication in the last three months.



Benzodiazepines were the most common substances reported by Emergency Medicine physicians to be positive on urine toxicology, followed by opioids and cannabinoids (Figure 27). If oxycodone and methadone are grouped with the opioids, then the three together are the most common substance reported to be positive on urine toxicology. Five Emergency Medicine physicians reported having a patient with a positive urine toxicology screen for ethanol, three reported cocaine and amphetamines, and one Emergency Medicine physician each report lithium, acetaminophen, and barbiturates.

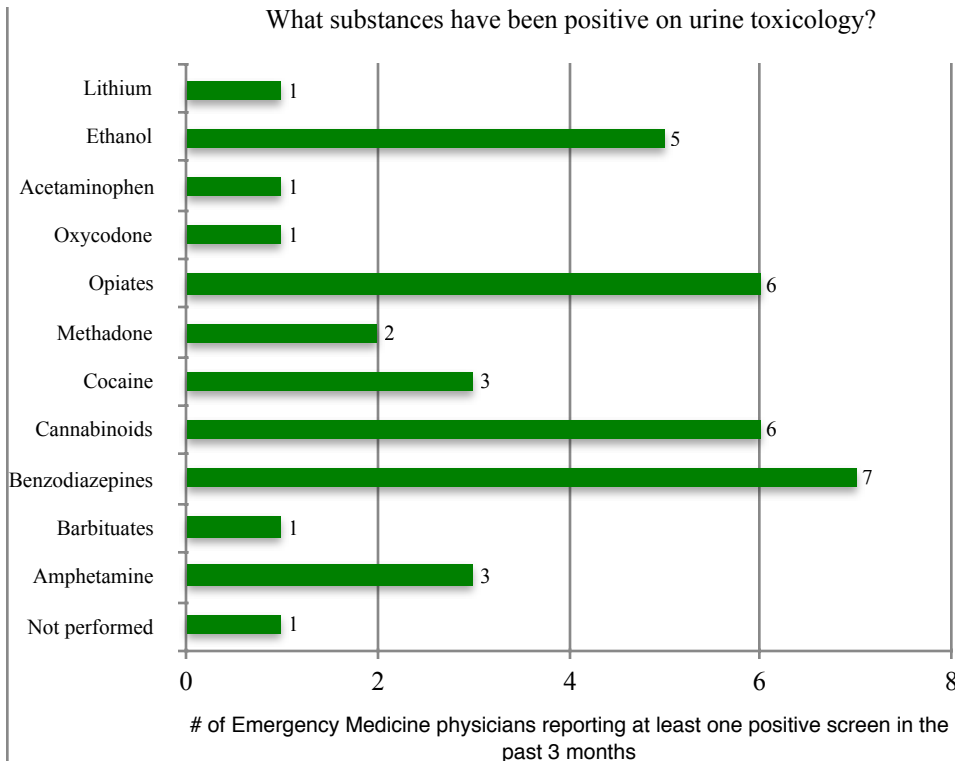


Figure 27 Frequency Distribution of Emergency Medicine Physicians Reporting Positive Result of Substance on Urine Toxicology

Of the patients seen for an overdose or intoxication, Emergency Medicine physicians reported that between zero and 80% of their patients were on gabapentin (Figure 28). This includes patients that reported being prescribed gabapentin and patients that were not prescribed gabapentin but reported to have taken the medication. The majority of Emergency Medicine physicians reported 0-5% of patients seen for an overdose or intoxication were on gabapentin, with Emergency Medicine physician I, who reported 80%, being an outlier.

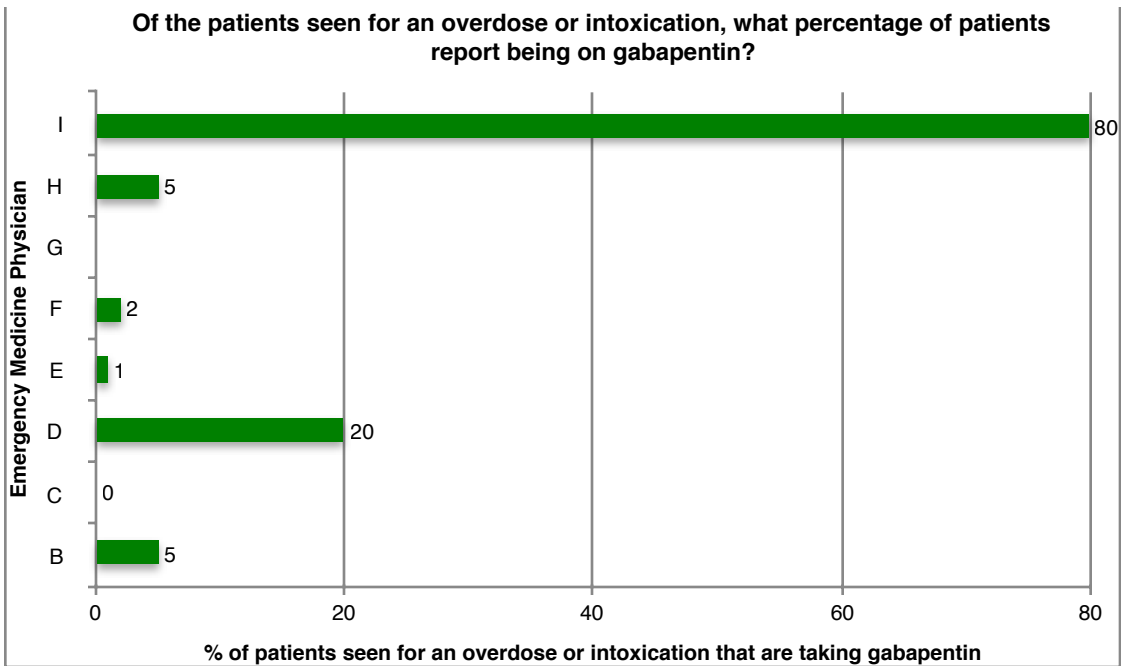


Figure 28 Percentage of Overdose or Intoxication Patients taking Gabapentin

The number of patients prescribed and “on” gabapentin that presented for an overdose is very similar (Figures 29 and 30). Emergency Medicine physician G did not report the number of overdose or intoxicated patients on gabapentin but reports one percent of them were prescribed gabapentin. Emergency Medicine physician A, who reported none of his or her patients being on gabapentin reported that 20% were prescribed gabapentin. Emergency Medicine physician I reported 80% of patients were on gabapentin and 90% were prescribed gabapentin.

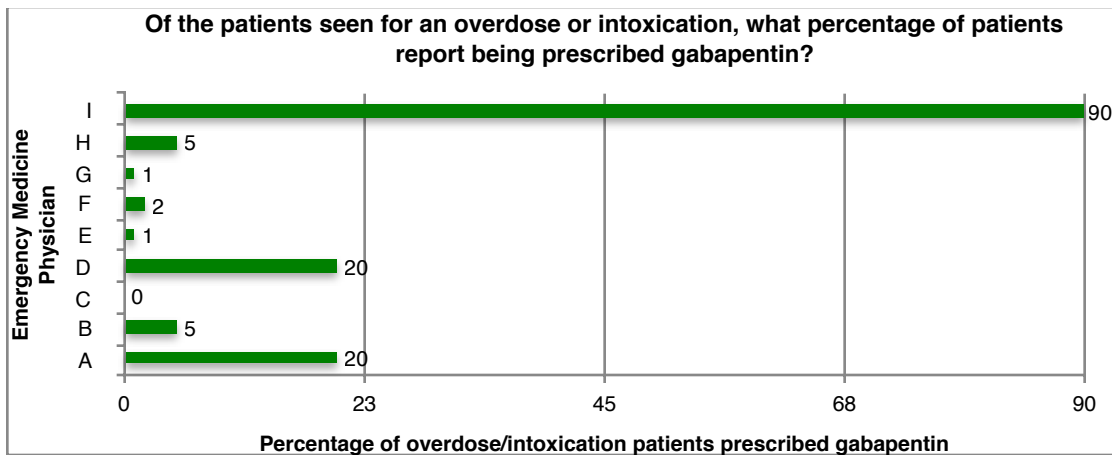


Figure 29 Percentage of Overdose or Intoxication Patients Prescribed Gabapentin

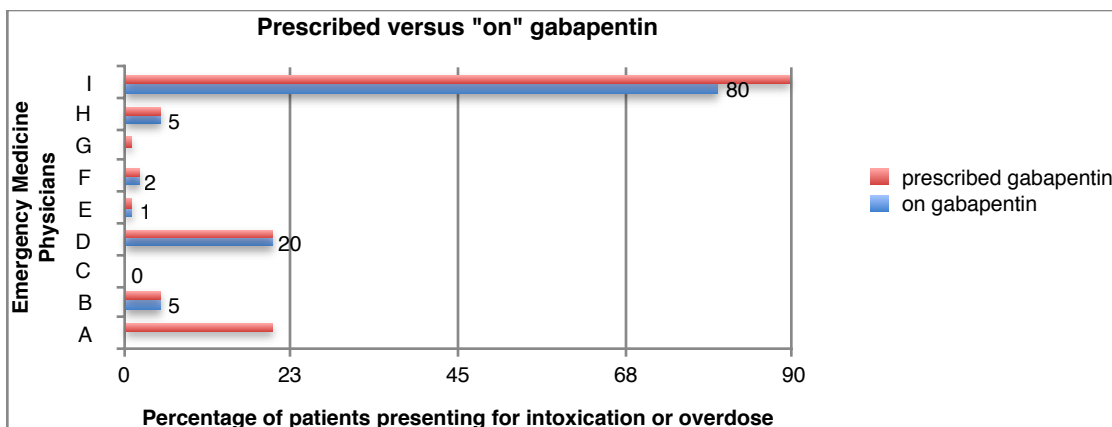


Figure 30 Percentage of Overdose or Intoxication Patients Prescribed Versus On Gabapentin

Finally, the Emergency Medicine physicians were asked whether, based on their experience, they believed gabapentin was leading to increased overdoses and/or intoxications (Figure 31). Six Emergency Medicine physicians felt that gabapentin was not leading to increased overdoses and/or intoxications while three felt that it was. Of the three that felt that gabapentin was leading to increased overdoses/intoxications, one of the Emergency Medicine physicians just finished a rotation at the New Jersey poison control center where they were seeing an increase in the number of gabapentin overdoses.

Emergency Medicine physician I, who also responded “yes”, may have misread the question because the physician added a comment about elderly patients accidentally taking benzodiazepines than prescribed. Of the six Emergency Medicine physicians who did not feel that gabapentin was leading to increased overdoses/intoxications, Emergency Medicine physician G wrote *“Not in our population. Our primary care doctors are pretty good about slow titration and monitoring of gabapentin prescriptions, primarily for chronic pain.”*

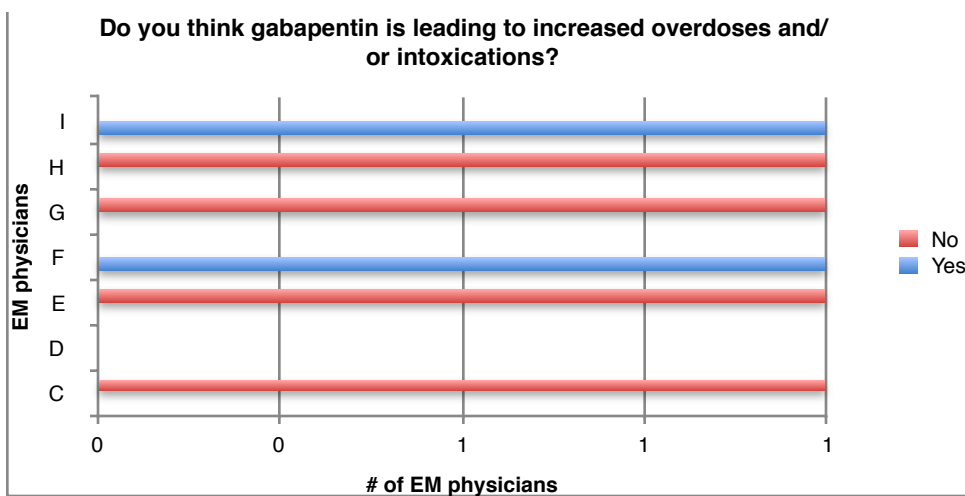


Figure 31 Frequency Distribution of Emergency Medicine Physicians That Think Gabapentin is leading to Increased Overdoses And/or Intoxications

DISCUSSION

The purpose of this study was to determine the various real-life off-label prescribing practices of gabapentin and physicians' perspectives with regard to particular advantages over other drugs and interventions. In addition, a secondary objective was to determine physicians' perspectives regarding whether gabapentin is being misused and whether making gabapentin a controlled medication will adversely affect prescribing patterns and patient care.

Sample Description

There were a total of 50 study participants who responded to the Qualtrics survey, with the majority being Family Medicine physicians (17 physicians, 34% of total participants), Psychiatrists (12 physicians, 24% of total participants), and Emergency Medicine physicians (9 physicians, 18% of total participants; Table 1). All but one of the Internists and the Intensivist prescribed gabapentin (Table 2). Intensivists are less likely to prescribe the medication given the acute setting of their practice, similar to Emergency Medicine physicians.

The majority of physicians reported that a small proportion of their patients were taking gabapentin, with 21 out of 39 physicians reporting that ten percent or less of their patients were taking gabapentin, less than one third reporting 11-20% (12 out of 39), four reporting 21-30%, and one physician, each, reporting 31-40% and 41-50% of their patients were taking the medication (Figure 3). This shows that

although gabapentin has several indications, it is still being prescribed sparingly among the majority of physicians in this study.

The Surgeon had the highest proportion of patients on the medication (41-50%), followed by Family Medicine physicians and then Psychiatrists (Figure 4). The Addiction Medicine physician wrote that prior to gabapentin becoming a scheduled medication, 50-60% of his or her patients were on the medication. Now it is between 0-10 percent. Given that only one Surgeon filled out the survey and that this Surgeon chose both "0-10%" and "41-50%," it is possible that one of the categories was picked accidentally. About half of the physicians with patients on gabapentin initiated the medication (Figure 5), with Psychiatrists placing a higher proportion of their patients on gabapentin than other physicians, followed by Family Medicine physicians. Psychiatrists and Family Medicine physicians use gabapentin more frequently than other physicians likely because of the diagnoses they treat. Psychiatrists in the study mentioned that most of the other medications available to their patients are more addictive (such as benzodiazepines) and/or have more side effects and interactions (Appendix C).

Gabapentin may be a safer alternative, especially for potentially suicidal patients [58, 63]. When gabapentin is prescribed appropriately, there is very little to any evidence of harm (Appendix C) [58, 63]. Between 2000-2001, 4,837 gabapentin-only exposures were reported to the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System. Of these, no medical adverse effects were seen in 1,353 individuals, minor effects were seen in 913,

moderate effects in 279, major effects in 25, and deaths were reported in three people. Doses associated with the three fatalities were 16.5 g, 48 g, and 59.4 g (about a 15-, 45- and 60-day dose, respectively) [63]. In that same year, there were 1,298 overdose death due to benzodiazepines, which steadily increased to 8,791 deaths in 2015 [69]. Similarly, ingestion of antidepressants were involved in 28% of suicidal ingestions reported to poison centers in the United States between 2000 and 2004— 84,670 involved ingestion of a single agent antidepressant. Of the single agent ingestions, 14.5% involved sertraline, 10% involved amitriptyline, bupropion was involved in 9.2%, fluoxetine in 8.5%, venlafaxine in 6.7%, and citalopram in 6.3%. Of the 8,316 amitriptyline overdoses, 54.2% of the required admission to the critical care unit, 1,220 patients suffered a major outcome³, and 61 were fatal. Of the 5,510 venlafaxine-only overdoses, 21.8% of them required admission to the critical care unit, 136 patients suffered a major outcome, and 12 were fatal. Of the 36 duloxetine-only overdoses, 22.2% of the required admission to the critical care unit, but luckily none suffered a major outcome or died [70].

³ A major outcomes was defined as life-threatening signs or symptoms or significant residual disability secondary to the exposure.

Conditions For Which Gabapentin is Prescribed

Neuropathic pain was the most common indication for prescribing gabapentin, followed by diabetic neuropathy, fibromyalgia and postherpetic neuralgia (Appendix B). This is not surprising as these are all FDA approved indications for gabapentinoids. Alcohol dependence or withdrawal and anxiety disorders were the most common indication for which the FDA has yet to approve a gabapentinoid, followed by insomnia. Psychiatrists most commonly prescribed gabapentin for anxiety disorders (83%), followed by for insomnia (67%; Table 5). Gabapentin is the drug of choice for one of the Psychiatrists for insomnia in a patient with alcoholism; otherwise it is used second-line for insomnia. Another Psychiatrist prescribes gabapentin second-line for anxiety in patients that did not respond to SSRIs, in order to avoid the use of a benzodiazepine. The Psychiatrist also prescribes gabapentin in patients developing anxiety secondary to cannabis use discontinuation. It is not surprising that Psychiatrists were prescribing gabapentin to treat anxiety given the addictive potential of anxiolytics, especially benzodiazepines, compared to gabapentin. Also, the risk of harm with overdose on gabapentin, compared to benzodiazepines, is small [58].

Interestingly, neither of the Neurologists prescribed gabapentin for partial seizures, although one Family Medicine physician and pediatrician had. Again, only two Neurologists participated in the survey, as compared to seventeen Family Medicine physicians. This finding is likely related to random chance.

Overall Benefits of Gabapentin

Some of the reasons for prescribing gabapentin included that the medication had the potential to help with more than one indication, it is generic, well-tolerated, safe, inexpensive, great response was seen in the past, has few side effects, not metabolized in the liver, the benefits outweigh the risks with respect to pain relief, moderate evidence of efficacy from patient studies, failure to respond to non-controlled medications and/or all other medications and modalities. Several physicians have mentioned that gabapentin is less addictive than other medications prescribed for the same indication.

Influence of Substance Use Disorder, Opioid Use Disorder, and Opioid Prescription of Physician Prescribing of Gabapentin

Most of the Psychiatrists would be more likely to prescribe gabapentin to a patient with a history of Substance Use Disorder (SUD), whereas most of the Family Medicine physicians would be less likely (Figure 22). Most of the Family Medicine physicians that responded to the survey practice in Kentucky, where there is a greater fear of gabapentin being combined with heroin or other opioids than other parts of the country. Psychiatrists that responded to the survey were scattered throughout the eastern half of the United States. Psychiatrists were more likely to prescribe gabapentin to patients with SUD given its therapeutic effects in patients with alcohol dependence and as a substitute for benzodiazepines and opioids. The same trends and comments were made with respect to OUD and in patients prescribed opioids (Figures 23 and 24).

The patient population, the indication, and alternative treatment options influence the decisions among the different specialties.

Impact of Gabapentin Becoming a Controlled Substance

The majority of physicians agreed that gabapentin becoming a controlled substance would affect their prescribing practices of the medication (Figure 25). Specifically, gabapentin becoming a controlled substance would affect the prescribing practices of 63% of Family Medicine physicians, 91% Psychiatrists, the Addiction Medicine specialist, the Rheumatologist, the Pulmonologist, and the Adult Neurologist. It would not affect the prescribing practices of the Surgeon, who does not practice in the US, the Pediatrician, the Occupational Medicine physician, and the Pediatric Neurologist. Physicians participating in the survey justified their response by mentioning that gabapentin becoming a controlled medication will lead to additional administrative tasks—a signed controlled substance contract, a six-month limit on the medication, and a paper script. Also, they feel that their practices are already scrutinized and their ability to practice medicine may be in jeopardy if their prescribing data ever falls outside of the normal range, regardless of the legitimacy of their reasons.

Experience of Emergency Medicine Physicians with Gabapentin

In the past 3 months, the Emergency Medicine physicians that answered the survey saw between 5 and 50 patients for an overdose or intoxication (Figure 26). Benzodiazepines were the most common substances reported by Emergency Medicine physicians to be positive on urine toxicology, followed by opioids and cannabinoids (Figure 27).

Of the patients seen for an overdose or intoxication, the majority of Emergency Medicine physicians reported that between 0 and 20% of their patients were on gabapentin (Figure 28). The significance of finding that 0- 20% of patients seen for an overdose or intoxication reported to be taking or prescribed gabapentin depends on the prevalence of gabapentin prescriptions. From Figure 4 we know that, at least in the population surveyed, 0- 40% of patients were prescribed gabapentin, with the distribution heavily skewed to the right. If 20% of overdose patients had gabapentin in their system and the prevalence of gabapentin prescriptions was 10%, this finding may be significant and it would be important to explore what separates patients more likely to misuse gabapentin from those who do not misuse gabapentin. On the other hand, if 10% of overdose patients had gabapentin in their system and the prevalence of gabapentin prescriptions was 10%, this may be an incidental finding.

Finally, Emergency Medicine physicians were asked whether, based on their experience, they felt that gabapentin was leading to increased overdoses and/or

intoxications (Figure 31). Six Emergency Medicine physicians felt that gabapentin was not leading to increased overdoses and/or intoxications while three felt that it was. Of the three that felt that gabapentin was leading to increased overdoses/intoxications, one of the EM physicians had just finished a rotation at the New Jersey poison control center where they were seeing an increase in the number of gabapentin overdoses. EM physician I, who also responded “yes”, may have misread the question because the physician had added a comment about elderly patients accidentally taking more benzodiazepines than prescribed. Of course, the sample size of Emergency Medicine physicians surveyed was small so it is difficult to draw any conclusions based on their responses. Someone who just spent the last month responding to all overdoses in a state is likely to believe all substances are more dangerous than they previously believed. Emergency Medicine physicians, on the other hand, who continue to remain in the same setting for decades are better equipped to notice trends.

Although no information was gathered regarding geographic location, there is a good chance that most, if not all of the Emergency Medicine physicians practiced on the East Coast, primarily in New Jersey, New York and Florida. The age-adjusted deaths due to opioid overdose in 2016 were 18.0, 23.2, and 23.7 per 100,000 people in New Jersey, New York and Florida, respectively. In Kentucky, the age-adjusted deaths due to opioid overdose in 2016 was 33.5 per 100,000 people [71]. Although this does not offer any information regarding Emergency Department visits, it can be inferred that the Emergency Medicine physicians are

working in states where the prevalence of OUD is less than in Kentucky. Therefore, the prevalence of misusing gabapentin together with opioids is likely lower in the states where the Emergency Medicine physicians surveyed work.

Limitations

The physicians' and healthcare facilities' characteristics such as the geographical location, type of facility (public or private), patients' health seeking behavior and perceived needs may influence the physicians' prescribing behaviors underscored in this analysis. A related limitation is that the sample size was small and a convenience sample was used, limiting generalizability. To allow the physicians to freely express their opinions and off-label practices, it was important to limit the number of questions asked that might reveal their identity. The number of questions asked was also limited as much as possible to increase the number of respondents.

Another limitation of any voluntary survey is responder bias. Responders with a particular view of making gabapentin a scheduled medication, or any particular view of gabapentin, were more likely to participate in the survey. There are two competing views physicians can have with respect to gabapentin—that it is a dangerous medication and needs to be monitored or that it is a safe medication and making it a scheduled medication would limit its use. Therefore, in a sense, the two biases cancel each other out. Also, part of the purpose of the survey was

to hear from physicians who have a particular view of the medication. Even if only a small portion of patients will be less likely to be prescribed gabapentin, if these patients would have benefited from it and are not likely to divert or misuse it, making gabapentin a controlled substance would negatively impact patient care. The purpose of the study was not to attempt to quantify the degree to which prescribing practices will be affected since the small sample size and convenience sampling would make such estimate unreliable. Rather, the purpose of the study was to determine if prescribing practices would be affected. The results of the survey suggest that they would be affected.

Limitations of Specific Questions

With respect to hot-flashes, the survey question asked specifically about cancer-related hot flashes. More physicians may have prescribed gabapentin for menopause-related hot flashes, but only one Family Medicine physician had written it in. In addition, OB/GYNs are more likely to have prescribed gabapentin for hot flashes given the results of the studies performed by their organization, the American College of Obstetrics and Gynecology (ACOG). The absence of survey respondents that are OB/GYNs likely led to fewer physicians reporting use of gabapentin for hot flashes and is a limitation of this study. The same can be said about the scarcity of Surgeons participating in the survey and thus the number of physicians prescribing gabapentin for post-operative pain.

Physicians' interpretation of "Substance Use Disorder" may have varied according to geographic location. In areas where alcoholism is more prevalent, physicians may have interpreted SUD to be primarily alcoholism and would be more likely to prescribe gabapentin for SUD, whereas in areas where OUD is more prevalent and alcoholism is less common, physicians may have interpreted the SUD to be primarily OUD, which may have affected their response. For this reason, physicians who responded that they would be more likely to prescribe gabapentin to a patient with SUD were asked a followup question— how would a history of OUD affect their prescribing practices?

Unfortunately, routine toxicology screens in the Emergency Department do not include gabapentin, fentanyl, and fentanyl analogues. Therefore, it is difficult to determine how often these overdoses are seen in the Emergency Department. Having said this, patients overdosing on opioids laced with fentanyl will require more naloxone than patients overdosing on just fentanyl alone.

With respect to patients presenting to the Emergency Department for an overdose or intoxication that were taking gabapentin, Emergency Medicine physician I may have misunderstood the question because he or she commented that most of his or her patients are old and use benzodiazepines almost daily. Therefore, the 80% may be the percentage of patients overdosing on benzodiazepines, not gabapentin.

Public Health Implications

On average 115 Americans die after overdosing on opioids every day [72]. Opioid dependence and misuse is a grave national problem that affects multiple aspects of public health. The total national economic burden of prescription opioid misuse, including the costs of healthcare, substance use treatment, lost productivity, and criminal justice is estimated to be \$78.5 billion annually [73]. Gabapentin may be a contributing partner to this crisis, despite all of its favorable medical effects. Here are my hypotheses. First, Gabapentin alone has less severe side effects and is useful for multiple disorders. This is likely why many physicians use it off-label and explains the positive opinions represented by the physicians in the survey.

My second hypothesis is that gabapentin potentiates the impact of opioids. This explains why a lower dose of opioids are needed to treat pain when the two medications are used together and also explains the street appeal of the medication when combined with heroin.

This leads to three recommendations.

Recommendations

1. To ensure current laws and regulation protect health and ensure safety, it would be important to conduct further research on the pharmacological effects of gabapentin alone and in combination of opioids, especially at higher doses.

This will help to implicate gabapentin as a causative factor in opioid overdose deaths as opposed to a mere correlation.

2. Population-based studies should be done examining outcomes with respect to morbidity and mortality in patients on both opioids and gabapentin versus gabapentin alone, controlling for confounders, such as fentanyl.
3. Physicians should be educated about the possible potentiating effect of gabapentin when used with opioids and the risk of diversion. Physicians in states where OUD is prevalent are aware of this risk. However, physicians in states where OUD is not as prevalent may not yet be aware of this risk. Therefore, it would be important for the public health community to spread this knowledge to physicians throughout the country.

Conclusions

Medicine is full of difficult decisions and nuances. From the results presented above, it appears that gabapentin is often either used as a last resort or in patients with dual/multiple diagnoses. Physicians consider a host of factors in order to come up with an appropriate plan of action for a patient. It is important that the public health world make the clinical world aware of new trends such as an increase in opioid overdose deaths among patients taking gabapentin. However, it is equally important that the additional administrative burden on physicians associated with the new restrictions on gabapentin not outweigh the benefits to public health or take time away from patient care.

It is too early to determine how making gabapentin a scheduled medication in Kentucky affected clinical practice and opioid overdose deaths, but from the limited data gathered in this study, it appears that clinical practice will be affected.

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APPENDICES

Appendix A

What is your clinical specialty?

- Anesthesiology
- Cardiology
- Dermatology
- Emergency Medicine
- Endocrinology
- ENT
- Family Medicine
- Gastroenterology
- Hematology/Oncology
- Immunology
- Infectious Disease
- Intensive Care Medicine
- Internal Medicine
- Nephrology
- Neurology
- Obstetrics/Gynecology
- Other
- Occupational Medicine
- Ophthalmology
- Orthopedic surgery
- Pain Management
- Pathology
- Pediatrics
- Physical Medicine and Rehabilitation
- Plastic surgery
- Preventive Medicine
- Pulmonology
- Psychiatry
- Radiology
- Rheumatology
- Surgery
- Urology

Have you ever prescribed gabapentin for a patient?

- Yes
- No
- Comments and/or clarification _____

What percentage of your patients is taking gabapentin?

- 10%
- 11-20%
- 21-30%
- 31-40%
- 41-50%
- 51-60%
- 61-70%
- 71-80%
- 81-90%
- 91-100%
- Comments and/or clarification _____

Of your patients that are taking (prescribed) gabapentin, what percentage did you start on gabapentin (as opposed to another physician)?

- 0-10%
- 11-20%
- 21-30%
- 31-40%
- 41-50%
- 51-60%
- 61-70%
- 71-80%
- 81-90%
- 91-100%
- Comments and/or clarification _____

For which of the following clinical indications have you prescribed gabapentin? (Feel free to write in any comments in the text box).

- | | |
|---|--|
| <input type="radio"/> Partial Seizures | <input type="radio"/> Bipolar disorder |
| <input type="radio"/> Postherpetic Neuralgia | <input type="radio"/> Alcohol dependence or withdrawal |
| <input type="radio"/> Restless legs syndrome | <input type="radio"/> Brachioradial pruritus |
| <input type="radio"/> Cocaine withdrawal | <input type="radio"/> Chronic cough (refractory) |
| <input type="radio"/> Insomnia | <input type="radio"/> Fibromyalgia |
| <input type="radio"/> Diabetic neuropathy | <input type="radio"/> Hiccups |
| <input type="radio"/> Tremors in multiple sclerosis | <input type="radio"/> Postoperative pain |
| <input type="radio"/> Cancer-related hot flashes | <input type="radio"/> Uremic pruritus |
| <input type="radio"/> Amyotrophic Lateral Sclerosis | <input type="radio"/> Neuropathic Pain |
| <input type="radio"/> Anxiety disorders | |
| <input type="radio"/> Other _____ | |
| <input type="radio"/> Comments and/or clarification _____ | |

What other medication(s) and/or interventions did you try in your patient(s) for before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Pramipexole
- Ropinirole
- Rotigotine transdermal patch
- Pregabalin
- None
- Other _____
- Comments and/or clarification _____

What other medication(s) and interventions did you try in your patient(s) for cocaine withdrawal before or in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- None
- Other _____
- Comments and/or clarification _____

What other medication(s) and/or interventions did you try in your patient(s) for before prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Behavioral therapy
 - Melatonin agonist
 - Doxepin
 - Zolpidem
 - Zaleplon
 - Eszopiclone
 - Triazolam
 - Lorazepam
 - Flurazepam
 - Other _____
 - Comments and/or clarification _____
- Quazepam
 - Diazepam
 - Ramelteon
 - Tasimelteon
 - Melatonin
 - Suvorexant
 - Diphenhydramine
 - None

What other medication(s) and/or interventions did you try in your patient(s) for Diabetic Neuropathy before prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Amitriptyline
 - Nortriptyline
 - Doxepin
 - Desipramine
 - Duloxetine
 - Venlafaxine
 - Pregabalin
 - Valproate
 - Carbamazepine
 - Capsaicin
 - Mexiletine
 - Lidocaine patch
 - Alpha-lipoic acid
 - Other _____
 - Comments and/or clarification _____
- Isosorbide dinitrate topical spray
 - Transcutaneous Electrical Nerve Stimulation
 - Dextromethorphan
 - Tramadol
 - Oxycodone
 - Morphine
 - Acetyl-L-carnitine
 - Ibuprofen
 - Sulindac
 - None

What other medication(s) /intervention(s) did you try in your patient(s) for tremors related to multiple sclerosis before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Deep Brain Stimulation
- None
- Other _____
- Comments and/or clarification _____

What other medication(s) /intervention(s) did you try in your patient(s) for cancer-related hot flashes before/in addition to prescribing gabapentin? In the comment box, please describe your

experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Estrogens
- Progestins
- Acupuncture
- Paroxetine
- Venlafaxine
- Citalopram
- Duloxetine
- None
- Other _____
- Comments and/or clarification _____

What other medication(s) /intervention(s) did you try in your patient(s) for ALS before/in addition to prescribing gabapentin (either for symptom-relief or potential disease modifying treatment)? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Quinine sulfate
 - Levetiracetam
 - Carbamazepine
 - Phenytoin
 - Baclofen
 - Tizanidine
 - Zolpidem
 - Amitriptyline
 - Mirtazapine
 - Chloral hydrate
 - Diphenhydramine
 - Flurazepam
 - Riluzole
 - Edaravone
 - Ceftriaxone
 - Celecoxib
 - Ciliary neurotropic factor
 - Other _____
 - Comments and/or clarification _____
- Coenzyme Q10
 - Creatine
 - Dexamiprexole
 - Lamotrigine
 - Lithium
 - Minocycline
 - Ozanezumab
 - Recombinant Insulin-like growth factor type I
 - Talampanel
 - TCH346
 - Topiramate
 - Valproic acid
 - Verapamil
 - None

What other medication(s) /intervention(s) did you try in your patient(s) for anxiety before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Paroxetine
 - Sertraline
 - Citalopram
 - Escitalopram
 - Fluoxetine
 - Fluvoxamine
 - Venlafaxine
 - Duloxetine
 - Buspirone
 - Pregabalin
 - Alprazolam
 - Bromazepam
 - Chlordiazepoxide
 - Other _____
 - None
 - Comments and/or clarification _____
- Clonazepam
 - Chlorazepate
 - Diazepam
 - Lorazepam
 - Oxazepam
 - Prazepam
 - Imipramine
 - Mirtazapine
 - Vilazodone
 - Vortioxetine
 - Quetiapine
 - Tiagabine
 - Hydroxyzine

What other medication(s) /intervention(s) did you try in your patient(s) for bipolar disorder before/ in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Aripiprazole
 - Asenapine
 - Olanzapine
 - Quetiapine
 - Risperidone
 - Ziprasidone
 - Lithium
 - Divalproex
 - Valproate
 - Lamotrigine
 - Carbamazepine
 - Other _____
 - Comments and/or clarification _____
- Haloperidol
 - Clozapine
 - Electroconvulsive therapy
 - Ketamine
 - Psychotherapy
 - Allopurinol
 - Tamoxifen
 - Paliperidone
 - Lorazepam
 - None

What other medication(s) /intervention(s) did you try in your patient(s) for alcohol withdrawal or dependence before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Thiamine
 - Folate
 - Multivitamin
 - Isotonic saline with 5% dextrose
 - Diazepam
 - Lorazepam
 - Chlordiazepoxide
 - Oxazepam
 - Other _____
 - Comments and/or clarification _____
- Phenobarbital
 - Dexmedetomidine
 - Propofol
 - Carbamazepine
 - Levetiracetam
 - Clonidine
 - None

What other medication(s) and/or interventions did you try in your patient(s) for Brachioradial pruritus before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Topical capsaicin 0.025% cream
- Topical 1% menthol
- Amitriptyline
- Lidocaine
- Pregabalin
- Ketoprofen
- Lamotrigine
- Cervical spine manipulation
- Surgery
- None
- Other _____
- Comments and/or clarification _____

What other medication(s) and/or interventions did you try in your patient(s) for chronic cough before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Brompheniramine
- Pseudoephedrine
- Chlorpheniramine
- Clemastine
- Cetirizine
- Fexofenadine
- Loratadine
- Intranasal azelastine
- Intranasal ipratropium bromide
- Intranasal glucocorticoid
- Inhaled budesonide
- Oral leukotriene receptor antagonist
- Dextromethorphan
- Other _____
- Comments and/or clarification _____
- Codeine
- Morphine
- Pregabalin
- Benzonatate
- Guaifenesin
- Thalidomide
- Nebulized lidocaine
- Breathing exercises
- Speech therapy
- Cough suppression techniques
- None

What other medication(s) and/or interventions did you try in your patient(s) for Fibromyalgia before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Exercise
- Amitriptyline
- Duloxetine
- Pregabalin
- Milnacipran
- Physical therapy
- Cognitive Behavioral Therapy
- Other _____
- Comments and/or clarification _____
- Tai chi
- Yoga
- Cyclobenzaprine
- Desipramine
- Venlafaxine
- None

What other medication(s) and/or interventions did you try in your patient(s) for hiccups before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Valsalva maneuver/Vagal stimulation
- Chlorpromazine
- Metoclopramide
- Baclofen
- Phenytoin
- Pregabalin
- Carbamazepine
- Amitriptyline
- Methylphenidate
- Quinidine
- Other _____
- Comments and/or clarification _____
- Nefopam
- Olanzapine
- Marijuana
- Amantadine
- 2% lidocaine solution
- Acupuncture
- Hypnosis
- Phrenic nerve block
- Implantable vagus nerve stimulator
- None

What other medication(s) and/or interventions did you try in your patient(s) for postoperative pain before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Morphine
- Hydromorphone
- Fentanyl
- Sufentanil
- Alfentanil
- Remifentanil
- Meperidine
- Ketamine
- Lidocaine
- Magnesium
- IV acetaminophen
- Ketorolac
- Ibuprofen
- Diclofenac
- Other _____
- Comments and/or clarification _____
- Bupivacaine
- Ropivacaine
- Ketamine
- Neostigmine
- Clonidine
- Celecoxib
- Etoricoxib
- Parecoxib
- Dexmedetomidine
- Pregabalin
- Tramadol
- None

What other medication(s) and/or interventions did you try in your patient(s) for uremic pruritus before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Increasing dose of dialysis
- Vitamin D derivatives
- Calcimimetics
- Parathyroidectomy
- Glycerol/Paraffin Emollient
- Pramoxine
- Capsaicin
- Cromolyn sodium
- Pregabalin
- Hydroxyzine
- Diphenhydramine
- Loratadine
- Ketotifen
- Ondansetron
- Doxepin
- Sertraline
- Ultraviolet B phototherapy
- Other _____
- Comments and/or clarification _____
- Naltrexone
- Intranasal butorphanol
- Nalbuphine
- Omega-3 fatty acid
- Omega-6 fatty acid
- Turmeric
- Zinc
- Activated charcoal
- Cholestyramine
- Nicergolin
- Thalidomide
- Ketotifen
- Sericin cream
- Endocannabinoids
- None

What other medication(s) and/or interventions did you try in your patient(s) for Neuropathic pain before/in addition to prescribing gabapentin? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Neuromodulation
 - Pregabalin
 - Capsaicin
 - Lidocaine
 - Duloxetine
 - Venlafaxine
 - Amitriptyline
 - Nortriptyline
 - Valproic acid
 - Tramadol
 - Other _____
 - Comments and/or clarification _____
- Opioid
 - Dextromorphan
 - Tizanidine
 - Baclofen
 - Botulinum toxin injection
 - Intrathecal ziconodine
 - Carbamazepine
 - Oxcarbazepine
 - None

What other medication(s) and/or interventions did you try in your patient(s) for this indication before/in addition to prescribing gabapentin (please specify the indication)? In the comment box, please describe your experience with using gabapentin for this indication. Is there a particular patient profile that appears to respond better to gabapentin? Any other notable factors that you consider?

- Other medications/interventions tried _____
- Comments and/or clarification _____

Why did you choose to prescribe gabapentin for this (these) indication(s)?

- Rationale _____

Have you successfully weaned any patients off of gabapentin?

- Yes
- No
- Comments and/or clarification _____

Why were they weaned off of gabapentin?

- Reason _____

If a patient had a history of substance use disorder, would it influence your decision to prescribe gabapentin? If so, what substances would influence your decision?

- Yes, I would be MORE likely to prescribe gabapentin
- Yes, I would be LESS likely to prescribe gabapentin
- No to both
- Other _____
- Comments and/or clarification _____

If a patient had a history of opioid use disorder, would it influence your decision to prescribe gabapentin?

- Yes, I would be MORE likely to prescribe gabapentin
- Yes, I would be LESS likely to prescribe gabapentin
- No to both
- Other _____
- Comments and/or clarification _____

If one of your patients were taking opioids, would it influence your decision to prescribe gabapentin?

- Yes, I would be MORE likely to prescribe gabapentin
- Yes, I would be LESS likely to prescribe gabapentin
- No
- Other _____
- Comments and/or clarification _____

If gabapentin became a controlled substance, would it affect your prescribing practices of the medication? (For physicians in Kentucky, has gabapentin becoming a controlled substance last July affected your prescribing practices of the medication?)

- Yes
 - No
 - Other _____
 - Comments and/or clarification _____
-

How many of your patients have come in for an overdose or intoxication in the past 3 months? (If it's easier, type in the percentage of your patients that came in for an overdose or intoxication in the past 3 months)

- Number of patients in the past 3 months: _____
- Percentage of patients in the past 3 months: _____

What substances have been positive on urine toxicology (and specific screens), if performed?

- Not performed
- Amphetamine
- Barbiturates
- Benzodiazepines
- Cannabinoids
- Cocaine
- Methadone
- Opiates
- Oxycodone
- Phencyclidine
- Acetaminophen
- Salicylates
- Ethanol

Of the patients seen for an overdose or intoxication, what percentage of patients report being on gabapentin?

- Percentage: _____
- Comments and/or clarification _____

Of the patients seen for an overdose or intoxication, what percentage of patients report being prescribed gabapentin?

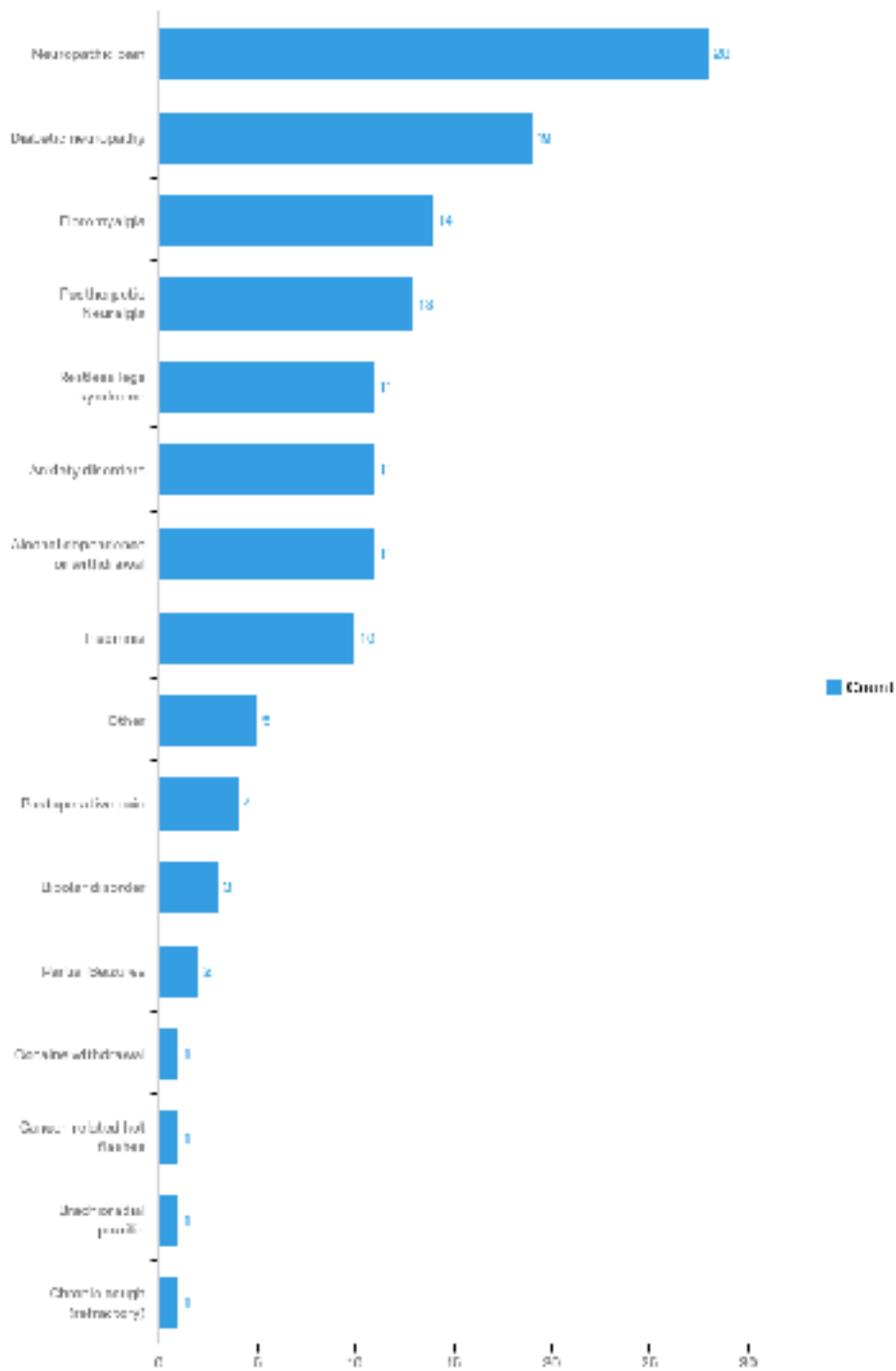
- Percentage: _____
- Comments and/or clarification _____

Do you think gabapentin is leading to increased overdoses and/or intoxications?

- Yes
- No
- Comments and/or clarification _____

Appendix B

For which of the following clinical indications have you prescribed gabapentin?



Appendix C

Side Effects

	Gabapentin	Pregabalin	Duloxetine	Venlafaxine	Amitriptyline	Lorazepam	Citalopram	Tramadol
CARDIOVASCULAR								
Atrioventricular conduction disturbance, arrhythmia, heart block	<1%	<1%	<1%	<1%	Frequency not defined.	≤1%	<1%	?
Cardiomyopathy	?	?	<1%	?	Rare	?	?	?
Flushing	?	?	3%	?	?	?	?	8% to 16%
Hypotension	?	2%	?	<2%	?	≤2%	≥1%	<1%
Myocardial infarction	<1%	?	<1%	?	Frequency not defined.	?	<1%	<1%
Orthostatic hypotension	?	<1%	<1%	<2%	Frequency not defined.	?	≥1%	2% to 5%
Peripheral edema	2% to 8%	4% to 16%	?	?	?	?	<1%	1% to <5%
Prolonged QT interval on ECG	?	Frequency not defined	?	<1%	?	?	2%	?
Stroke	<1%	?	?	?	Frequency not defined.	?	<1%	?
Syncope	?	?	<1%	<2%	Frequency not defined.	?	<1%	<1%
NEUROLOGIC & PSYCHIATRIC								
Abnormal gait	2%	1% to 8%	<1%	0	?	<1%	<1%	<1%
Abnormality in thinking	2% to 3%; children 2%	1% to 6%	<1%	0	Frequency not defined.	<1%	?	<1%
Ataxia	1% to 13%	2% to 9%	?	<1%	Frequency not defined.	<1%	<1%	1% to <5%

Side Effects

CNS stimulation	?	?	?	?	Frequency not defined.	Frequency not defined.	?	7% to 14%
Coma	?	<1%	?	?	Frequency not defined.	≤1%	?	?
Delusions	?	<1%	?	?	Frequency not defined.	?	<1%	<1%
Dizziness	17% to 28%; children 3%;	3% to 45%	8% to 9%	16%	Frequency not defined.	≤7%	?	10% to 33%
Drowsiness	19% to 21%; children 8%;	≤36%	9% to 11%; dose related	15%	Frequency not defined.	2% to 4%	18%; dose related	7% to 25%
Emotional lability	children 4% to 6%	?	<1%	?	?	?	<1%	?
Fatigue	11%; children 3%	4% to 11%	7% to 11%; dose related	<1%	Frequency not defined.	Frequency not defined.	5%; dose related	2%
Hallucinations	?	<1%	<1%	<2%	Frequency not defined.	<1%	<1%	<1%
Headache	children and adolescents >2%	2% to 14%	13% to 14%	<1%	Frequency not defined.	1%	Migraine ≥1%	4% to 32%
Hostility	children 5% to 8%	<1%	<1%	?	?	Frequency not defined.	<1-3%	?
Hyperkinesia (restlessness and hyperactivity)	children 3% to 5%	<1%	?	?	Frequency not defined.	<1%	<1%	1% to <5%
Insomnia	?	4%	7% to 10%; dose related	18%	Frequency not defined.	?	15%; dose related	2% to 11%
Seizures	?	?	<1%	<2%	Frequency not defined.	<1%	<1%	<1%
Tremor	7%	1% to 3%	2% to 3%; dose related	5%	Frequency not defined.	<1%	8%	1% to <5%
DERMATOLOGIC								

Side Effects

Rash	1%	<1%	<1%	<2%	Frequency not defined.	Frequency not defined.	≥1%	1% to <5%
Diaphoresis	?	?	6%	11%	Frequency not defined.	?	11%; dose related	2% to 9%
Pruritus	1%	≥1%	≥1%	<2%	Frequency not defined.	?	≥1%	3% to 12%
Skin photosensitivity	?	<1%	?	<2%	Frequency not defined.	?	<1%	?
GASTROINTESTINAL								
Abdominal pain	3%	≥1%	children and adolescents: 13%, adults: 5%	?	?	?	3%	1% to <5%
Constipation	1% to 4%	3% to 10%	9% to 10%; dose related	9%	Paralytic ileum: Frequency not defined.	?	?	9% to 46%
Nausea	3% to 4%; children 8%	3% to 5%	18% to 23%	30%	Frequency not defined.	<1%	21%	15% to 40%
Vomiting	3% to 4%; children 8%	1% to 3%	children and adolescents: 9%; adults: 3% to 4%	4%	Frequency not defined.	<1%	4%	5% to 17%
Xerostomia	2% to 5%;	≤15%	adults: 11% to 14%; dose related, children and adolescents: 2%	15%	Frequency not defined.	?	20%	3% to 13%
GENITOURINARY								
Ejaculatory disorder	<1%	≤1%	2%	≤10%	?	?	6%	?

Side Effects

Impotence	2%	≥1%	?	5%	Frequency not defined.	?	3%; dose related	?
ENDOCRINE & METABOLIC								
Decreased libido	<1%	?	3%	5%	Frequency not defined.	?	1% to 4%	<1%
Weight loss	?	?	children and adolescents: 14%, adults: ≥1%	<2%	Frequency not defined.	?	≥1%	1% to <5%
Weight gain	?	2% to 14%	≥1%	<2%	Frequency not defined.	?	≥1%	?
NEUROMUSCULAR & SKELETAL								
Weakness	6%	4% to 7%	≤7% to ≤11%; dose related	13%	Frequency not defined.	<4%	?	4% to 12%
HEMATOLOGIC								
Bone marrow depression	leukopenia (1%)	Thrombocytopenia (3%)	?	?	Frequency not defined.	?	?	?
INFECTION								
Infection	viral: children 11%	6% to 8%	?	?	?	<1%	5%	1% to <5%
OPHTHALMIC								
Visual field loss	<1%	13%		?	?	?		?
Blurred vision	3% to 4%	≤12%	≥1% to 3%	?	Frequency not defined.	Frequency not defined.		1% to <5%

Drug Interactions

	Gabapentin	Pregabalin	Amitriptyline	Duloxetine	Venlafaxine	Citalopram	Lorazepam	Tramadol
Abiraterone Acetate:			D	C	D			
Acidinium:			X					
Antiplatelet Medications				C	C	C		
Alcohol	C	C	C	D	D	D	C	
Alpha-/Beta-Agonists:			D	D	D			
Alpha2-Agonists			D	C	C			
Alvimopan								D
Amifampridine						X		C
Amphetamines			C	C				C
Antiemetics (5HT3 Antagonists):			C	C	C	C		C
Anti-Parkinson Agents (Monoamine Oxidase Inhibitor)								D
Antipsychotic Agents:			C	C	C	C		
Antacids	D							
Asunaprevir			D		D			
Azelastine (Nasal):	X	X	X				X	X
Benznidazole:							X	
Blonanserin:	D	D	D				D	D
Bromopride:	C		X	X	X	X		C
Bromperidol:	X	X	X				X	X
Buprenorphine:	D	D	D			C	D	
Bupropion			D			D		C
Buspiron						D		
Cannabis:	C	C	C	C			C	C

Drug Interactions

	Gabapentin	Pregabalin	Amitriptyline	Duloxetine	Venlafaxine	Citalopram	Lorazepam	Tramadol
Carbamazepine								X
Chlormethiazole	D	D	D				D	D
Cimetidine						D		
Cimetropium			D					
Cisapride			X					
Citalopram			D					
Clozapine				C			D	
CNS Depressants:	C	C	C			C	C	D
Codeine				C				
Conivaptan:				X		X		
CYP1A2 Inducers (Moderate): Cyproterone,				C				
CYP1A2 Inhibitors (Moderate): Deferasirox,				C				
CYP1A2 Inhibitors (Strong):				X				
CYP2C19 Inducers (Strong)						D		
CYP2C19 Inhibitors (Moderate)						D		
CYP2D6 Inhibitors (Strong):			D	C	D			C
CYP2D6 Substrates (High risk with Inhibitors):				C				
CYP3A4 Inducers (Moderate): Fosaprepitant					C	C		C
CYP3A4 Inducers (Strong):					D	D		D
CYP3A4 Inhibitors (Moderate):					C	C		

Drug Interactions

	Gabapentin	Pregabalin	Amitriptyline	Duloxetine	Venlafaxine	Citalopram	Lorazepam	Tramadol
CYP3A4 Inhibitors (Strong): Dabrafenib					D	D		D
Dapoxetine:			X	X	X	X		
Dextromethorphan						D		
Dosulepin						X		
DOXOrubicin (Conventional):				D				
Dronedarone			X					
Dropriodol:	D	D	D				D	D
Eliglustat:				D				
Eluxadoline			X					X
Enzalutamide					D	D		D
Escitalopram:			D					
Fluconazole						X		
Flunitrazepam:	D	D	D				D	D
Fluoxetine			D					
Fluvoxamine			D					
Fusidic Acid (Systemic):					X	X		
Glycopyrrlate (Oral Inhalation)			X					
Herbs (Anticoagulant/ Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry)				D	D	D		
HYDROcodone:	D	D	D				D	D
Hydroxychloroquin e						X		
Idelalisib:					X	X		
Indapamide						D		

Drug Interactions

	Gabapentin	Pregabalin	Amitriptyline	Duloxetine	Venlafaxine	Citalopram	Lorazepam	Tramadol
Iobenguane I 123			X	X	X	X		
Iohexol			D					D
Iomeprol			D					D
Iopamidol			D					D
Ipratropium (Oral Inhalation)			X					
Levosulpiride			X					
Linezolid:			X	X	X	X		D
Lithium			D			D		
Macimorelin						X		
Magnesium Salts:	D	C	C				C	C
Mefloquine	D	D						
Methotrimeprazine :	D	D	D				D	D
Methylene Blue:			X	X	X	X		X
Metoclopramide:			D	D	D	D		C
Metoprolol:				D				
Mexiletine						D		
Mifepristone			D		D	X		
Mitotane						D		D
Mizolastine						X		
Moclobemide								X
Monoamine Oxidase Inhibitors:			X	X	X			
Nalmefene								D
Naltrexone								D
Opioid Analgesics:	D	D	D	C	C	C	D	X
Orphenadrine:	X	X	X				X	X

Drug Interactions

	Gabapentin	Pregabalin	Amitriptyline	Duloxetine	Venlafaxine	Citalopram	Lorazepam	Tramadol
Oxememazine:	X	X	X				X	X
OxyCODONE:	D	D	D				D	D
Panobinostat:			D		D			
Paraldehyde	X	X	X				X	X
PARoxetine:			D	D				
Perampanel:	D	D	D				D	D
Perhexiline:			C	D		C		
Pimozide:						X		
Pitolisant			C		D	D		D
Potassium Chloride			X					
Potassium Citrate			X					
Pramlintide			D					
Probenecid:							D	
Probucol:						X		
Promazine:						X		
QTc-Prolonging Agents (Highest Risk):			D		D	X		
Quinidine			D					
Secretin			D					
Sertraline			D					
Sodium Oxybate:	D	D	D				D	D
St John's Wort:			D		D	D		D
Stiripentol:					D	D		
Suvorexant:	D	D	D				D	D
Tamoxifen:				D				
Tapentadol:	D	D	D				D	D

Drug Interactions

	Gabapentin	Pregabalin	Amitriptyline	Duloxetine	Venlafaxine	Citalopram	Lorazepam	Tramadol
Terbinafine (Systemic)			D					
Thalidomide	X	X	X				X	X
Theophylline Derivatives							D	
Thioridazine:				X				
Tiotropium			X					
Trazodone					D			
Tricyclic Antidepressants						D		
Tryptophan						X		
Umeclidinium			X					
Urokinase:				X	X	X		
Valproate Products							D	
Vemurafenib				D				
Vinflunine						X		
Zolpidem:	D	D	D				D	D

Disease-related Concerns

	Gabapentin	Pregabalin	Duloxetine	Venlafaxine	Amitriptyline	Lorazepam	Citalopram	Tramadol
Cardiovascular disease		Yes		Yes	Yes		Yes	
CNS Depression/Coma								Yes
Diabetes			Yes		Yes			
Head trauma								Yes
Hepatic impairment			Yes	Yes	Yes	Yes	Yes	Yes
HTN			Yes	Yes				
Mania/Psychosis			Yes	Yes	Yes		Yes	Yes
Prostatic hyperplasia/urinary stricture								Yes
Psychiatric disorders						Yes		Yes
Renal impairment:	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Respiratory disease						Yes		Yes

Disease-related Concerns

	Gabapentin	Pregabalin	Duloxetine	Venlafaxine	Amitriptyline	Lorazepam	Citalopram	Tramadol
Seizure disorders			Yes	Yes	Yes		Yes	Yes
Sleep-disordered breathing								Yes
Substance Use		Yes				Yes		Yes
Thyroid Dysfunction								Yes
Withdrawal:	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes