2016

Exploration of the Misuse, Abuse, and Diversion of Gabapentin

Rachel Vickers Smith
University of Kentucky, rachelannvickers@gmail.com
Author ORCID Identifier:
http://orcid.org/0000-0002-7224-8916
Digital Object Identifier: https://doi.org/10.13023/ETD.2016.517

STUDENT AGREEMENT:

I represent that my thesis or dissertation and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained needed written permission statement(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine) which will be submitted to UKnowledge as Additional File.

I hereby grant to The University of Kentucky and its agents the irrevocable, non-exclusive, and royalty-free license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless an embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student's thesis including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Rachel Vickers Smith, Student

Dr. Jennifer R. Havens, Major Professor

Dr. Steven Browning, Director of Graduate Studies

EXPLORATION OF THE MISUSE, ABUSE, AND DIVERSION OF GABAPENTIN

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Public Health
at the University of Kentucky

By

Rachel Vickers Smith

Lexington, Kentucky

Director: Dr. Jennifer R. Havens, Associate Professor of Behavioral Science

Lexington, Kentucky

2016

ABSTRACT OF DISSERTATION

EXPLORATION OF THE MISUSE, ABUSE, AND DIVERSION OF GABAPENTIN

Gabapentin is currently approved by the Food and Drug Administration (FDA) as an adjunctive anti-convulsant and an analgesic for post-herpetic neuralgia. Though gabapentin was initially presumed to have limited or no abuse potential, which may have contributed to its widespread off-label prescribing, there have been increasing anecdotal and published reports of its misuse by substance abusers in the community and penal system. However, to date, there has been limited systematic evaluation of the scope and risk of gabapentin misuse and its associated effects. This dissertation assesses the etiology and prevalence of gabapentin misuse, abuse, and diversion in a multi-faceted approach, namely by the individual, ecological, and pharmacoepidemiological factors associated with this phenomenon. Due to the importance of conducting theory-driven epidemiological research, this dissertation uses an adaptation of the Concurrent Triangulation Mixed Method Multilevel Theoretical Model to guide the study. Through qualitative analysis of focus group data in an existing cohort of opioid users, a systematic review of peer-reviewed published literature, and a pharmacovigilance assessment of adverse events reported to the FDA, this dissertation describes the present state of gabapentin misuse. Findings are important for providers and may help inform policy to establish for whom prescription of gabapentin is most appropriate.

KEYWORDS: gabapentin, substance abuse, theory-driven epidemiological research, mixed method analysis, prescription drug misuse

Rachel Vickers Smith
Student Signature

November 30, 2016
Date

EXPLORATION OF THE MISUSE, ABUSE, AND DIVERSION OF GABAPENTIN

By

Rachel Vickers Smith

Jennifer R. Havens, PhD
Director of Dissertation

Steven R. Browning, PhD
Director of Graduate Studies

November 30, 2016
Date

Dedicated to Arlene, Larry, Lajeania, and Shane

ACKNOWLEDGEMENTS

First I want to thank my committee members for their continued support and encouragement of this project. Their input has made these chapters substantially more thoughtful and impactful. A special thank you to my mentor, Dr. Jennifer Havens – thank you for taking me on as a new doctoral student. I have learned so much being a part of your study team. Thank you to Dr. April Young, who has been a helpful guide through my entire doctoral study. Thank you to Dr. Richard Charnigo – you have constantly encouraged me from the start of my Master's program many years ago. Thank you for pushing me and for serving as a voice of honesty and motivation. To Drs. Lofwall and Walsh - it has been a pleasure to work alongside you over the last few years. Thank you for sharing your knowledge and expertise and helping to make this project the best it can be.

I owe a debt of gratitude to the fellow members of my cohort. They have been a huge support system from the beginning and I could not have made it this far without them. Thank you also for fantastic lunches, various celebrations, and watching UK games together – your friendship has been such a gift.

Finally, to my family – thank you for setting an example of working hard, making goals, and achieving them. This success is not mine alone, but a culmination of many who have invested in me, most of all my parents and husband. I love you dearly.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE

Introduction

Gabapentin was approved in 1993 by the Food and Drug Administration (FDA) for the treatment of epilepsy as an adjunct to anti-convulsant therapy and in 2004 was approved as an analgesic for post-herpetic neuralgia.[1] Gabapentin is an analog of GABA,[2] however, it does not bind to GABA receptors (A or B), but it can increase GABA and can decrease glutamate concentrations.[3,4] One of its speculated analgesic mechanisms of action is that gabapentin may reduce the release of pain-related peptides and may decrease opioid-induced hyperalgesia.[5] Because its exact mechanism of action is unclear and has been presumed to have no abuse potential, gabapentin has been prescribed prolifically off-label for a vast array of disorders, including insomnia, drug and alcohol addiction, anxiety, bipolar disorder, borderline personality disorder, menopausal conditions, vertigo, pruritic disorders, and migraines. In fact, off-label use of gabapentin has been estimated to range from 83 to 95% of all its use,[6,7] which is estimated to account for over 90% of its sales.[1] Due to illegal marketing (i.e., promoting off-label uses) of gabapentin, Pfizer was fined $420 million after it was acquired from Warner-Lambert.[8] As a result, it has been relatively easy to access gabapentin by prescription, especially since it has been historically opined that gabapentin has *no* abuse potential.[9-13] Compounded by gabapentin's modest, if not free, cost,[14] such factors have enabled gabapentin to flood the market and it has been referred to among the drug using population as "a cheap man's high" (personal communication). In a seminal manuscript published in *American Journal of Psychiatry*, Smith et al. reported a near 3000% increase in the

use of gabapentin "to get high" among a cohort of 503 non-medical prescription drug users in Appalachian Kentucky from 2008 to 2014.[15] Despite these significant findings, there has yet to be a systematic assessment of gabapentin misuse/abuse in the general population, nor within higher-risk subpopulations (e.g., substance abuse groups). Further, gabapentin is not controlled under the Controlled Substance Act. Notably, its close structural relative, pregabalin, was approved *after* gabapentin and is considered a Schedule V drug, meaning that it should be considered to be at risk for abuse potential.[16] There is data suggesting that pregabalin has euphoric and sedative properties similar to other frequently abused substances, that it can produce dependence, and that it can induce withdrawal symptoms when discontinued.[17] As such, because gabapentin and pregabalin presumably have a similar mechanism of action,[18] it is critical to systematically study the abuse potential of gabapentin.

The present study proposes a multi-faceted exploratory evaluation of gabapentin's abuse potential through the novel application of a peer-reviewed theoretical model that has been previously used in other non-drug related studies.[19-22] Due to the increasing importance of conducting *theory-driven* epidemiological studies,[23,24] we will use an adaptation of the Concurrent Triangulation Mixed Method Multilevel Theoretical Model[25] (Figure 1.1) to inform the following chapters. It is important to note that this dissertation is focused on the misuse, abuse, and diversion of gabapentin, however, the methods described herein are designed to be applied to any currently used unscheduled drug with unclear abuse potential (e.g., quetiapine).

Throughout the dissertation, the terms misuse, abuse, dependence, and diversion will be used repeatedly, thus they are defined here. *Misuse* is defined as the use of a drug in a manner or for a purpose other than indicated, including, but not limited to, taking another person's medication, unprescribed or non-recommended route of administration, or a higher dosage than prescribed;[26] thus, missing prescribed doses or dose reduction is not included in our definition. *Abuse* consists of persistent use of a drug despite negative consequences.[26] *Dependence* refers to the physical and psychological elements associated with abuse, which include compulsion, withdrawal, and tolerance.[26] *Diversion* is defined as the unauthorized selling or sharing of prescription medications, which can be either intentional (e.g., selling personal medication to someone without a prescription for that particular drug) or unintentional (e.g., theft). Diversion can occur at any point along the drug manufacturing and delivery process, however, at the core of this definition is unlawful movement of licit and regulated pharmaceuticals to the illicit marketplace.[27,28]

Concurrent Triangulation Mixed Method Multilevel Theoretical Model

The proposed theoretical model (Figure 1.1) was first introduced by Tashakkori and Teddlie (2003).[25] The model can be broken down into 4 main components. First, triangulation refers to "obtaining different but complementary data on the same topic,"[29] with the goal of converging strengths from varying data types that simultaneously have non-overlapping weaknesses.[30,31] Second, the data from each aim will be collected and analyzed concurrently, implicitly meaning that findings from one aim will not influence how the other aims are conducted or analyzed.

Third, both quantitative (QUAN) and qualitative (QUAL) methods will be used throughout the proposed study, hence the mixed method portion of the model; Chapters 2 and 3 will use both QUAN and QUAL, while Chapter 4 will only use QUAN. Chapter 2 will merge QUAL and QUAN results during the interpretation stage, giving equal weight to each data type; likewise for Chapter 3. Upon completion of all 3 studies, the results will again be merged with equal weight to assess the abuse potential of gabapentin. Fourth, where the theoretical model uses levels of data, implying a hierarchy, it was slightly adapted to the use of "domains," or "facets" as we refer to them, since no nesting was present in our data. Chapters 2, 3, and 4 describe the multi-faceted component of theoretical model corresponding to the individual, ecological, and pharmacoepidemiological facets, respectively.

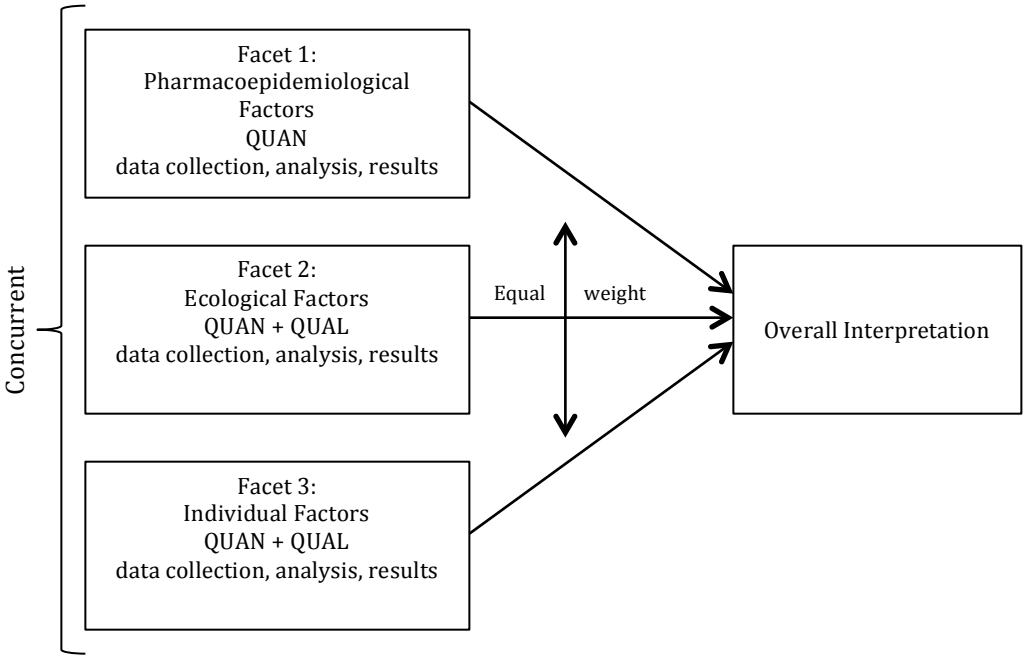
Each of the proceeding chapters is dedicated to addressing the following aims:

Aim 1/Chapter 2. To describe gabapentin misuse at the individual level among existing cohorts of drug users in Appalachia.

Aim 2/Chapter 3. To estimate the prevalence and effects of, motivations behind, and risk factors for gabapentin misuse, abuse, and diversion ecologically.

Aim 3/Chapter 4. To evaluate gabapentin misuse and abuse in the FDA Adverse Event Reporting System (FAERS) using traditional and innovative pharmacovigilance signal measures.

Figure 1.1. Visual depiction of the modified Concurrent Triangulation Mixed Method Multilevel Model.



QUAN: quantitative data; QUAL: qualitative data.

CHAPTER TWO

"A cheap man's high": a qualitative analysis of gabapentin misuse and diversion among drug users

Introduction

Long perceived as a drug with no abuse potential,[9,10,12] evidence has begun to emerge to point to significant abuse potential for gabapentin.[15,32] Limited research has provided a telescopic snapshot of this phenomenon, with a prevalence approximation of 1% in the general population[33] and a much higher estimation of 15% to 22% in substance misusing populations.[15,32,34] In the United States, gabapentin is currently not controlled by the Federal Drug Enforcement Administration (DEA), however, its close structural relative, pregabalin, has been classified as a Schedule V drug, meaning that it has abuse potential. While it appears that much of the misuse is linked to achieving desirable effects (e.g., dissociation, euphoria, potentiate effects of drug treatment pharmacotherapies),[32,35,36] gabapentin has also been linked with impaired driving[37] and implicated in 1% of drug related deaths in Scotland,[32] highlighting the potential public health concern with gabapentin misuse. A recent review of international gabapentin misuse and diversion summarized current knowledge on this issue[38] and highlighted the many gaps in our understanding, such as how and why individuals initiate gabapentin misuse and what are the factors influencing continued misuse.

The purpose of the present qualitative study was to explore such questions in the context of two samples of individuals who primarily use prescription opioids non-medically that were engaging in gabapentin misuse. A recent study from one of

the samples noted a nearly 3000% increase from 2008 to 2014 in gabapentin misuse for the explicit purpose of getting "high," and though many received gabapentin from a prescriber, over a third obtained it through drug dealers indicating its street value.[15] Findings will expand the current body of literature on the practice of intentional gabapentin misuse and provide necessary information for prescribing providers and regulatory policy.

Methods

This study was derived from longitudinal findings from two ongoing cohort studies in Appalachian Kentucky, described in detail elsewhere.[39,40] Briefly, the first is a cohort of 503 active male and female drug users participating in an ongoing community-based study of social networks and HIV risk in Appalachia.[39] The second is a cohort of 400 rural Appalachian women serving time in jail who agreed to participate in an ongoing study examining the relationship of drug use and HIV/HCV risk behaviors.[40] Data from both studies independently noted a rapid increase in the unintended/non-medical use of gabapentin among their participants.[15] Thus, the principal investigators of each cohort (JRH and MST) and the first author recognized the necessity of gathering qualitative data to gain perspective into this unexpected rise in gabapentin use. The present study presents the qualitative findings from four focus groups conducted among cohort participants who agreed to participate. The University of Kentucky Institutional Review Board approved the protocol. All participants agreed to be audio recorded and were compensated for their time.

Participants

Individuals were recruited from two ongoing cohorts of recently active drug users in Appalachian Kentucky to participate in a focus group session. Eligible participants were those individuals who reported gabapentin use at their most recent follow-up study visit. Research assistants from both cohort studies intentionally selected individuals to approach about participating in the focus groups whom they felt would be open about sharing their experiences. A total of 33 subjects participated in the four focus group sessions.

Data collection

Focus groups were moderated by the first author using a semi-structured list of questions and follow-up probes. Questions were developed by the authors (RVS, AMY, MRL, MST, JRH) drawing on the current published and anecdotal knowledge regarding experiences of gabapentin misuse and were intended to explore this further. Each session lasted between 30 and 60 minutes and was digitally audio-recorded. Data collection was continued until saturation was met, which was after completion of 4 focus groups. Focus groups were conducted from March to September 2015.

Analysis

Descriptive statistics were derived from the last follow-up visit in the cohort studies. Comparisons were made using Fisher's exact tests and independent samples t-tests. The audio recording of each focus group was transcribed verbatim by the authors (RVS and AQ). Two authors were designated as readers (RVS and EMB); each of whom independently created a list of codes based on the semi-structured focus group questions using a directed content analysis approach.[41] The

readers convened and discussed these lists and derived the initial draft of the codebook, which included codes, sub-codes, definitions, and exemplars. The first transcript was independently coded by each reader. Afterward, the readers again convened and reviewed the entire transcript together, discussing and coming to a consensus on discrepant coding situations, addressing the need for additional codes in the codebook, and then redefining existing codes. The first draft of the codebook was subsequently revised and was used to code the next transcript as well as re-coding the first transcript. This iterative process of reading, coding, resolving discrepant assignments, revising the codebook, and re-coding previously coded transcripts was continued until all the data was coded. SPSS version 24 (IBM Corp., Armonk, New York) was used to analyze the quantitative data and MAXQDA software (VERBI GmbH, Berlin, Germany) was used to analyze the qualitative data. Several quotes presented herein were slightly grammatically edited for readability.

Results

Participants in the focus groups were in their mid-thirties, on average, and the majority was unemployed (Table 2.1). Over half of the focus group subjects from both cohorts reported recent (i.e., past 30 day) nonmedical use of prescription opioids (jail group: 73%; community group: 67%), though individuals from the jail cohort reported less drug use than the community group for all other drug types except cocaine (18.2 vs. 4.8%, respectively). Focus group participants were more likely to report recent nonmedical prescription opioid use compared to their respective cohorts (jail cohort: 73 vs. 36%, $p = .02$; community cohort: 67 vs. 41%, $p = .02$); there were no significant differences for other types of drugs. Individuals

who participated in the focus groups were not significantly different from other recent gabapentin users in their respective cohort study with regard to demographics and substance use. Based on information gathered in the focus group sessions, participants varied in their drug of abuse preference; several indicated opioids, others said cocaine, while still others noted they preferred gabapentin.

Four main themes, with subthemes, emerged in the qualitative analysis: (1) initiation, (2) motivation for continued use, (3) prominence of gabapentin, and (4) perceptions of providers' behaviors.

Initiation

Time since initiation

The majority of responses expressed introduction to gabapentin more than ten years ago. Several reported initiation between 5-10 years ago and few initiated within the past two years.

First source

Prescription from a doctor for indications such as pain, anxiety, and to help with opioid detox was the most common initial source of gabapentin. As described by one individual: 'That's how everybody got introduced to Neurontin, it's through doctors, because that's all they'd write anybody.' Several others reported a family member or friend giving gabapentin to them for the first time. One woman described her initiation experience: 'Well, I couldn't sleep like I said. My mother-in-law gave them to me [because] I couldn't sleep – I was withdrawing on oxycodone back then and couldn't sleep. She give me a couple and I was out like a light, slept the whole night. And I love them after that.' One individual noted trying gabapentin

in the penal system: 'Well I started doing it in federal prison [in] 2003, and been doing it ever since.'

Reasons for first use

Primarily for early initiators (e.g., more than 5 years ago), many started taking gabapentin because their doctor prescribed it to address their presenting symptoms, as this woman expressed: 'I was put on it by a psychiatrist for anxiety in 2005 … that's what they prescribed it to me to begin with and I've been on it ever since … but that is legitimately how it started, but then there ain't no legitimate reason to abuse it, you know, and I was abusing it.'

Another common response was that people began trying gabapentin due to word of mouth. As one woman put it: 'I mean it's like more and more and more … as years went on, people just started [gabapentin]. You'd hear other people talking about taking them, and I was like 'well, let me try it' [and it] went from there.' One man said, '[I took gabapentin] on account of my cousin, he said they was good.'

Physical experience

Initial experiences with gabapentin included a range of effects such as muscle relaxation, pain reduction, hallucination, sleep induction, feeling drunk, and feeling 'high.' One woman recounting her first experience said, 'I got it for lupus, but I had never tried it. My mom actually gave it to me first, before I had it prescribed to me, and made me high as all get out. It did, and I was like, 'yes!' {laughs} I didn't know anything about it! It was new, know what I mean?' Another woman described her initiation: 'I actually started taking them to get off of drugs because I was really in

pain and they did help my pain. Like she said they relax your muscles and your bones - that's the way I got off the opiates.'

Motivation for continued use

There were several reasons for continued use of gabapentin, though the primary reason could be explained by its pharmacodynamic effects. Participants talked about gabapentin saying that 'they make you feel so much better' and describing it as 'very helpful.' A common response was that gabapentin worked better for easing pain than opioids. Several others indicated the effectiveness of gabapentin in helping to withdraw from several substances such as cocaine, buprenorphine, and oxycodone. Though participants also noted they could still get 'high' from gabapentin. 'You can use them to get high on if you want to, ease pain, it's just all the above,' said one individual, and another describing her usage of gabapentin: 'It's just the way an addict takes them. If I want to get high off of them, then I'll get high off of them, but if I don't I won't.' Several participants likened a gabapentin high to one reminiscent of a 'shot of cocaine' or an opioid high. Other effects experienced included increased energy, increased appetite, a 'mellow' feeling, and 'nodding.'

There tended to be few negative effects associated with gabapentin use; one woman described gabapentin making her 'twitch' and several others indicated occasions where they felt like they were 'smothering' or 'couldn't move,' though these were not their typical experiences and these individuals did not elaborate on the circumstances surrounding those events (e.g., dose, concomitant substances). However, a considerable number of respondents did recount painful withdrawals

from gabapentin and described them as similar to, but not as long-lasting as, opioid or depressant (e.g., alcohol, alprazolam) withdrawals.

Participants highlighted the inexpensiveness of gabapentin for the purpose of getting high, which seemed to be a facilitator for its continued use. One participant said, 'That's a lot of reason is why people does them is because it's a cheap high,' and another noted that not only was it cheap, but nearly 'always available.'

Prominence of gabapentin – current and trends

Though many of respondents in the focus groups have known about and have been using gabapentin for many years, a common theme was noticing its rise in popularity in the community, particularly over the last two years. While the consensus was that it was generally easy to access gabapentin, there were also concerns about it being scarce at times as a result of using more than prescribed and sharing with others. To put the popularity of gabapentin in perspective, one individual said, 'They're actually harder to find than 30s [roxycodone] now,' a commonly preferred drug of abuse in the area.

Interestingly, several individuals observed that 'younger' drug users (i.e., adolescents) were choosing gabapentin. There was a sense that participants were feeling their access is threated by the gabapentin 'craze': 'And then … all these younger people are abusing [gabapentin] so now that puts us in a messed up situation' and others expressed concern about gabapentin becoming a scheduled drug, as one man stated, 'And that's why they [gonna] make them schedule[d]…cause everybody's getting them.'

Perceptions of providers' behaviors – helping versus barriers

There were mixed reports on individuals' experiences obtaining gabapentin from a provider (i.e., physician, pharmacist). While some said that they did not face any resistance in obtaining prescribed gabapentin from a provider, others reported believing that their providers made access to gabapentin more difficult. For instance, when asked if they thought doctors recognized that people were using gabapentin to get high, several participants responded 'no' and one said, 'I don't feel like they do because they're still writing them like crazy. That's the one thing that they will write.' Another participant reported easily getting a prescription for gabapentin: 'Yeah, all I done was walk in and said, 'Hey, I need some Neurontin.' They's like, 'What milligram?' I was like '800s.''

Conversely, other participants reported difficulty in getting gabapentin prescribed or getting a prescription filled, saying the doctors and pharmacies 'make a bigger deal out of [gabapentin] than what it is.' One woman said, 'Tell them that it worked for you before, and because of the Neurontin, gabapentin epidemic, they're calling it, they won't write them for you.' Another reported:

> 'I have been to doctor X and he give me everything under the sun, and I went there trying to get Neurontins. Did this, dealt with this man for six months, and he still would not come off with the Neurontin – not one.'

Still another woman described a recent pharmacy visit to pick up her gabapentin prescription:

> 'I went on a Saturday and I was like, 'I thought it was my day to get [gabapentin]' and the lady was like, 'you can come back Monday to get them.' Well, I went back Monday. 'Well I can't give them to you.' And I was like, 'no,

you told me to come back Monday.' I said, 'I can't be coming up here, coming to get my medicine.' And she said, 'well, ok. I'll go ahead and do it for you.' And then they give me my blood pressure medicine, too, and I said, 'man, hold up. I just got the blood pressure medicine last week' … I handed [the blood pressure medicine] back.'

Discussion

The current study aimed to help characterize and explain the observed recent rise in gabapentin misuse by conducting a qualitative analysis of focus group data among males and females who abuse drugs in rural Appalachia. This study explored constructs that influence or prohibit gabapentin misuse among Appalachian drug users.

The individuals participating in this study were more likely to report recent nonmedical prescription opioid use than their cohort counterparts that did not participate in the focus groups, though focus group participants were not different from their cohort counterparts that also reported gabapentin use. Others have also recently observed the correlation between opioid and gabapentin use.[15,32,34,42] There are a number of hypotheses as to why this association may occur such as common co-prescription of gabapentin with opioids for pain patients,[38] using gabapentin to potentiate the effects of opioid-use treatment to achieve a 'high,'[32] or user substitution of harder to access, more expensive prescription opioids for gabapentin.[42] These speculations would be well served by controlled experiments, particularly of pharmacological nature, to further explore the relationship between opioids and gabapentinoids.

Many participants reported initiating gabapentin after receiving a prescription from their doctor. Though it may be possible that some individuals were prescribed gabapentin for one of its two FDA-approved usages (i.e., adjunctive therapeutic for epilepsy or analgesic for post-herpetic neuralgia), it appears as though the majority were prescribed for an off-label indication (e.g., treatment of anxiety, non-herpetic pain, and drug withdrawal). Because of the consequences of the opioid epidemic, there have been large-scale efforts focused on reducing opioid prescribing. In the 2016 guidelines for chronic pain opioid prescribing produced by the Centers for Disease Control and Prevention (CDC), an entire section was dedicated to pharmacologic alternatives to opioids for pain management, in which gabapentin was recommended as a first-line treatment.[43] So, even though there are signals emerging that gabapentin may have abuse potential, it seems that, overall, policy makers and prescribers are unaware and under the impression it is safe to prescribe, particularly for neuropathic pain. Unfortunately, since gabapentin's market release in 1993, there have been no further experiments in the human laboratory to reassess and quantify its abuse liability, which is especially important among high-risk populations such as drug users. Because there is clear evidence (also echoed by focus group participants in the present study) that gabapentin has central nervous system and psychoactive effects,[15,32,36,38,44] and potential to alleviate opioid[45] and benzodiazepine[46] withdrawal, there is a discernible justification to examine whether or not gabapentin is appropriately labeled and controlled.

We also observed reports that younger people were misusing gabapentin. Due to the high saturation of gabapentin in the community as a result of liberal

prescribing practices, it would be incredibly easy for someone to access it, though demand seems to limit diverted access. This begs the question – are young drug users/adolescents initiating prescription drug abuse with gabapentin? Further, does use of gabapentin among this population lead to use of other, more harmful prescription or illicit drugs? Though these are merely questions to consider; the observation shared by several long-term drug users raises enough alarm to warrant investigation of gabapentin misuse among the younger population.

Several limitations exist in the present study. It is unclear the extent to which interpersonal dynamics influenced what was shared within the focus groups. Difficulty in analyzing such data can arise particularly when an individual dominated a session or when a normative view of gabapentin use was formed within the group.[47] However, these concerns were at least somewhat mitigated by highlighting diverse voices within the analysis. Further, we conducted multiple focus groups in different locations (both community and jail settings) and found the same themes emerging throughout, giving support for the reliability and validity of our findings. The study was conducted in rural Appalachian Kentucky among individuals already participating in research studies, thus generalizability may be limited, although it should be noted that this is one area of the country where signals of the impending prescription opioid epidemic first began. Additionally, the focus group members were people who were willing to speak about their experience and, therefore, may not be representative of all gabapentin users in the parent studies.

Despite limitations, this study provides a valuable in-depth look into the experience of gabapentin misuse within a sample that has the only hypothesized risk factor for it: a history of or current substance (i.e., opioid) abuse.[48,49] It is necessary for prescribers to understand how individuals begin and continue their misuse of gabapentin and to focus on prescribing only for those individuals for whom it is properly indicated. Our findings also underscore the necessity of more rigorous studies to elucidate the abuse potential of gabapentin, as well as a thoughtful consideration of its scheduling.

Table 2.1. Sociodemographic characteristics and drug use behaviors of focus group participants and their cohort counterparts.

	Jail cohort – FG (n=11)	Jail cohort – GBP users[a] (n=101)	Jail cohort[b] (n=393)	Community cohort – FG (n=21)[c]	Community cohort - GBP users[a] (n=157)	Community cohort[b] (n=361)
Sociodemographic characteristics						
Age – mean (SD)	35.3 (8.4)	35.5 (8.5)	34.3 (8.2)	32.1 (10.3)	39.3 (8.9)	38.1 (8.4)*
median (IQR)	35.0 (15.0)	34.0 (12.5)	33.0 (11.0)	39.0 (15.0)	39.0 (12.5)	37.0 (11.0)
Employment status						
Employed[d]	3 (27.3)	10 (10.0)	79 (20.1)	1 (4.8)	42 (26.7)*	115 (31.8)
Unemployed	7 (63.8)	68 (67.4)	271 (68.9)	13 (61.9)	69 (43.9)*	143 (39.6)
Recent drug use						
Alcohol to intoxication	2 (18.2)	17 (16.8)	37 (9.4)	21 (100)	156 (99.4)	358 (99.2)
Heroin	0 (0.0)	11 (10.9)	26 (6.6)	20 (95.2)	151 (96.8)	352 (97.8)
Prescription opioids	8 (72.7)	58 (57.4)	140 (35.6)*	14 (66.7)	85 (54.1)	148 (41.0)*
Legal buprenorphine	0 (0.0)	18 (17.8)	38 (9.7)	1 (4.8)	10 (6.4)	15 (4.2)
Illicit buprenorphine	1 (9.1)	46 (45.5)	93 (23.7)	3 (14.3)	49 (31.2)	67 (18.6)
Benzodiazepines	3 (27.3)	57 (56.4)	122 (31.0)	7 (33.3)	66 (42.0)	98 (27.1)
Cocaine	2 (18.2)	19 (18.8)	39 (9.9)	1 (4.8)	22 (14.0)	38 (10.5)
Methamphetamine	2 (18.2)	32 (31.7)	92 (23.4)	20 (95.2)	153 (98.1)	356 (98.9)
Marijuana	4 (36.4)	51 (50.5)	121 (30.8)	21 (100)	154 (98.7)	355 (98.6)

SD: standard deviation; IQR: interquartile range; GBP: gabapentin. FG: focus group.
Note: recent drug use is defined as any use in the past 30 days; comparisons were made between the focus group participants and (1) other GBP users from their cohort and (2) the rest of their cohort (including other GBP users).
[a]Individuals from the cohort that reported recent gabapentin use, but did not participate in a focus group.

[b]All cohort members excluding those that participated in a focus group.
[c]One participant did not complete quantitative survey.
[d]Includes full and part time work.
*$p < .05$

CHAPTER THREE

Gabapentin misuse, abuse, and diversion: A systematic review

Introduction

Gabapentin is an analog of GABA [2]; however, it does not bind to $GABA_A$ or $GABA_B$ receptors (or benzodiazepine, opioid or cannabinoid receptors), but it can increase GABA and can decrease glutamate concentrations [3,4]. Its mechanisms of antiepileptic and analgesic actions are unknown, although some have speculated, in the case of the latter, that gabapentin may reduce the release of pain-related peptides and may decrease opioid-induced hyperalgesia [5]. However, a unique gabapentin binding protein has been identified [50,51] as a subunit of the voltage-dependent calcium channel complex [52], suggesting a less specific mechanism of action through modulation of neurosignaling.

Gabapentin was approved in 1993 by the US Food and Drug Administration (FDA) initially only for treatment of epilepsy as an adjunct to anticonvulsant therapy, but in 2004 was also approved as an analgesic for post-herpetic neuralgia [1]. The European Medicines Agency approved gabapentin in 2006 for epilepsy and certain types of neuropathic pain [53] and the UK National Institute for Clinical Excellence (NICE) recommends gabapentin as a first-line treatment for all neuropathic pain [54]. Because its mechanism of action is unclear and it is assumed to have no abuse potential, gabapentin is widely used off-label to treat an array of disorders, including insomnia, various neuropathic pain conditions, drug and alcohol addiction, anxiety, bipolar disorder, borderline personality disorder, menopausal conditions, vertigo, pruritic disorders, and migraines. In fact, estimates

of the off-label usage of gabapentin are reported to range from 83-95% of all gabapentin use [6,7], which is estimated to account for over 90% of its sales [1]. Due to illegal marketing (promoting off-label uses) of gabapentin, Pfizer was fined $420 million after it was acquired from Warner-Lambert [8].

Gabapentin is safely tolerated over a very broad range of doses from approximately 800-1800 mg/day (although package inserts suggest that patients may be treated with doses as high as 3600 mg/day). In clinical practice, dosing is typically titrated starting from lower doses (i.e., <400 mg/day) and moving rapidly upward. The European Medicines Agency [55] and the Physician Prescribing Information generally recommends dosing up to 1800 mg in adults. While substantially higher doses have been tested in clinical trials, no additional clinical benefit has been observed [56]. However, other studies have examined gabapentin as acute doses in the higher dose range, and it was well tolerated. At least one imaging study has reported that gabapentin (1200 and 2400 mg) significantly (and rapidly) increased measurable concentrations of brain gamma-aminobutryric acid (GABA), one of its presumed mechanisms of action [4]. Hart and colleagues (2004) examined gabapentin (600 and 1200 mg) for its potential to reduce the reinforcing effects of cocaine in the human laboratory [57]. Their data reveal reductions in ratings of anxiety with both gabapentin doses (in the absence of cocaine) compared to placebo. Lile (2013) examined 600 and 1200 mg yielding significant differences from placebo on numerous outcomes, including liking, take again and good effects [58]. Bisaga and Evans (2006) examined gabapentin in combination with alcohol at acute doses of 1000 and 2000 mg [59]. In this dose range, gabapentin produced some direct effect on

psychomotor function but was still safely tolerated in combination with alcohol.

Despite initial views that gabapentin had no abuse potential [9-13], there have been numerous published case reports of gabapentin abuse by substance abusers in the community and penal system [35,44,60-70]. The purpose of this review is to describe the international scope of gabapentin abuse (i.e., prevalence, risk factors, motivations behind misuse, how it is misused, illicit value, effects experienced) and to identify implications for practice and future research.

Methods

Definitions

The definitions presented here were used to guide article selection and are used throughout the present article to facilitate discussion. *Gabapentin* refers to the capsules, tablets, and oral solutions of which gabapentin (1-(aminomethyl)cyclohexaneacetic acid) is the active ingredient. This definition includes the prodrug of gabapentin, gabapentin enacarbil. When discussing case reports, the dose and formulation of gabapentin will be specified, when that information is available. *Misuse* is defined as the use of a drug in a manner or for a purpose other than indicated, including, but not limited to, taking another person's medication, unprescribed or non-recommended route of administration, or a higher dosage than prescribed [26]; thus, missing prescribed doses or dose reduction is not included. *Abuse* consists of persistent use of a drug despite negative consequences [26]. *Dependence* refers to the physical and psychological elements associated with abuse, which include compulsion, withdrawal, and tolerance [26]. *Diversion* is defined as the unauthorized selling or sharing of prescription medications, which can be

either intentional (e.g., selling personal medication to someone without a prescription for that particular drug) or unintentional (e.g., theft). Diversion can occur at any point along the drug manufacturing and delivery process, however, at the core of this definition is unlawful movement of licit and regulated pharmaceuticals to the illicit marketplace [27,28].

Search strategy and article selection

This review sought to identify peer-reviewed, published manuscripts describing cases of gabapentin misuse and/or abuse in accordance with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. The databases PubMed, Web of Science (all databases), CINAHL, PsycINFO, and Cochrane were searched utilizing terms and strategies specific to each database (Appendix A) developed in collaboration with a qualified librarian and peer-reviewed by two additional medical librarians. All searches were conducted between May and August 2015. Only those articles written in English that described occurrences of gabapentin misuse/abuse among human populations were included. Studies describing only gabapentin toxicity, withdrawal, or dependence without misuse/abuse were excluded, as were articles describing only pregabalin misuse/abuse. Grey literature, as defined by the Institute of Medicine [71], was excluded; a well-constructed preliminary examination in Google Scholar provided over 21,000 results, exclusion of which highlighted a vast body of evidence of gabapentin misuse. Snowball sampling (i.e., reviewing references of included papers) was then used to identify any additional articles that may have been excluded after applying index-based filters.

Data extraction was performed by the first author; all of the selected articles were reviewed by the second and third authors to assess whether they met inclusion criteria. Any disagreements regarding inclusion were discussed among all authors until agreement was reached.

Results

The initial search yielded 1,128 unique citations, of which 1,067 were excluded based on title or abstract (Figure 3.1). Sixty-one articles were read in their entirety to assess whether they met inclusion criteria. Thirty were excluded because they did not actually describe gabapentin misuse, abuse, or diversion. The remaining 31 articles met all inclusion criteria. Snowball sampling identified 351 unique publications; 346 were excluded based on title or abstract, 2 met criteria and were included in the review. In total, this systematic review analyzed 33 articles. There were 47 case studies of gabapentin misuse/abuse found in 23 published articles from 1993 to 2015 and 11 epidemiological reports published over the same time frame (one article described both types [37]). Notably, one review article was included in this paper not due to the content of the review, but rather a statement in the introduction, which mentioned a personal communication of large-scale gabapentin abuse occurring within a drug using population in Pittsburgh, Pennsylvania [62].

The present review attempted to summarize rigorously conducted and well-presented findings on gabapentin misuse/abuse. As such, the quality of case reports could not be evaluated; therefore, this presentation focused on epidemiological and toxicological studies using case studies as secondary data. It would be detrimental to have excluded case reports, as they provide rich context from which the

population data may arise. Therefore, unless clearly noted in the manuscript text that the article was a case report, the reader could assume that the study was sample-based.

Study base and data sources

The 11 epidemiological studies (all cross-sectional) selected for this analysis obtained data from unique sources (Table 3.1); four publications involved substance misuse/abuse populations [15,32,34,72], two examined toxicology records [37,73], one used a population-based sample [33], two involved reports to a poison center [74,75], and two analyzed websites with qualitative information regarding gabapentin abuse [36,76].

Over half of the case report articles (n=14) arose from patients presenting to a hospital or general clinic with overdose or withdrawal-like symptoms [60,61,64,67,68,70,77-84]; two came from substance abuse clinics [62,66], three from psychiatric facilities [44,63,69], two from the penal system [35,65], one from postmortem toxicology findings [85], and one from poison center reports [75].

Demographic and geographical distribution

Five epidemiology/toxicology papers provided demographic characteristics of their sample. Two toxicology studies using poison center data indicated slightly higher representation of females (60-65%) [74,75], while another study among opioid dependent patients found no significant difference in representation by gender (51% male, p=0.58)[34]. One article noted that females were significantly more likely to misuse gabapentin than males in a cohort of opioid users (percent difference=17.3%, 95% confidence interval=10.4-24.6%) [15]. A toxicology paper by Peterson (2009) observed no difference in gender in the likelihood of being a

positive gabapentin driving impairment case (50% male)[37]. Among case studies, males had slightly higher representation than females (15 males vs. 13 females), although gender was incompletely specified in two reports [66,75]. The mean age of samples ranged between 21 and 43 in studies in which it was reported [34,37,73-75]. The calculated mean age of case reports was 41.

Published reports came from the United States (67%, n=22), the United Kingdom (12%, n=4), Germany (3%, n=1), Finland (3%, n=1), India (3%, n=1), South Africa (3%, n=1), France (3%, n=1), and two analyzed websites not specific to a particular country (6%). While all of the articles in this review described gabapentin misuse/abuse, 12 (36%) were documented reports of overdose involving gabapentin [60,61,67,74,75,78-82,84,85].

Misuse and abuse of gabapentin

Prevalence. Only one article gave an estimate of lifetime prevalence of gabapentin abuse in the general population; Kapil and colleagues (2013) surveyed a UK population-based sample of 1500 and found that 1.1% reported ever misusing gabapentin [33].

Over half of the studies described gabapentin misuse that occurred among samples with a history of or current substance misuse/abuse/dependence (n=6), the majority of which discussed opioid misuse, specifically (n=5). Smith (2012) and Baird (2013) gave reports of gabapentin misuse within Scottish populations that attended substance misuse clinics, which likely included individuals who abuse alcohol and/or drugs [32,72]. Recent cross-sectional studies of opioid abuse samples in the US and UK estimated gabapentin misuse to be between 15-22% [15,32,34] and

gabapentin abuse with a prescription ranged from 40-65% [15,33,34,75]. There was little evidence of gabapentin abuse among those with a positive history of alcohol abuse or dependence. In fact, Wilens and colleagues (2015) conducted a survey among opioid dependent individuals seeking substance detoxification in the US and found no gabapentin abuse among those undergoing alcohol detoxification [34]. Conversely, for opioid dependent patients, 40% reported using more gabapentin than prescribed and 13% reported using unprescribed gabapentin [34].

In Scotland in 2010, approximately 1% of all drug-related deaths were directly attributed to gabapentin [32]. Further, two articles assessed toxicological results in primarily substance misusing populations; the first examined 23,479 impaired driving cases in the US and found gabapentin was involved in 0.6% of them [37], while a Finnish study reviewed 13,766 medico-legal postmortem investigations and identified gabapentin in 0.3% of the cases [73].

Doses, Cost, and Diversion. Studies indicate gabapentin is misused/abused over a wide range of doses, from within therapeutic range (900-3600 mg/day) to supratherapeutic doses. All but two articles discussed the dosage involved in gabapentin misuse [32,33]. Evidence from the US suggested that gabapentin misuse among individuals with prescriptions for gabapentin involved a higher amount than prescribed [34,73,86]. For example, as previously mentioned, a US study found that 22% of a sample of 162 opioid-dependent patients had a prescription for gabapentin, of which 40% indicated they used more than prescribed [34]. Potential explanations for this trend are tolerance and addiction as described in two clinical case discussions from France and the US, respectively [44,70]. Interestingly, according to American and

European case reports, those who used gabapentin, but did not have a prescription for it, often took doses that fell within clinical guidelines, regardless of motivations behind use, though the doses were not spread out over the course of a day and it was unclear how often an individual dosed per day [66,68].

Over half of the articles (n=7) mentioned or referred to diversion of gabapentin. Studies in the UK and US identified health services/physicians as one of the major sources of misused gabapentin, with rates ranging from 52-63% (the 63% also may include baclofen and pregabalin) [15,33]. Other sources included family or acquaintances, Internet, bought abroad [33], and drug dealers [15].

Case reports support these findings from epidemiological studies. Reports from India, the UK and US also identify family members or acquaintances as gabapentin sources. Behaviors that are markers of abuse liability, such as doctor shopping, exaggeration of symptoms, and fabrication of prescriptions, were reported in case studies from France and the US [66,70]. Due to widespread gabapentin abuse in a US correctional facility, Reccoppa and colleagues (2004) inventoried dispensed medications and found only 19 of 96 prescriptions in the possession of the inmate receiving the prescription [65].

There is a street market demand for gabapentin. An American case study stated that, "{gabapentin} tablets were sometimes sold or traded for illicit drugs" [66]. In Scotland, the Drug and Crime Enforcement Agency identified the growing use of gabapentin as a cutting agent in heroin [72]. In the UK and US, epidemiological studies reported the illicit market value for gabapentin ranged from <1-7 USD per pill depending on strength [15,32,72].

Combination with other substances. Three toxicology studies elucidated the most commonly found substances with gabapentin. The first, by Häkkinen and colleagues (2014), examined Finnish postmortem toxicological samples positive for gabapentin from 2010-2011 and found that all cases classified as gabapentin abuse also involved the use of alcohol and/or opioids (most commonly buprenorphine and tramadol) [73]. Peterson (2009) conducted a study in the US, also utilizing toxicological data, which examined the presence of gabapentin in driving impairment cases. Only 7% of gabapentin-positive blood samples detected solely gabapentin; the remainder were polysubstance cases, with benzodiazepines (44%), opioids (43%), antidepressants (43%), other CNS depressants (e.g., trazodone, zolpidem; 36%), antiepileptics (25%), cannabinoids (15%), stimulants (11%), and ethanol (6%) [37]. Smith and colleagues (2012) stated that postmortem toxicology reports in Scotland revealed 75% of those identifying gabapentin also included morphine and/or methadone, which the authors said may be indicative of recent opioid dependence [72]. The toxicology studies, while helpful for providing a picture of what classes of medicines were commonly found in combination with gabapentin, did not address unprescribed mixing of licit or illicit drugs.

Alternatively, several epidemiological studies did identify simultaneous combination of gabapentin with other substances for the explicit purpose of misusing them. One article discussed the misuse of gabapentin in combination with buprenorphine for the purpose of "getting high" [15]. Similarly, Baird and colleagues (2014) stated that 38% of a substance misuse sample in Scotland took gabapentin

(and/or pregabalin) in combination with prescribed methadone to potentiate the effects of methadone [32].

Studies in US and UK substance abuse populations, by Smith (2015) and Smith (2012) respectively, identified a greater likelihood for those misusing gabapentin to also be misusing prescription opioids [15,72]. Smith (2015) also found that individuals who reported using gabapentin to get "high" were also more likely to be misusing benzodiazepines [15], which supports the finding by Peterson (2009; discussed earlier) that benzodiazepines were the most commonly detected class of drugs in combination with gabapentin [37].

Use of gabapentin and ethanol were commonly reported together; in addition to the two toxicology studies discussed earlier [37,73], another mentioned the misuse of gabapentin in combination with alcohol [36]. An international review of recreational gabapentin misuse anecdotes described other substances that have been reported in conjunction with misused gabapentin including cannabis, SSRIs, LSD, amphetamine, and GHB (gamma-Hydroxybutyric acid) [36].

Case studies have corroborated the epidemiological findings and have also identified buprenorphine/naloxone and quetiapine as combinations of abuse with gabapentin [35,66,76].

Motives. A variety of motivations behind gabapentin misuse were identified, many that related to substance abuse behaviors in general, which included: recreational use [15,32,36,72], control mood and/or anxiety [37], potentiate the effects of drug abuse treatment [32], and intentional self harm [75]. Case reports substantiated those intentions [35,44,61,63-69,76,78,82,84,85], and also identified the following: pain [77],

reduce cravings for/manage withdrawal from other drugs [63,64,69], substitute for other drugs [35,63,66], and addicted to gabapentin [44,70].

Effects Experienced. Only three epidemiological studies mentioned the effects sought by misusing gabapentin [32,36,72]; these findings were not presented as inference from a sample, rather examples accumulated from individual reporting. Six case reports also described feelings achieved from gabapentin misuse/abuse [35,63-66,69]. Therefore, the two types of articles were combined in this section to provide a comprehensive catalog of individual effects experienced and consequently should be interpreted with caution.

Several case studies mentioned experiencing euphoria after gabapentin misuse that was reminiscent of, but not as strong as, opioids [35,66,69]. This feeling was achieved in combination with other drugs (e.g., buprenorphine/naloxone, methadone, baclofen, quetiapine, alcohol) [32,35,36,66] as well as by using gabapentin alone [69,72], in dosages ranging from 1500-12000 mg, though only three articles give actual amounts misused [35,66,69]. One case study described individuals snorting gabapentin powder from capsules and experiencing a high similar to that felt after snorting cocaine [65]. Another commonly reported sensation from gabapentin misuse was sedation/relaxation/calmness, which was described in six studies [35,36,63,64,66,72]. As with euphoria achieved from gabapentin misuse, sedation/relaxation/calmness was experienced in combination with other substances (e.g., quetiapine, alcohol, cannabis, buprenorphine/naloxone) [35,64,66] or by taking gabapentin alone [36,63], and over a range of dosages (e.g., 600-4800 mg). Other effects experienced included: improved sociability [36,72], marijuana-like "high" [36,72], cocaine-like "high" [65],

"amphetamine rush" [36], disassociation [36], MDMA-like "high" [36], increased energy and focus [69], improved quality of sleep [69], and becoming more talkative [36].

Discussion

Gabapentin has been presumed to have no abuse potential historically [9-13], however, this review reports evidence to the contrary. Of the 11 population-based studies and 23 case reports included here, nearly one-third report gabapentin misuse/abuse for recreational purposes and epidemiological studies from the US and UK estimate abuse rates between 40-65% just among individuals with a gabapentin prescription. Studies from the UK indicate that gabapentin has developed a prominent place as a drug of abuse; in Scottish prisons, gabapentin is among the top-requested prescription drugs of abuse [32]. However, the rise in popularity of recreationally used gabapentin is occurring in the US, as well. Smith and colleagues (2015) describe a near 3000% increase in the use of gabapentin to get "high" from 2008 to 2014 among a cohort of 503 prescription drug users in the Central Appalachian region of the US [15].

Motivations for misused gabapentin can be classified largely into three basic categories: recreational (e.g., get high or substitute for more expensive drugs), self-harm, and self-medication (e.g., for pain or withdrawal symptoms from other substances). The majority of case reports involved individuals who had prescriptions for gabapentin, but took higher dosages than they were prescribed. Descriptive reports on gabapentin reveal an array of subjective experiences evocative of opioids (e.g., euphoria, talkativeness, increased energy, sedation), benzodiazepines (e.g., sedation), and psychedelics (e.g., dissociation). These effects

do not appear to be specific to a particular dose and may occur well within the therapeutic range. No pattern was observed in terms of dose taken or interactions between dose and motive or dose and effects achieved, which may be partially explained by the unpredictable pharmacokinetics and non-linear bioavailability of gabapentin [87]. To date, no carefully controlled human laboratory studies have been published that sought to examine and characterize the abuse potential profile of gabapentin in comparison to other prototypic drugs of abuse. Overall, further empirical research is clearly needed to better evaluate and characterize gabapentin psychopharmacology and the risks associated with gabapentin use, especially among those using it recreationally.

It is difficult to ascertain risk factors for gabapentin misuse/abuse except history of or current drug abuse, particularly opioids, is likely one from reports available to date. While no studies to date have formally assessed a history of or current substance abuse (especially drug abuse) as a risk factor for gabapentin misuse, it was the most common characteristic detected here. This is particularly important because it indicates that the increasing trend in gabapentin abuse, notably among populations with opioid misuse, has the potential to affect an estimated 0.6-0.8% of the world's population aged 15-64 that has used opioids in the past year [88]. It is important to note, however, that this review may overrepresent individuals who have abused substances, illustrating the importance of examining gabapentin misuse in the general population. Further, grey literature was excluded, which may have provided more information from which to infer risk factors for misuse, along with other characteristics of gabapentin misuse/abuse. Still, the

present review emphasizes the paucity of peer-reviewed research on this important emerging topic, and provides key starting points for subsequent examination.

Gabapentin is relatively inexpensive and, in fact, many individuals can acquire it for free or a drastically reduced price under subsidy plans [14,89,90]. Further, due to its widespread off-label prescribing worldwide [1,6,7], it is relatively easy to receive gabapentin by prescription, as illustrated by physicians and the health care system being the primary source of misused gabapentin in the US and UK. These factors have enabled the market to be flooded with gabapentin and it has been referred to among the drug using population as "a cheap man's high" (personal communication). It is important that prescribers recognize the current diversion of gabapentin and dispense judiciously.

Gabapentin requires a prescription, but generally has no additional controls [90-93]; however, pregabalin, its close structural relative, which was approved after gabapentin, was placed into Schedule V (abuse potential) in the US [16] and included in the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)-Europol annual report on new psychoactive substances of abuse [94]. It was found that pregabalin had euphoric and sedative properties similar to other frequently abused substances; moreover, as it is known that tolerance and physical dependence (with withdrawal symptoms upon discontinuation) may occur in response to repeated dosing, these factors may contribute to the escalation or continued misuse of gabapentin in those abusing the drug for its psychoactive effects [17]. Our review, and other non-abuse reports falling outside the scope of this study [95-101], identified that gabapentin, too, produces these effects (i.e., tolerance, physical dependence, and

withdrawal) thereby warranting reevaluation of its abuse potential. However, it is important to consider in reexamination that gabapentin may be an appropriate treatment for many individuals (e.g., those in alcohol withdrawal, chronic pain, epilepsy) that may face impediments to receiving their medication upon increased control. Therefore, a risk-benefit analysis is necessary prior to any abuse potential labeling.

From published reports presented here, gabapentin is most often misused in combination with other substances, especially opioids, benzodiazepines, and alcohol, although details in this area are sparse and necessitate systematic data collection and analysis. Concomitant use is particularly important because gabapentin is often co-prescribed with opioids, and pain patients often receive prescriptions for benzodiazepines due to anxiety and/or difficulty sleeping. Moreover, its uncontrolled status leads doctors to believe that it lacks abuse potential; thus, they may feel confident in their prescribing of gabapentin to patients with substance use histories. NHS England released advice for gabapentin prescribers that strongly recommends using it as approved, offering alternative interventions for conditions outside the licensing indications [93]. Finally, benzodiazepines have been used to treat delirium resulting from gabapentin withdrawal [64] and gabapentin has been used to treat withdrawal from both benzodiazepines [46] and alcohol [9,11]. These findings suggest that these three agents may share a common neuropharmacological pathway for abuse and dependence; however, further research is necessary to explore this hypothesis.

In summary, findings from the present review suggest that gabapentin is misused/abused internationally for recreation, self-medication, or self-harm, with an array of subjective experiences. Substance abuse populations, especially individuals with a history of or current opioid misuse, appear to be at particular risk for misuse/abuse. Further studies to identify risk factors for gabapentin misuse and to characterize gabapentin's abuse liability are recommended.

Table 3.1. Summary of gabapentin misuse in reviewed articles

Study, year, and reference	*Country*	*Type of study*	*Sample size and characteristics*	*Prevalence of gabapentin misuse /abuse*	*Dose*	*Cost, Source, Diversion*	*Other substances in simultaneous combination*	*Motives*	*Effects experienced*	*Route of administration*
Baird 2013 (42)	Scotland	Paper survey	N=129 from six substance misuse clinics	19%	Not mentioned	Not mentioned	Methadone; possibly benzodiazepines	To become intoxicated, to potentiate the effects of methadone	Feeling 'high' or 'stoned'	Not mentioned
Hakkinen 2014 (46)	Finland	Analysis of toxicological autopsies	N=22,421 medico-legal autopsies with toxicology samples; 8 cases of gabapentin abuse; 75.0% of gabapentin abuse cases were male; median age of gabapentin abuse cases (range): 30 (24-47)	0.31% involved in postmortem cases; 18% of those were related to drug abuse	For abuse cases, median concentration in postmortem femoral blood: 12 mg/L (range =0.62-45)	Not mentioned	Alcohol (37.5% of gabapentin abuse cases); opioids (87.5% of gabapentin abuse cases)	Not mentioned	Not mentioned	Not mentioned
Kapil 2013 (47)	UK	Online survey	N=1500 market research panel members; 49.1% male; 9.1% age 16-20, 40.5% age 21-39, 21.1% age 40-49, 29.3%	1.1% lifetime prevalence	Not mentioned	57.8% received from family or acquaintances; 47.3% from the Internet; 7.8% abroad	Not mentioned	Not mentioned	Not mentioned	Not mentioned

			age 50-59 yo							
Klein-Schwartz 2003 (49)	USA	Analysis of poison control cases	N=20 gabapentin exposures reported to three poison control centers; 60% female; mean age for asymptomatic cases (± SD): 21.8 ± 29.0; mean age for symptomatic cases (± SD): 23.0 ±13.9	20 of 77 gabapentin-involved cases were gabapentin-only	Mean dose (± SD) for asymptomatic cases: 1906 mg ±2238; mean dose for symptomatic cases: 6320 mg ±10926	65% involved the patient's own medication	52 of 77 cases involved co-ingestants, but did not specify what they were and were excluded from analysis	55% was intentional suicide attempt; 5 cases of therapeutic error; 4 unintentional (general) cases	Drowsiness (x8), ataxia (x2), tachycardia (x2), dizziness (x3), hypotension (x2), nystagmus (x1), nausea/vomiting (x2), diarrhea (x1), syncope (x1), bradycardia (x1), none (x5)	Not mentioned
Peterson 2009* (41)	USA	Analysis of blood samples	N=23,479 driving impairment cases in Washington state from 2003-2007; 50% male; mean age (± SD): 43.0 ±10.9	0.6% were positive for gabapentin	Mean concentration (±SD): 8.4 mg/L ±5.4; median: 7.0	Not mentioned	Only 9 of the gabapentin cases were positive for gabapentin only. Of the remainder, 44% also contained benzodiazepines, 43% opioids, antidepressants 43%, other CNS depressants 36%, antiepileptic drugs 25%, 15% cannabinoids, 11% stimulants, and 6% ethanol.	Not mentioned	Not mentioned	Not mentioned
Schifano 2011 (50)	Online review	Qualitative analysis of websites	N=108 websites in English, German, Spanish, Italian, Dutch, Norwegian, Finnish, and	Not mentioned	Varying doses mentioned in subjective reports ranging from 900 to 4800 mg	Mentioned online pharmacies as a source, but likely not sole source	Baclofen, cannabis, alcohol, SSRIs, LSD, ampthetamine, GHB	Not clear, but likely recreational use	Reminiscent of "amphetamine rush," "fully sedated opiate buzz," "disassociation like DXM," "talkative,"	Oral and intramuscular

			Swedish						"comparable to cannabis," "buzz slightly reminiscent of MDMA"	
Seale 2014 (51)	Online review	Brief summary of website findings	Drug forums and pharmacist blogs	Not mentioned	Not mentioned	Not mentioned	Buprenorphine /naloxone	To get "high"	Not mentioned	Not mentioned
Smith 2012 (43)	Scotland	- Qualitative reports - Prescribing data - Clinical data - Postmortem examinations	- Qualitative reports arose from from clinical experiences and a police report, unreported sample size - Prescribing data: arose from Tayside region in Scotland from 1993-2011, unreported sample size - Clinical data arose from substance misuse services in Tayside, Scotland in 2009, n=251 of those who	Of 251 individuals in substance misuse clinics, 5.2% receiving prescribed gabapentin; Of 1400 postmortem toxicology examinations, 48 included gabapentin, of which 36 also included methadone and/or morphine	The 5.2% receiving prescription gabapentin have a mean dose of 1343 mg	Can purchase on the street market for approximately 1 GBP per 300 mg; gabapentin is being used as a cutting agent in heroin according to a police report	Nonmedical use of prescription analgesics, morphine, methadone	Not clear, but likely recreational use	Euphoria, improved sociability, a marijuana-like 'high', relaxation, sense of calm, 'zombie-like' effects	Not mentioned

			had used misuse services for 4+ years - Postmortem examinations came from Central, Tayside, and Fife Scotland in 2011, n=1400							
Smith 2015 (44)	USA	Questionnaire	N=503 nonmedical prescription opioid users from 2008 to 2014; 77.8% of gabapentin misuse cases were female	15% in past 6 months	Not mentioned	Physicians (52%) and drug dealers (36%); costs less than 1 USD per pill	Unclear if simultaneous use, but were more likely than non-gabapentin users to report past 30-day use of: immediate-release oxycodone, buprenorphine, benzodiazepines	Recreational, "to get high"	Not mentioned	Not mentioned
Wilens 2015 (45)	USA	Survey	N=162 opioid dependent patients seeking detoxification; 51% male; mean age (±SD): 33 (±10)	22% received prescription gabapentin; 40% of which reported using more than prescribed; 13% used unprescribed gabapentin; in total, 22% misused gabape	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned

				ntin (either more than prescribed or taking unprescribed)						
Wills 2014 (48)	USA	Medical chart review	N=347 poison center reports; 69.5% female; median age (IQR): 30 (20-44)	116 cases of gabapentin overdose	Median dose: 6000 (IQR: 2700-12000)	Not mentioned	Co-ingestion cases were excluded	Not mentioned	10% neuromuscular symptoms, 2% seizures, 41% CNS symptoms, 6% GI symptoms, 11% cardiac symptoms, 16% blood pressure, 5% metabolic signs	Not mentioned
Case Reports										
Study, year, and reference	*Country*	*Gender and age*	*History of substance abuse*	*Dose*	*Cost*	*Source/ Diversion*	*Other substances in simultaneous combination*	*Motives*	*Effects experienced*	*Route of administration*
Barrueto 2002 (52)	USA	34 yo male	No	8000 mg/day	Not mentioned	Patient's own medication	None	Manage pain	Withdrawal	Presumed oral, but not explicitly mentioned
Cantrell 2015 (24)	USA	47 yo female	Yes (D)	Up to 15.6 g once	Not mentioned	Daughter's medication	None	Not clear	Death	Oral
Fernandez 1996 (53)	USA	32 yo male	Not mentioned	91 g once	Not mentioned	Unclear if patient's own medication or not	Valproic acid, alcohol	Suicide	Nystagmus, slurred speech, dizziness, drowsy	Oral
Fischer 1994 (25)	USA	16 yo female	Yes (D)	48.9 g once	Not mentioned	Father's medication	None	Self harm	Dizziness, liquid stool, lethargy, dysphoria, emotional lability	Oral
Howland 2014 (26)	USA	Not mentioned	Yes (D)	Not mentioned	Not mentioned	Mentioned street market for selling	Opiate agents	"get high"	Not mentioned	Not mentioned

						gabapentin				
Jones 2002 (58)	USA	46 yo female	Not mentioned	2 additional doses over prescribed once	Not mentioned	Patient's own medication	None	Not mentioned	Somnolence, hypoxia, tremulous, and hyperreflexic	Presumed oral, but not explicitly mentioned
Koschny 2014 (59)	Germany	21 yo female	Not mentioned	16 g once	Not mentioned	Not mentioned	Carvedilol, amlodipine, amitriptyline, torsemide, nicotinic acid, ketoprofen	Suicide	Cardiac failure	Oral
Kruszewski 2009 (27)	USA	38 yo male	Yes (A)	4800+ mg/day	Not mentioned	Patient's own medication	Not clear – possibly alcohol, buspirone, bupropion	Control moods and anxiety	Delirium, addiction	Presumed oral, but not explicitly mentioned
Markowitz 1997 (28)	USA	41 yo female	Yes (D)	600-1500 mg/day	Not mentioned	Husband's medication	None	Substitute for crack cocaine	Reduced crack cocaine cravings, relaxation	Presumed oral, but not explicitly mentioned
Middleton 2011 (60)	USA	62 yo female	No	Up to 45 g once	Not mentioned	Unclear, possibly patient's own medication	Clonazepam	Suicide	Death	Not explicitly mentioned
Peterson** 2009 (41)	USA	44 yo male	Not mentioned	< 2.0 mg/L	Not mentioned	Implies no medication because states the patient is "self-medicating", but no indication of source	Quetiapine	Self medication for bipolar disorder	Lack of focus, lethargy	Presumed oral, but not explicitly mentioned.
Pittenger 2007 (29)	USA	1. 33 yo male 2. 63 yo male	1. Yes (A, D) 2. Yes (A)	1. 3600 mg/day 2. 4900 mg/day	Not mentioned for either case	Both patients used their own medication	1. Not clear – possibly cannabis, paroxetine, quetiapine 2. Not clear – possibly oxycodone	1. Control mood and withdrawals 2. Not mentioned	1. Felt cal mer and reduced alcohol cravings, withdraw	Presumed oral for both cases, but not explicitly mentioned for either

									2. al Withdrawal	
Rasimas 2006 (54)	USA	44 yo female	Not mentioned	7 mg/L once	Not mentioned	Unclear, possibly patient's own medication	Nefazodone, possibly alcohol	Intentional self-poisoning	Tachycardia, lethargy, depressed mental status	Oral
Reccoppa*** 2004 (30)	USA	29-45 yo males	Yes (D)	300-400 mg	Not mentioned	Some misused their own medication, others misused others' prescriptions	Not clear – possibly tricyclic antidepressants, SSRIs, valproic acid, carbamazepine	"get high"	Altered mental state like snorting cocaine	Nasal insufflation
Reeves 2014 (32)	USA	38 yo male	Yes (D)	2400 mg once	Not mentioned	Not mentioned	Buprenorphine/naloxone	"get high"	Euphoria	Presumed oral, but not explicitly mentioned
Reeves 2014 (31)	USA	1. 42 yo male 2. Female 3. Unknown 4. Unknown 5. Unknown	1-2. Yes (D) 3-5. Not mentioned	1. Up to 1500 mg each dose 2. Up to 1200 mg each dose 3-5. 900-1800 mg each dose	Sold or traded for illicit drugs; specific price not mentioned	Sold or traded, or patients received their own prescription by exaggerating symptoms or false prescriptions	1. Quetiapine 2. Quetiapine and alcohol 3-5. Quetiapine	1-2. Substitute/replace cocaine 3-5. Not mentioned	1-2. Sedation and euphoria 3-5. Not mentioned	Presumed oral for all cases, but not explicitly mentioned
Roberge 2002 (33)	USA	44 yo female	Yes (D)	"handful" once	Not mentioned	Patient's own medication	Mexilitine, valproic acid, alcohol	"get high"	Slurred speech, somnolence, anisocor	Oral

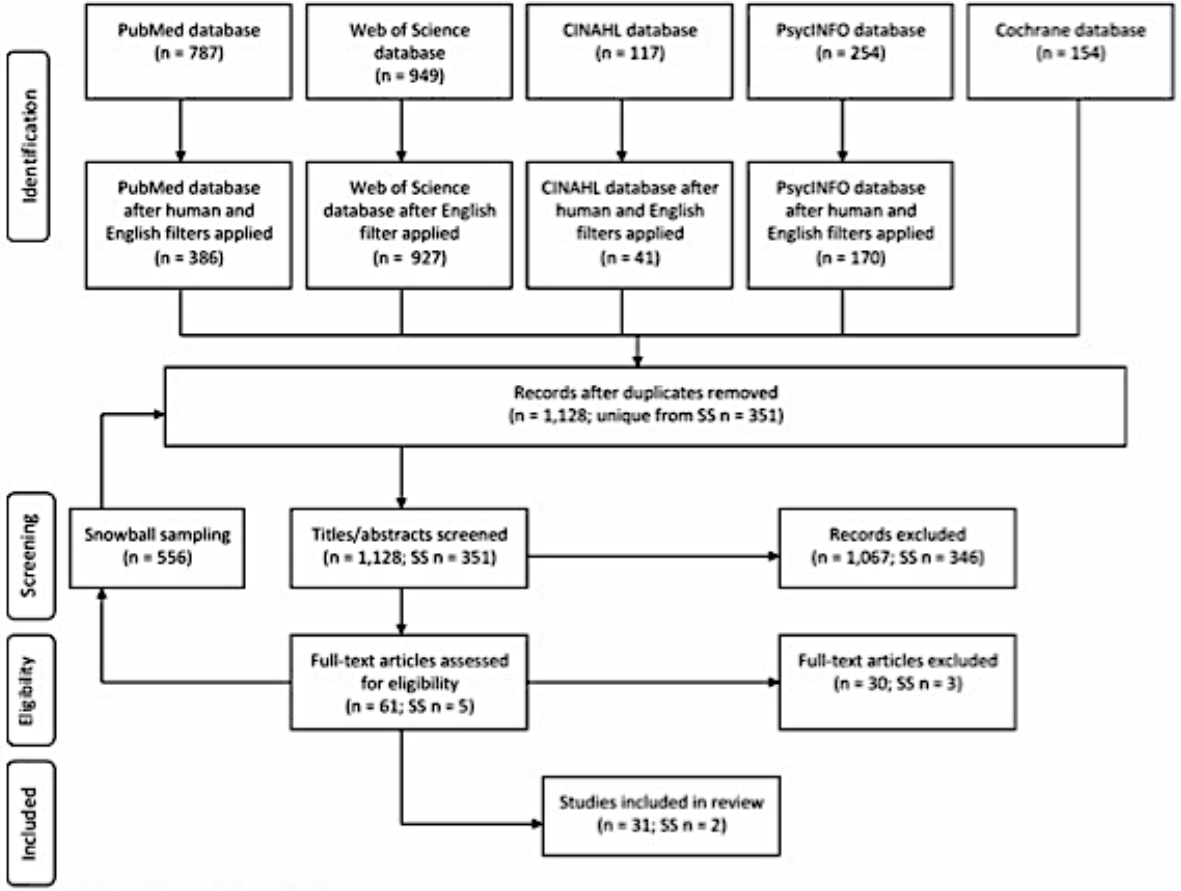
									ia, sluggishly reactive pupils, depressed gag reflex, obtundation	
Rohman 2014 (34)	UK	26 yo male	Yes (D)	1600 mg once	Not mentioned	Friend	None	Recreational	Dystonia	Oral
Satish 2015 (35)	India	26 yo male	Yes (D)	400 mg – 2 g/day	Not mentioned	Initially a friend, unclear if patient eventually received own prescription	None	Recreational	Dependency, sense of well-being, increased energy, improved mood and sleep quality, increased attention span	Presumed oral, but not explicitly mentioned
Schauer 2013 (57)	USA	59 yo female	No	90 g once	Not mentioned	Patient's own medication	Hydrocodone/acetaminophen	Suicide	Nausea and mild sedation	Oral
Spiller 2002 (55)	USA	61 yo female	Not mentioned	Up to 54 g once	Not mentioned	Patient's own medication	Quetiapine	Not clear - possibly suicide	Coma, respiratory depression	Oral
Stopforth 1997 (56)	South Africa	17 yo female	Not mentioned	12 g once	Not mentioned	Not clear, but likely own patient's medication since she was epileptic	Lamotrigine	Not mentioned	Drowsy with slurred speech	Oral
Victori-Vigneau 2007 (36)	France	67 yo female	Yes (A)	7200+ mg/day	Not mentioned	Patient's own medication	Not clear – possibly naproxen, amitriptyline	Not mentioned	Withdrawal, dependency	Presumed oral, but not explicitly mentioned

*Article is a mixed methods analysis of qualitative and quantitative data. Therefore, this article appears in both the first and second sections of this table. **Article described 4 cases, only one of which may have been gabapentin misuse and is therefore the only incident included in summary. ***Article combined information for 5 cases.

A = alcohol abuse; CNS = central nervous system; D = drug abuse; DXM = dextromethorphan; GBP = British pound; GHB = 4-hydroxybutanoic acid; GI =

gastrointestinal; IQR = interquartile range; LSD = lysergic acid diethylamide; MDMA = 3,4-methylenedioxyamphetamine; SD = standard deviation; SSRIs = selective serotonin reuptake inhibitors; USD = United States dollar.

Figure 3.1. Flow diagram of systematic article selection



SS: snowball sampling method

CHAPTER FOUR

Drug misuse signals in gabapentin: a pharmacovigilance assessment using the FDA Adverse Event Reporting System

Introduction

Gabapentin is approved by the United States Food and Drug Administration (FDA) for post-herpetic neuralgia and as an anti-epileptic, but is often used off label (e.g., for non-herpetic pain, mood disorders) and is currently being investigated as a pharmacotherapeutic for alcohol withdrawal. In the latest guidance report for pain prescribing, the Centers for Disease Control (CDC) suggested gabapentin as a first line medication for treating chronic pain.[102] Since its market release in 1993, gabapentin has been touted as having no abuse potential, which has likely led to its prolific off label prescribing. In fact, it has been estimated that between 83-95% of all gabapentin prescriptions are for a non-approved usage.[6,7] However, since the first published report of gabapentin misuse in 1994,[61] a significant number of accounts of gabapentin misuse and abuse have followed. A recent systematic review identified 23 published case studies and epidemiological reports of gabapentin misuse/abuse from seven different countries.[38]

Evidence on the prevalence of gabapentin misuse has been limited. A single study has estimated the population prevalence of gabapentin misuse as 1% in the United Kingdom.[33] However, 3 studies have estimated the prevalence of gabapentin misuse within substance misuse samples in the United States and the United Kingdom between 15-22%,[15,32,34] a number which apparently is increasing as more drug users become aware of the desirable effects of gabapentin [personal

communication]. How gabapentin produces analgesic and anticonvulsant effects is unknown, though it likely interacts with calcium channels to reduce neurotransmitter release in the central nervous system neuronal tissues.[87] There is a wide spectrum of the subjective effects of gabapentin, particularly when not used as intended (e.g., larger doses than prescribed), including: dissociation, euphoria, sedation/relaxation/calmness, elevated mood, disinhibition, delirium, feeling "high", and feeling drunk.[35,36,66,69]

Without definitive controlled pharmacological studies to reassess gabapentin's abuse potential, we must look to available data to estimate the presence and risk of gabapentin misuse in a timely manner. One such resource is the FDA Adverse Event Reporting System (FAERS), a publicly available, regularly maintained database. In the United States, postmarketing adverse events (AEs) associated with any drug or biologic product can be reported to the FDA through their passive surveillance program called FAERS. Approximately 5% of AEs reported to FAERS are generated voluntarily by health professionals (e.g., physicians, pharmacists, nurses) and consumers (e.g., patients, family members, lawyers), who can submit AEs via the online submission system called MedWatch.[103] The other 95% of FAERS reports come from voluntary AE reporting to the drug sponsor or manufacturer, who is then required to forward the report on to the FDA.[103] The Center for Drug Evaluation and Research (CDER), a subsidiary of the FDA, monitors reports and follows up with further evaluation on concerns identified through FAERS.[104] If findings indicate drug or product safety concern, the FDA can choose to take regulatory action, including, but not limited to: updating labeling information,

restricting use, communicating safety information to the public, or removing from the market.[104] To date, FAERS has received over 12 million reports, two million of those from 2016 alone.[103]

Pharmacovigilance (PhV), which is the collection, study, detection, and prevention of drug adverse events, is a useful tool for hypothesis-generation or hypothesis-support of drug-AE pairs, though it is prerequisite to have a theoretical conceptualization of the drug-AE combination one intends to investigate.[105] PhV studies typically use several assessment measures to detect a "signal" for a particular drug.[106] A signal is a previously unknown possible causal association of an adverse event resulting from taking a drug.[107] Signals are disproportionality measures based on a 2x2 contingency table (Table 4.1) and determine whether a drug-AE pair is occurring more often than expected by comparing signal values to published thresholds.[108-111]

This study will use the FAERS database to calculate signal measures for reporting of gabapentin and abuse-related AEs (AR-AEs) and compare these findings to a negative and positive control. The AR-AEs of interest will be selected *a priori* based on effects experienced with gabapentin misuse according to current body of literature.[36,38] However, signals of misuse/abuse/addiction may not be identified through observation of a single AE at a time (e.g., report of gabapentin and ataxia doesn't necessarily indicate abuse). Rather, it may be more useful to examine joint occurrence of several AEs that are indicative of drug misuse/abuse/addiction. Therefore, in addition to the traditional signal measures, this study will use a novel

application of loglinear modeling to assess the frequency of concurrent reporting of AEs associated with gabapentin misuse/abuse.

Methods

Data source

All FAERS quarterly data from January 1, 2004 to December 31, 2015 were downloaded from the FDA website,[112] however, since pregabalin was not approved by the FDA until December 30, 2004,[113] data from 2004 were excluded. Each quarterly data set contained 7 data files: (1) patient demographic and administrative information; (2) drug/biologic information for as many medications as were reported for the event; (3) all Medical Dictionary for Regulatory Activities (MedDRA)[114] terms coded for the adverse event; (4) patient outcomes for the AE; (5) report sources for the AE; (6) drug therapy start and end dates for the reported drug(s); and (7) all MedDRA terms for the indications/diagnoses for use for the reported drug(s).[115] For the purposes of this analysis, only the demographic, drug, and reaction data tables were used.

We used positive and negative controls to compare our gabapentin findings. Pregabalin, a structural cousin of gabapentin with a theoretically similar mechanism of action, has been classified as a Schedule V drug because of its abuse potential, which made it an ideal candidate for the positive control. Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has been recommended as a first line medication for the treatment of neuropathic pain[43] (gabapentin is also recommended as a first line treatment[43]) due to its efficacy and because it is rarely

associated with substance use disorder, thus it was selected it as the negative control.

Based on the proposed methodology of Moore et al. (1997), a case/non-case approach was used, where each drug-AE pair of interest denoted a case and all other possible pairs as non-cases.[116] In every FAERS AE drug file, role codes had been assigned to each reported drug and indicated as follows: primary suspect drug (PS), secondary suspect drug (SS), interacting (I), or concomitant (C). Often, only PS, SS, and I medications are considered as cases. However, several have raised concerns about excluding C medications as cases, particularly if it is an unexpected drug-AE association. As explained in the EudraVigilance data analysis guidelines, "In our case, it is quite often the case that drug-event associations are not commonly established until knowledge of the potential signal [is] available."[117] Therefore, due to the historic opinion that gabapentin had no abuse liability it was apt to include cases where gabapentin (and pregabalin and duloxetine) was listed as a concomitant medication.

Case identification - drugs

Drug cases (i.e., AE reports [AERs] which included gabapentin, pregabalin, and/or duloxetine) were identified in the FAERS drug table using a fuzzy matching algorithm. First, medication names in the FAERS file were truncated. The SAS SOUNDEX procedure was employed to identify potential drug case matches by both brand and generic name of the case drugs. The SOUNDEX procedure works through phonetic matching and can help reduce the effect of variations in spelling.[118-120] The potential matches identified through the fuzzy matching algorithm were manually

scanned by the first author to determine whether or not it was a true case. Only matches with a frequency of five or more were considered eligible to be cases. SAS version 9.4 (Cary, North Carolina) was used.

Data cleaning

Each AER in FAERS has a unique "ISR number," which can be used to link files across all seven data tables. A Case number also identifies an AER, however, it may encompass several ISR numbers (AERs) due to follow-up reporting for the same event. Once the drug files were merged with their corresponding demographic files by ISR number, the AER in each Case ID series with the most recent date was kept, according to FAERS cleaning protocol,[121] and duplicates were removed. The demographic/drug file was then merged with the MedDRA AE file by the ISR number.

Case identification - AEs

Using a variety of sources[122-124] we created a list of MedDRA preferred terms (PT) that were explicit indications of abuse (e.g., drug diversion, drug addiction) and those that could be indicative of abuse (e.g., ataxia, falls, euphoric mood, dissociation). Here *abuse-related* will be used to incorporate both explicit abuse MedDRA terms, as well as MedDRA terms that are possible indicators of abuse. The list was reviewed by well-qualified individuals (pharmacologist [SLW] and psychiatrist [MRL}) and revised until a final list was agreed upon by the authors. The 48 selected abuse-related MedDRA terms included: addiction; aggression; ataxia; confusional state; delirium; delusion; dependence; disorientation; dissociation; dizziness; drug abuse; drug abuser; drug addict; drug dependence;

drug diversion; drug tolerance; drug withdrawal syndrome; euphoric mood; elevated mood; fall; feeling abnormal; feeling drunk; feeling of relaxation; gait disturbance; hallucination; hallucination, auditory; hallucination, visual; hallucination, mixed; incoherent; intentional (drug) misuse; intentional overdose; intoxication; mood altered; multiple drug overdose; off label use; overdose; prescription drug use without a prescription; psychosis; acute psychosis; rebound psychosis; substance induced psychosis; transient psychosis; somnolence; substance abuse; substance abuser; substance use; thinking abnormal; tolerance increased. The terms addiction, drug addict, intoxication, prescription drug use without a prescription, psychosis, transient psychosis, and tolerance increased had no associated AERs, and were excluded from further analysis. It should be noted that each AER could, and most often did, include more than one MedDRA term.

Signal calculation

Since AE reporting can be affected by many external factors, cumulative signal measures were calculated,[105] that is, data were aggregated over the 11-year study period rather than calculated quarterly. Descriptive statistics were calculated for each drug-AR-AE pair. Traditional signal measures consisted of the proportional reporting ratio (PRR),[109] reporting odds ratio (ROR),[111] the information component,[108] and the empirical Bayesian geometric mean (EBGM).[110] Published criteria for each signal measure are as follows:[105]

PRR: $n \geq 3$, $PRR \geq 2$, $\chi^2 \geq 4$;

ROR: lower limit of 95% confidence interval > 1;

IC: lower limit of two-sided 95% credible interval > 0;

EBGM: n>0, lower one-sided 95% credible interval > 2.

First, a composite AR-AE variable was created, that is, any AER that reported at least one of the 41 AR-AEs was coded as 1 and those AERs that did not were coded as 0. Signal measures were calculated for each drug-composite AR-AE pair. Then signal measures were calculated for individual AR-AE-drug pairs. The traditional signal measures differ in their sensitivity and specificity. Therefore, we decided that for our purposes, a drug-AE pair would be significant if all four signal measures met the thresholds described above. The R package, PhVid,[125] was used to obtain all signal scores.

Loglinear analysis

Loglinear models allow for the simultaneous examination of the association between more than two categorical variables, essentially an extension of the 2x2 contingency table to a 2x2x…x2 table, particularly useful when there is more than one response variable. This type of model can describe the joint distribution of any number of K categorical factors.

First, a composite abuse-specific (AS-AE) variable was created where any AER that reported at least one AE-AE was coded as 1 and AERs that did not were coded as 0. The AS-AEs included: addiction, dependence, drug abuse, drug dependence, drug diversion, intentional misuse, intentional overdose, multiple drug overdose, overdose, substance abuse, and substance use. MedDRA terms drug abuser and substance abuser were not included as AS-AEs because those refer to the social circumstances surrounding the event. Therefore, information may be provided in

the AER that the individual had a history of drug misuse, but that does not necessarily indicate that abuse has taken place.

Next, loglinear modeling was used to evaluate the association between the co-occurrence of an AS-AE and each AE that was a possible indicator of abuse (e.g., ataxia, substance abuser) in AERs for gabapentin and pregabalin, with duloxetine as the referent group. Figure 4.1 depicts an exemplary graphical representation of what was modeled, particularly for AS-AE-feeling drunk co-reporting. All data were assumed to have come from a Poisson distribution. Further, AERs that co-indicated any of the case drugs together (e.g., AER with gabapentin and pregabalin; AER with pregabalin and duloxetine) were not included in the loglinear analysis in an attempt to reduce potential conflation of effects. SPSS version 24 (IBM Corp., Armonk, New York) was used to conduct the analyses.

Results

From 2005-2015 there were 6,685,853 unique AE reports (AERs) submitted to the FDA. Of those, 111,607 included gabapentin, 80,251 included duloxetine, and 111,012 included pregabalin. Overall, the number of reports for each case drug increased annually (Figure 4.2). Interestingly, AERs for gabapentin, pregabalin, and duloxetine shared many of same most frequently reported AEs including drug ineffectiveness, pain, nausea, fatigue, dizziness, and falls (Table 4.2).

Nearly one-quarter of all gabapentin reports involved an abuse-related AE (23%; Table 4.3). That percentage was slightly higher for pregabalin and duloxetine (26 and 29%, respectively). Of all the gabapentin-AR-AE pairs, dizziness was reported with the highest frequency (5%), followed by falls (5%), and somnolence

(3%). Dizziness and somnolence were also the most frequently reported AR-AEs reported for pregabalin (7 and 5%, respectively), while dizziness (8%), drug withdrawal syndrome (6%), and feeling abnormal (5%) were most common for duloxetine.

When examining signal measures of gabapentin, only four pairs did not achieve the threshold for at least one measure (n=37) and nearly half of the calculated gabapentin-AR-AE pairs met published threshold criteria for all four measures (n=16; Table 4.4). The highest gabapentin signal was produced by the PT substance abuser (ROR=14.7), though this drug-AE pair had a frequency of only 2. The other largest signals for gabapentin were produced with ataxia, drug tolerance, feeling drunk, multiple drug overdose, substance-induced psychosis, and abnormal thinking. The largest signal produced for pregabalin was with the PT, feeling drunk (PRR=11.6, ROR=14.1, IC=3.5, EBGM=11.5), followed by euphoric mood, somnolence, feeling of relaxation, abnormal thinking, and drug tolerance. The largest signal for duloxetine was produced with drug withdrawal syndrome (PRR=13.8, ROR=16.2, IC=3.7, EBGM=13.0), with abnormal thinking and dissociation as the next strongest signals. Signals common to all three case drugs included confusional state, disorientation, euphoric mood, feeling drunk, hallucination, visual hallucination, and abnormal thinking. Drug-AR-AE pair signals unique to gabapentin (compared to pregabalin and duloxetine) were with the AEs falls, incoherence, multiple drug overdose, and substance induced psychosis. Drug-AR-AE signals that were found with gabapentin and pregabalin, but not duloxetine, were ataxia, drug dependence, drug tolerance, gait disturbance, and somnolence.

There were no drug-AR-AE pairs that produced signals with gabapentin and duloxetine, but not pregabalin. Using the composite AR-AE variable, pregabalin and duloxetine produced signals with all 4 measures, and gabapentin produced signals with all measures except the EBGM. Using the composite AS-AE variable, gabapentin, pregabalin, and duloxetine all produced signals with the ROR and IC, but not the PRR or EBGM.

Co-reporting between two or more of each drug accounted for between 7 and 19% of all AERs for each drug. When the number of reports was reduced to exclude overlap between gabapentin, pregabalin, and/or duloxetine the number of unique reports for each drug was 97,235 for gabapentin, 103,732 for pregabalin, and 65,179 for duloxetine. AS-AEs accounted for approximately 3% of each drug's reduced number of AERs. For gabapentin, somnolence, drug withdrawal syndrome, and falls were most often co-reported with an AS-AE (Table 4.5). Somnolence was also the most often co-reported with a pregabalin AS-AE, while drug withdrawal syndrome had the highest co-occurrence for duloxetine.

Based on results from the loglinear models, compared to duloxetine, gabapentin had nearly 10 times the odds of a co-report of drug abuse and drug withdrawal syndrome; pregabalin also had increased odds of this simultaneous report compared to duloxetine, but not as high as gabapentin (Table 4.6). Gabapentin and pregabalin also had significantly increased odds of a co-report for an AS-AE with auditory hallucinations (OR: 5.25 and 4.12, respectively), delusions (OR: 3.15 and 4.77, respectively), and euphoric mood (OR: 2.69 and 2.24, respectively) compared to the negative control. Interestingly, an abuse-specific

event and ataxia were reported together with significantly increased odds for gabapentin compared to duloxetine, but pregabalin did not have significantly increased odds; this occurred with an AS-AE-somnolence co-report, as well.

Discussion

This study was the first post-market pharmacovigilance study to examine gabapentin reporting in the FDA Adverse Event Reporting System and compare findings to a negative and positive control. Though gabapentin, pregabalin, and duloxetine reports all produced signals for any abuse-related and abuse-specific adverse events, important differences appeared when evaluating AE-ARs individually. Specifically, the strongest gabapentin-AER associations occurred with ataxia, drug tolerance, and feeling drunk, all three of which were among the highest pregabalin-AER signals, as well. This is not surprising given that gabapentin and pregabalin have similar mechanisms of action, and are likely to produce similar effects.

Another novel aspect of the current study is that we evaluated AERs where drug abuse was indicated and assessed which effects were most often co-reported with abuse. Drug withdrawal syndrome, auditory hallucinations, delusions, and euphoric mood were more often endorsed in combination with drug abuse for gabapentin or pregabalin compared to the negative control, duloxetine. While it is not necessarily remarkable that such effects have been reported for gabapentin and pregabalin (in fact several of these AEs are listed on the package inserts), what is particularly notable is that they were reported as occurring with drug abuse, which gives insight into the psychoactive effects that may be sought through misuse of

these drugs. In a study by Schifano and colleagues (2011), data were accumulated from online anecdotes of recreational misuse of gabapentinoids and the effects achieved echoed those identified in this study.[36] Though pregabalin has been recognized by Drug Enforcement Agency in the United States[16] and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)-Europol[94] as having abuse liability, gabapentin is still assumed to have no abuse potential. However, the similarities between gabapentin and pregabalin of reported effects in combination with drug abuse underscore the necessity of revisiting evaluation of the abuse liability of gabapentin.

Interestingly, drug abuse was co-reported with somnolence and ataxia with significantly higher odds for gabapentin compared to duloxetine, but this effect was not observed with pregabalin. Ataxia and somnolence are common experiences of alcohol intoxication;[126,127] gabapentin has produced similar effects in the human laboratory[59] and, in a study by Peterson (2009), gabapentin was identified in 137 driving impairment cases in Washington.[37] Studies to examine how gabapentin misuse may impact psychomotor effects are warranted.

Gabapentin abuse signals were identified using national AE reporting data from the United States, however, this is not just an American phenomenon. As mentioned earlier, a review by Smith et al. (2016) noted that gabapentin misuse reports have also come from the United Kingdom, Germany, Finland, India, South Africa, and France. Further, in a recent paper by Chiappini and Schifano (2016) similar methodologies as those conducted in the present study were used to examine gabapentinoid misuse in the European Medicines Agency Suspected

Adverse Drug Reactions database.[128] The authors identified nearly 5% of misuse/abuse/dependence spontaneous AE reports were associated with gabapentin.[128] Evaluation of the Canadian Vigilance Adverse Drug Reaction Online Database also demonstrated gabapentin misuse.[129]

The current study has several limitations. FAERS has a low spontaneous reporting rate, containing an average of only 6% of all occurring drug-associated AEs.[130] As a result, causality, incidence, and prevalence cannot be determined.[131,132] However, the abuse signals detected herein provide a critical indication that further examination is required,[133] especially in the context of a growing number of case reports of gabapentin misuse. Also, many external factors affect FAERS reporting such as the "notoriety effect,"[134] which is the uptick in reporting resulting from a safety alert, or the "ripple effect" where reporting is accelerated following notoriety of a drug in the same class,[134] among others.[135-137] By cumulating data over the 11-year study period, we at least partially mitigated the impact of any fluctuations present in the data. It is important to note that some of the signals detected could be confounded by the population for whom they are being prescribed (e.g., gabapentinoids prescribed off label for mood disorders) as well as due to interactions with concomitant medications. However, the purpose of this study was not to assess cause-and-effect, rather to attempt to corroborate described effects in case reports and to provide hypotheses for future controlled clinical studies.

This study identified abuse-related signals for gabapentin, as well as elucidated several CNS effects that may be associated with its abuse. Future studies are necessary to determine whether these are a direct result of gabapentin and

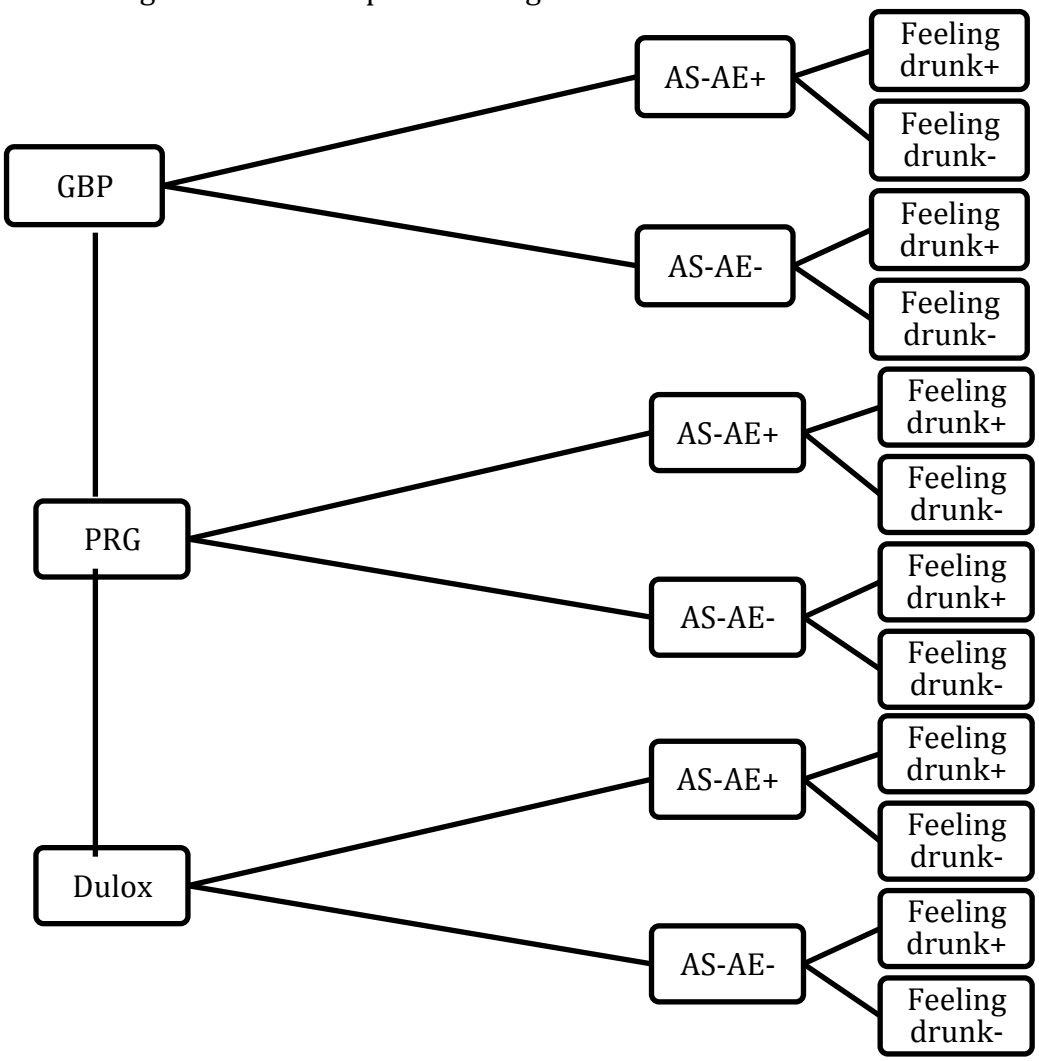
investment in larger, controlled pharmacological studies is warranted. Prescribers should be aware of gabapentin's abuse liability and effects that may accompany its misuse.

Table 4.1. 2x2 contingency table used for pharmacovigilance measures.

	With AE of interest	Without AE of interest	Total
Drug of interest	n_{11}	n_{12}	n_{1+}
Without drug of interest	n_{21}	n_{22}	n_{2+}
Total	n_{+1}	n_{+2}	n

n_{1+}: marginal frequency of the drug of interest; n_{+1}: marginal frequency of the AE of interest; n: total sample size.

Figure 4.1. Tree diagram of an example of the loglinear model.



GBP: gabapentin; PRG: pregabalin; Dulox: duloxetine; AS-AE: abuse-specific-adverse event; +: present; -: absent.

Figure 4.2. Adverse reporting trends by quarter, 2005-2015

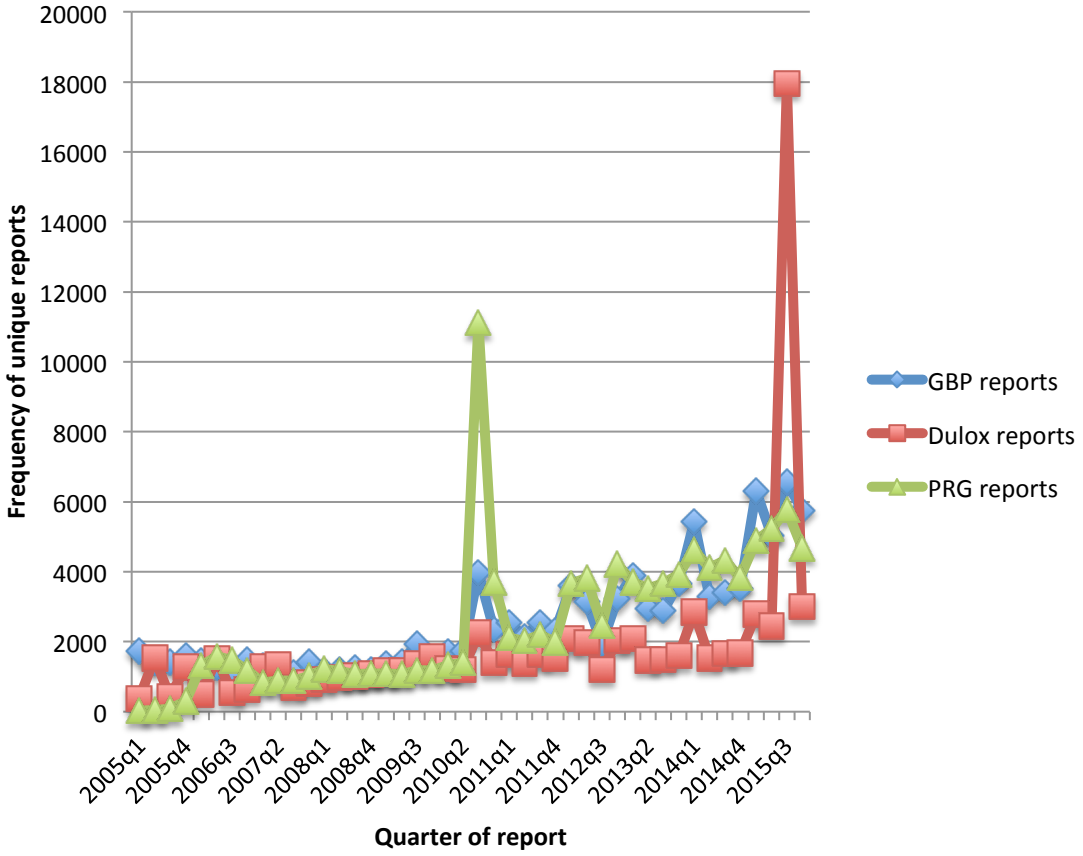


Table 4.2. Highest frequency of adverse events by drug, 2005-2015

Gabapentin (n)	Pregabalin (n)	Duloxetine (n)
Drug ineffective (10668)	Pain (11568)	Nausea (7945)
Pain (8370)	Drug ineffective (10199)	Dizziness (6307)
Nausea (7348)	Dizziness (7478)	Headache (5516)
Fatigue (6610)	Weight increased (6591)	Pain (5464)
Dizziness (5936)	Somnolence (5744)	Fatigue (5300)
Headache (5585)	Nausea (5119)	Drug ineffective (5291)
Fall (5285)	Malaise (4738)	Drug withdrawal syndrome (4870)
Dyspnea (5173)	Pain in extremity (4698)	Depression (4577)
Diarrhea (5130)	Fatigue (4687)	Insomnia (4481)
Depression (4899)	Feeling abnormal (4445)	Feeling abnormal (4106)

Table 4.3. Frequency of abuse-related adverse event reports by case drug, 2005-2015

Preferred term	Gabapentin (n=111607) n(%)	Pregabalin (n=111012) n(%)	Duloxetine (n=80251) n(%)
Addiction	0 (0)	0 (0)	0 (0)
Aggression	667 (.60)	596 (.54)	746 (.93)
Ataxia	298 (.27)	267 (.24)	117 (.15)
Confusional state	2902 (2.60)	2733 (2.46)	2057 (2.56)
Delirium	451 (.40)	408 (.37)	300 (.37)
Delusion	196 (.18)	125 (.11)	180 (.22)
Dependence	97 (.09)	76 (.07)	51 (.06)
Disorientation	840 (.75)	824 (.74)	625 (.78)
Dissociation	58 (.05)	97 (.09)	109 (.14)
Dizziness	5921 (5.31)	7508 (6.76)	6270 (7.81)
Drug abuse	597 (.53)	766 (.69)	294 (.37)
Drug abuser	134 (.12)	33 (.03)	33 (.04)
Drug addict	0 (0)	0 (0)	0 (0)
Drug dependence	614 (.55)	704 (.63)	248 (.31)
Drug diversion	11 (.01)	11 (.01)	30 (.04)
Drug tolerance	105 (.09)	111 (.10)	47 (.06)
Drug withdrawal syndrome	1059 (.95)	1618 (1.46)	4857 (6.05)
Elevated mood	6 (.01)	20 (.02)	20 (.02)
Euphoric mood	190 (.17)	597 (.54)	159 (.20)
Fall	5290 (4.74)	4381 (3.95)	3212 (4.00)
Feeling abnormal	3064 (2.75)	4425 (3.99)	4103 (5.11)
Feeling drunk	242 (.22)	670 (.60)	177 (.22)
Feeling of relaxation	11 (.01)	28 (.03)	18 (.02)
Gait disturbance	3090 (2.77)	3443 (3.10)	1667 (2.08)
Hallucination	1082 (.97)	1061 (.96)	904 (1.13)
Hallucination, auditory	166 (.15)	140 (.13)	191 (.24)
Hallucination, visual	295 (.26)	290 (.26)	208 (.26)

Hallucination, mixed	48 (.04)	57 (.05)	48 (.06)
Incoherent	156 (.14)	128 (.12)	92 (.11)
Intentional (drug) misuse	651 (.58)	726 (.65)	513 (.64)
Intentional overdose	535 (.48)	373 (.34)	409 (.51)
Intoxication	0 (0)	0 (0)	0 (0)
Mood altered	312 (.28)	386 (.35)	382 (.48)
Multiple drug overdose	275 (.25)	47 (.04)	53 (.07)
Off label use	2325 (2.08)	2118 (1.91)	3058 (3.81)
Overdose	1500 (1.34)	1053 (.95)	865 (1.08)
Prescription drug use without a prescription	0 (0)	0 (0)	0 (0)
Psychosis	0 (0)	0 (0)	0 (0)
Acute psychosis	13 (.01)	1 (<.01)	7 (.01)
Rebound psychosis	1 (<.01)	0 (0)	0 (0)
Transient psychosis	0 (0)	0 (0)	0 (0)
Somnolence	3667 (3.29)	5722 (5.15)	2585 (3.22)
Substance abuse	79 (.07)	24 (.02)	26 (.03)
Substance abuser	2 (<.01)	0 (0)	0 (0)
Substance induced psychosis	23 (.02)	10 (.01)	7 (.01)
Substance use	7 (.01)	5 (<.01)	1 (<.01)
Thinking abnormal	676 (.61)	637 (.57)	588 (.73)
Tolerance increased	0 (0)	0 (0)	0 (0)
Any AR-AE	26049 (23.34)	29159 (26.27)	23320 (29.06)

AR-AE: abuse-related adverse event.
Note: Percentages are out of the total number of reports for each case drug.

Table 4.4. Signal scores for gabapentin-, pregabalin-, and duloxetine-associated abuse-related adverse events.

Preferred term	Gabapentin				Pregabalin				Duloxetine			
	PRR (χ^2)	ROR (95% CI)	IC (IC025)	EBGM (EB05)	PRR (χ^2)	ROR (95% CI)	IC (IC025)	EBGM (EB05)	PRR (χ^2)	ROR (95% CI)	IC (IC025)	EBGM (EB05)
Aggression	1.55 (131.29)	**1.56 (1.49, 1.64)**	**0.63 (0.36)**	1.55 (1.45)	1.38 (63.52)	**1.39 (1.31, 1.47)**	**0.46 (0.24)**	1.38 (1.29)	**2.39 (606.42)**	**2.43 (2.36, 2.51)**	**1.25 (0.79)**	**2.38 (2.23)**
Ataxia	**3.48 (535.24)**	**3.64 (3.52, 3.75)**	**1.80 (3.96)**	**3.48 (3.14)**	**3.12 (389.30)**	**3.23 (3.11, 3.36)**	**1.64 (1.01)**	**3.11 (2.79)**	1.88 (48.73)	**1.90 (1.72, 2.08)**	**0.91 (0.44)**	1.88 (1.59)
Confusional state	**2.73 (3143.98)**	**2.81 (2.77, 2.85)**	**1.42 (0.95)**	**2.68 (2.60)**	**2.56 (2579.04)**	**2.63 (2.59, 2.67)**	**1.33 (0.89)**	**2.52 (2.44)**	**2.66 (2099.99)**	**2.71 (2.67, 2.76)**	**1.39 (0.92)**	**2.62 (2.52)**
Delirium	**2.08 (254.89)**	**2.11 (2.02, 2.21)**	**1.05 (0.63)**	2.07 (DNE)	1.88 (168.84)	**1.90 (1.80, 2.00)**	**0.90 (0.53)**	1.87 (1.72)	1.90 (129.05)	**1.92 (1.81, 2.04)**	**0.92 (0.53)**	1.90 (1.71)
Delusion	1.94 (90.18)	**1.97 (1.83, 2.11)**	**0.95 (0.52)**	1.94 (1.70)	1.23 (5.58)	**1.24 (1.06, 1.41)**	**0.30 (0.03)**	1.23 (1.06)	**2.45 (155.92)**	**2.49 (2.35, 2.64)**	**1.29 (0.74)**	**2.45 (2.14)**
Dependence	1.81 (35.83)	**1.84 (1.63, 2.04)**	**0.86 (0.39)**	1.81 (1.51)	1.42 (9.48)	**1.43 (1.20, 1.65)**	**0.50 (0.11)**	1.42 (1.16)	1.31 (3.80)	**1.32 (1.04, 1.59)**	0.39 (0.00)	1.31 (1.02)
Disorientation	**2.55 (800.29)**	**2.62 (2.55, 2.69)**	**1.35 (0.87)**	**2.54 (2.39)**	**2.50 (748.40)**	**2.56 (2.49, 2.63)**	**1.32 (0.84)**	**2.49 (2.34)**	**2.61 (625.58)**	**2.67 (2.59, 2.75)**	**1.38 (0.88)**	**2.60 (2.43)**
Dissociation	**2.00 (29.5**	**2.04 (1.77,**	**1.00**	2.00	**3.34 (161.**	**3.48**	**1.74**	**3.34**	**5.18 (371.**	**5.46**	**2.37**	**5.17**

	1)	**2.30)**	**(0.42)**	(1.56)	**83)**	**(3.28, 3.69)**	**(0.99)**	**(2.75)**	**61)**	**(5.27, 5.65)**	**(1.43)**	**(5.60)**
Dizziness	1.91 (2469.29)	**1.94 (1.91, 1.97)**	**0.90 (0.60)**	1.86 (1.82)	**2.45 (6138.12)**	**2.51 (2.49, 2.54)**	**1.24 (0.84)**	**2.36 (2.31)**	**2.86 (7062.65)**	**2.92 (2.89, 2.95)**	**1.44 (0.97)**	2.71 (DNE)
Drug abuse	1.54 (113.67)	**1.55 (1.47, 1.63)**	**0.62 (0.35)**	1.54 (1.43)	1.97 (371.66)	**2.01 (1.93, 2.08)**	**0.98 (0.61)**	1.97 (1.85)	1.04 (0.47)	1.04 (0.93, 1.16)	0.06 (0.00)	1.04 (0.94)
Drug abuser	1.87 (54.76)	**1.89 (1.72, 2.07)**	**0.90 (0.44)**	1.87 (1.60)	0.46 (21.44)	0.45 (0.11, 0.80)	**-1.12 (0.01)**	0.46 (0.35)	0.63 (7.15)	0.63 (0.29, 0.97)	-0.66 (0.00)	0.63 (DNE)
Drug dependence	**2.56 (588.20)**	**2.63 (2.54, 2.71)**	**1.35 (0.85)**	**2.55 (2.37)**	**2.93 (903.80)**	**3.03 (2.95, 3.10)**	**1.54 (1.00)**	**2.92 (2.73)**	1.42 (30.76)	**1.42 (1.30, 1.55)**	**0.50 (0.22)**	1.42 (1.27)
Drug diversion	0.52 (4.84)	0.52 (-0.07, 1.11)	-0.93 (0.00)	0.52 (0.33)	0.52 (4.87)	0.52 (-0.07, 1.11)	-0.93 (0.00)	0.52 (0.33)	1.97 (14.42)	**1.99 (1.63, 2.35)**	**0.98 (0.28)**	1.97 (1.38)
Drug tolerance	**4.07 (247.19)**	**4.30 (4.10, 4.49)**	**2.02 (1.19)**	**4.07 (3.34)**	**4.30 (285.44)**	**4.55 (4.36, 4.75)**	**2.10 (1.26)**	**4.30 (3.56)**	**2.51 (43.09)**	**2.55 (2.26, 2.85)**	**1.33 (0.60)**	2.51 (DNE)
Drug withdrawal syndrome	**2.07 (590.03)**	**2.11 (2.05, 2.17)**	**1.04 (0.66)**	2.06 (1.95)	**3.17 (2415.25)**	**3.29 (3.24, 3.35)**	**1.65 (1.10)**	**3.14 (3.01)**	**13.77 (54725.12)**	**16.16 (16.13, 16.19)**	**3.70 (2.54)**	**13.00 (12.92)**
Elevated mood	0.76 (0.48)	0.75 (-0.05, 1.56)	-0.41 (0.00)	0.76 (0.39)	**2.51 (18.54)**	**2.58 (2.13, 3.03)**	**1.33 (0.40)**	2.51 (1.57)	**3.46 (35.49)**	**3.57 (3.13, 4.02)**	**1.79 (0.71)**	**3.46 (2.09)**
Euphori	**2.45**	**2.51**	**1.2**	**2.4**	**7.72**	**8.7**	**2.9**	**7.6**	**2.83**	**2.8**	**1.5**	**2.8**

c mood	**(165.91)**	**(2.37, 2.66)**	**9 (0.75)**	**5 (2.15)**	**(3534.35)**	**1 (8.63, 8.80)**	**4 (1.96)**	**9 (7.64)**	**(189.41)**	**9 (2.73, 3.05)**	**0 (0.88)**	**2 (2.44)**
Fall	**2.50 (4626.41)**	**2.57 (2.54, 2.60)**	**1.28 (0.86)**	**2.43 (2.38)**	**2.05 (2310.74)**	**2.09 (2.06, 2.12)**	**1.01 (0.67)**	2.01 (1.96)	**2.07 (1738.93)**	**2.10 (2.07, 2.14)**	**1.02 (0.68)**	2.03 (DNE)
Feeling abnormal	**2.03 (1587.00)**	**2.07 (2.03, 2.10)**	**1.00 (0.66)**	2.00 (1.94)	**2.97 (5635.13)**	**3.07 (3.04, 3.10)**	**1.53 (1.03)**	**2.89 (2.82)**	**3.84 (8264.66)**	**3.97 (3.94, 4.00)**	**1.88 (1.28)**	**3.69 (3.60)**
Feeling drunk	**4.17 (592.69)**	**4.41 (4.28, 4.54)**	**2.06 (1.30)**	**4.17 (3.67)**	**11.58 (6550.01)**	**14.11 (14.02, 14.19)**	**3.53 (2.37)**	**11.52 (11.33)**	**4.20 (436.17)**	**4.37 (4.22, 4.52)**	**2.07 (1.28)**	**4.19 (3.63)**
Feeling of relaxation	1.80 (3.98)	**1.83 (1.23, 2.43)**	0.85 (0.00)	1.80 (0.98)	**4.58 (79.60)**	**4.87 (4.49, 5.26)**	**2.19 (1.07)**	**4.58 (3.09)**	**4.06 (41.94)**	**4.21 (3.74, 4.69)**	**2.02 (0.81)**	**4.05 (2.33)**
Gait disturbance	**2.54 (2851.64)**	**2.61 (2.57, 2.64)**	**1.32 (0.88)**	**2.50 (2.42)**	**2.83 (4030.27)**	**2.92 (2.89, 2.96)**	**1.47 (0.99)**	**2.78 (2.70)**	1.87 (671.15)	**1.89 (1.84, 1.94)**	**0.89 (0.57)**	1.85 (1.78)
Hallucination	**2.44 (928.02)**	**2.50 (2.44, 2.56)**	**1.28 (0.83)**	**2.43 (2.30)**	**2.39 (864.88)**	**2.45 (2.39, 2.51)**	**1.25 (0.81)**	**2.38 (2.26)**	**2.81 (1056.83)**	**2.88 (2.81, 2.94)**	**1.48 (0.96)**	**2.79 (2.64)**
Hallucination, auditory	1.52 (29.76)	**1.53 (1.38, 1.69)**	**0.60 (0.26)**	1.52 (1.32)	1.28 (8.59)	**1.28 (1.12, 1.45)**	**0.35 (0.07)**	1.28 (1.10)	**2.41 (158.37)**	**2.45 (2.30, 2.59)**	**1.26 (0.73)**	**2.40 (2.11)**
Hallucination, visual	**2.38 (239.24)**	**2.44 (2.32, 2.55)**	**1.25 (0.75)**	**2.38 (2.14)**	**2.34 (224.67)**	**2.39 (2.27, 2.51)**	**1.22 (0.73)**	**2.33 (2.10)**	**2.31 (155.79)**	**2.35 (2.21, 2.48)**	**1.20 (0.70)**	**2.31 (2.03)**
Halluci	1.98	**2.01**	**0.9**	1.9	**2.35**	**2.4**	**1.2**	2.35	**2.73**	**2.7**	**1.4**	**2.7**

nation, mixed	(23.70)	**(1.73, 2.30)**	**9 (0.37)**	8 (1.51)	**(44.89)**	**0 (2.14, 2.67)**	**3 (0.57)**	(1.82)	**(53.09)**	**9 (2.50, 3.07)**	**5 (0.69)**	**3 (2.04)**
Incoherent	**2.59 (154.86)**	**2.66 (2.50, 2.82)**	**1.37 (0.78)**	**2.59 (2.23)**	**2.12 (77.24)**	**2.16 (1.99, 2.34)**	**1.09 (0.57)**	2.12 (1.81)	**2.10 (53.82)**	**2.13 (1.92, 2.34)**	**1.07 (0.52)**	2.10 (1.73)
Intentional (drug) misuse	1.69 (185.11)	**1.71 (1.63, 1.79)**	**0.75 (0.45)**	1.69 (1.58)	1.88 (303.50)	**1.91 (1.84, 1.99)**	**0.91 (0.56)**	1.88 (1.76)	1.83 (195.34)	**1.85 (1.76, 1.94)**	**0.87 (0.51)**	1.83 (1.69)
Intentional overdose	1.79 (188.25)	**1.81 (1.73, 1.90)**	**0.84 (0.49)**	1.78 (1.66)	1.24 (18.02)	**1.25 (1.15, 1.35)**	**0.31 (0.11)**	1.24 (1.14)	1.88 (170.37)	**1.90 (1.80, 2.00)**	**0.91 (0.53)**	1.88 (DNE)
Mood altered	1.70 (91.52)	**1.72 (1.61, 1.83)**	**0.77 (0.42)**	1.70 (1.54)	**2.10 (226.50)**	**2.14 (2.04, 2.25)**	**1.07 (0.64)**	2.10 (1.92)	**2.87 (469.88)**	**2.94 (2.84, 3.04)**	**1.52 (0.95)**	**2.86 (2.61)**
Multiple drug overdose	**4.07 (646.61)**	**4.30 (4.17, 4.42)**	**2.02 (1.28)**	**4.06 (3.62)**	0.69 (6.47)	0.69 (0.40, 0.98)	-0.53 (0.00)	0.69 (0.54)	1.08 (0.30)	1.08 (0.81, 1.35)	0.11 (0.00)	1.08 (0.85)
Off label use	1.61 (535.02)	**1.63 (1.59, 1.67)**	**0.68 (0.43)**	1.60 (1.54)	1.46 (308.27)	**1.47 (1.43, 1.52)**	**0.54 (0.33)**	1.45 (1.40)	**2.97 (3880.43)**	**3.04 (3.00, 3.07)**	**1.53 (1.03)**	**2.89 (2.80)**
Overdose	1.65 (381.65)	**1.66 (1.61, 1.72)**	**0.71 (0.44)**	1.64 (1.57)	1.15 (20.57)	**1.15 (1.09, 1.21)**	**0.20 (0.08)**	1.15 (1.09)	1.30 (60.96)	**1.31 (1.24, 1.38)**	**0.38 (0.19)**	1.30 (1.23)
Acute psychosis	0.70 (1.70)	0.70 (0.15, 1.24)	-0.51 (0.00)	0.70 (0.45)	--	--	**-4.22 (0.01)**	0.05 (0.03)	0.52 (3.16)	0.52 (-0.23, 1.26)	-0.95 (0.00)	0.52 (0.29)

Rebound psychosis	--	--	1.90 (0.00)	3.74 (0.41)	--	--	--	--	--	--	--	--
Somnolence	**3.04 (4937.41)**	**3.15 (3.11, 3.18)**	**1.57 (1.06)**	**2.97 (2.89)**	**4.83 (16761.46)**	**5.15 (5.12, 5.18)**	**2.21 (1.51)**	**4.63 (4.59)**	**2.95 (3257.42)**	**3.02 (2.98, 3.06)**	**1.53 (1.02)**	2.88 (DNE)
Substance abuse	1.50 (13.42)	**1.51 (1.29, 1.74)**	**0.59 (0.17)**	1.50 (1.23)	0.46 (15.92)	0.45 (0.05, 0.85)	**-1.14 (0.01)**	0.46 (DNE)	0.68 (3.98)	0.68 (0.29, 1.06)	-0.56 (0.00)	0.68 (0.49)
Substance abuser	--	**14.73 (13.18, 16.28)**	3.58 (0.00)	11.98 (0.99)	--	--	--	--	--	--	--	--
Substance induced psychosis	**4.02 (53.00)**	**4.23 (3.81, 4.66)**	**2.01 (0.88)**	**4.02 (2.53)**	1.74 (3.23)	**1.77 (1.14, 2.40)**	0.80 (0.00)	1.74 (0.93)	1.68 (1.96)	1.70 (0.95, 2.45)	0.75 (0.00)	1.68 (DNE)
Substance use	**2.81 (8.33)**	**2.90 (2.15, 3.66)**	**1.49 (0.08)**	2.81 (1.16)	**2.01 (2.57)**	**2.04 (1.15, 2.93)**	1.01 (0.00)	2.01 (0.78)	--	--	-0.85 (0.00)	--
Thinking abnormal	**4.48 (1843.94)**	**4.75 (4.68, 4.83)**	**2.16 (1.42)**	**4.45 (4.35)**	**4.21 (1576.28)**	**4.45 (4.37, 4.53)**	**2.07 (1.35)**	**4.19 (3.90)**	**5.36 (2097.80)**	**5.67 (5.58, 5.75)**	**2.41 (1.59)**	**5.33 (5.21)**
Any AR-AE	**2.15 (12547.84)**	**2.19 (2.18, 2.21)**	**0.91 (0.62)**	1.88 (1.86)	**2.50 (19668.62)**	**2.55 (2.54, 2.57)**	**1.07 (0.74)**	**2.11 (2.09)**	**2.86 (20271.95)**	**2.91 (2.89, 2.92)**	**1.22 (0.83)**	**2.32 (2.30)**
Any AS-AE	1.76 (1256.07)	**1.78 (1.75, 1.81)**	**0.79 (0.52)**	1.73 (1.68)	1.50 (546.52)	**1.51 (1.47, 1.54)**	**0.57 (0.36)**	1.48 (1.44)	1.40 (263.15)	**1.41 (1.37, 1.45)**	**0.48 (0.29)**	1.39 (DNE)

PRR: proportional reporting ratio; χ^2: chi-squared critical value; ROR: reporting odds ratio; 95% CI: 95% confidence interval; IC: information component; IC025: lower limit of the two-sided 95% credibility interval; EBGM: empirical Bayesian

geometric mean; EB05: lower one-sided 95% credible interval for the EBGM; DNE: does not exist; AR-AE: abuse-related adverse event; AS-AE: abuse-specific adverse event.
-- indicates the frequency was too low to calculate the signal measure
Boldface indicates published signal threshold criteria met.

Table 4.5. Frequency of co-reporting of an abuse-specific adverse event by case drug and non-specific-abuse-related adverse event, 2005-2015

Preferred term	Gabapentin (n=3936) n(%)	Pregabalin (n=3375) n(%)	Duloxetine (n=2303) n(%)
Aggression	90 (2.3)	89 (2.6)	40 (1.7)
Ataxia	49 (1.2)	17 (0.5)	4 (0.2)
Confusional state	186 (4.7)	119 (3.5)	88 (3.8)
Delirium	57 (1.4)	25 (0.7)	25 (1.1)
Delusion	31 (0.8)	24 (0.7)	7 (0.3)
Disorientation	45 (1.1)	41 (1.2)	20 (0.9)
Dissociation	1 (<0.1)	1 (<0.1)	3 (0.1)
Dizziness	175 (4.4)	158 (4.7)	135 (5.9)
Drug abuser	83 (2.1)	18 (0.5)	8 (0.3)
Drug tolerance	46 (1.2)	33 (1.0)	7 (0.3)
Drug withdrawal syndrome	247 (6.3)	165 (4.9)	155 (6.7)
Elevated mood	0 (0)	4 (0.1)	1 (<0.1)
Euphoric mood	44 (1.1)	95 (2.8)	9 (0.4)
Fall	203 (5.2)	142 (4.2)	74 (3.2)
Feeling abnormal	107 (2.7)	160 (4.7)	106 (4.6)
Feeling drunk	7 (0.2)	23 (0.7)	3 (0.1)
Feeling of relaxation	2 (0.1)	6 (0.2)	0 (0)
Gait disturbance	86 (2.2)	92 (2.7)	45 (2.0)
Hallucination	85 (2.2)	58 (1.7)	39 (1.7)
Hallucination, auditory	24 (0.6)	16 (0.5)	4 (0.2)
Hallucination, visual	20 (0.5)	15 (0.4)	8 (0.3)
Hallucination, mixed	3 (0.1)	12 (0.4)	1 (<0.1)
Incoherent	17 (0.4)	6 (0.2)	6 (0.3)
Mood altered	18 (0.5)	19 (0.6)	17 (0.7)
Off label use	79 (2.0)	104 (3.1)	109 (4.7)
Acute psychosis	0 (0)	0 (0)	1 (<0.1)
Rebound psychosis	0 (0)	0 (0)	0 (0)

Somnolence	266 (6.8)	278 (8.2)	102 (4.4)
Substance abuser	1 (<0.1)	0 (0)	0 (0)
Substance induced psychosis	0 (0)	1 (<0.1)	0 (0)
Thinking abnormal	45 (1.1)	23 (0.7)	25 (1.1)

AR-AE: abuse-related adverse event; AS-AE: abuse-specific adverse event.
Note: Frequencies and percentages exclude any cases where case drugs were co-reported.

Table 4.6. Loglinear odds ratio estimates for the interaction between a report of an abuse-specific adverse event and a possible indicator of abuse AE by drug.

Interaction	Gabapentin OR (95% CI)	Pregabalin OR (95% CI)	Duloxetine
AS-AE*Aggression	**2.35 (1.58, 3.48)**	**2.83 (1.91, 4.20)**	REF
AS-AE*Ataxia	**3.04 (1.11, 8.28)**	1.18 (.40, 3.45)	REF
AS-AE*Confusional state	1.14 (.87, 1.49)	.80 (.60, 1.07)	REF
AS-AE*Delirium	1.08 (.66, 1.79)	.54 (.31, .97)	REF
AS-AE*Delusion	**3.15 (1.37, 7.22)**	**4.77 (2.02, 11.27)**	REF
AS-AE*Disorientation	1.30 (.76, 2.22)	1.32 (.73, 2.18)	REF
AS-AE*Dissociation	--	--	--
AS-AE*Dizziness	1.15 (.91, 1.46)	.85 (.67, 1.08)	REF
AS-AE*Drug abuser	--	--	--
AS-AE*Drug tolerance	--	--	--
AS-AE*Drug withdrawal syndrome	**9.50 (7.58, 11.91)**	**3.11 (2.46, 3.94)**	REF
AS-AE*Elevated mood	--	--	--
AS-AE*Euphoric mood	**2.69 (1.25, 5.81)**	**2.24 (1.11, 4.51)**	REF
AS-AE*Fall	1.11 (.84, 1.46)	1.01 (.75, 1.35)	REF
AS-AE*Feeling abnormal	1.15 (.90, 1.58)	1.14 (.96, 1.60)	REF
AS-AE*Feeling drunk	1.24 (.34, 4.54)	1.24 (.40, 3.90)	REF
AS-AE*Feeling of relaxation	--	--	--
AS-AE*Gait disturbance	.66 (.46, .96)	.67 (.46, .96)	REF
AS-AE*Hallucination	1.44 (.97, 2.14)	1.05 (.69, 1.60)	REF
AS-AE*Auditory hallucination	**5.25 (1.86, 14.76)**	**4.12 (1.41, 12.01)**	REF
AS-AE*Visual hallucination	1.06 (.48, 2.36)	.89 (.38, 2.04)	REF
AS-AE*Mixed hallucination	--	--	--
AS-AE*Incoherence	--	--	--
AS-AE*Mood altered	1.05 (.53, 2.07)	.98 (.50, 1.91)	REF
AS-AE*Off label use	.77 (.57, 1.04)	1.31 (1.00, 1.75)	REF
AS-AE*Somnolence	**1.45 (1.14, 1.85)**	.95 (.75, 1.21)	REF
AS-AE*Thinking abnormal	1.27 (.77, 2.10)	.76 (.43, 1.35)	REF

OR: odds ratio; 95% CI: 95% confidence interval; AS-AE: abuse-specific adverse event; REF: referent group.

Note: Missing results correspond to occasions where at least one loglinear assumption was not met.
Boldface indicates a significant result.

CHAPTER FIVE

Discussion and Conclusions

The goal of this dissertation was to assess the etiology and prevalence of gabapentin misuse, abuse, and diversion. Though gabapentin was initially presumed to have limited or no abuse potential,[9-13] which may have contributed to its widespread off-label prescribing, there have been increasing anecdotal and published reports of its misuse by substance abusers in the community and penal system. However, to date, there has been limited systematic evaluation of the scope and risk of gabapentin misuse and its associated effects. Further, gabapentin is not controlled under the Controlled Substance Act, which may be a major omission, given that its close structural relative pregabalin is considered a Schedule V drug (i.e., abuse potential).[16] As such, critical insight is needed to better assess the scope and impact of the risk for gabapentin abuse.

Specifically, to best inform policy-makers and prescribers on the abuse potential of gabapentin, it is necessary to examine gabapentin misuse, abuse, and diversion in a multi-faced approach, namely by the individual, ecological, and pharmacoepidemiological factors associated with this phenomenon. Due to the importance of conducting theory-driven epidemiological research,[23,24] an adaptation of the Concurrent Triangulation Mixed Method Multilevel Theoretical Model[25] was used to guide the dissertation. Additionally, the proposed methodology took advantage of pre-existing data sources, including data collected from two NIH funded cohorts; published, peer-reviewed literature; and the publicly-available

Federal Adverse Event Reporting System data. The specific aims for this exploratory dissertation project were:

1. *To describe gabapentin misuse at the individual level among an existing cohort of drug users in Appalachia.* There is a significant gap in what is known about how gabapentin is misused, what effects make it desirable, how it is obtained for recreational purposes, and whether it has "street value." A qualitative analysis was used to elucidate the individual experience of obtaining and using illicit gabapentin, as well as the motivations behind and effects experienced from its misuse. Individuals were recruited from two existing cohorts of active drug users that indicated recent use of illicit gabapentin to participate in focus groups. Survey data relevant to gabapentin misuse, previously collected within the cohort parent studies, was used to supplement the qualitative data.

2. *To estimate the prevalence and effects of, motivations behind, and risk factors for gabapentin misuse, abuse, and diversion ecologically.* To date, there has not been a systematic assessment or assemblage of the evidence of gabapentin misuse, abuse, and diversion. Further, it is unknown what risk factors exist for gabapentin abuse. A thorough review was conducted of existing peer-reviewed literature on illicit and/or misused gabapentin to estimate the prevalence of its abuse and identify patterns that may suggest explicit risk for abuse. The review used a combination of statistical inference and qualitative analysis methods.

3. *To evaluate gabapentin misuse and abuse in the Federal Adverse Event Reporting System (FAERS) using traditional and innovative pharmacovigilance signal measures.* This aim drew on a nationally maintained, publicly available dataset of drug adverse

events (AEs) to evaluate the association between AEs indicative of misuse, abuse, and diversion and gabapentin. Traditional signal measures (i.e., proportional reporting ratio, reporting odds ratio, information component, empirical Bayes geometric mean) were used to estimate the strength of association between a particular AE and gabapentin. A novel application of loglinear modeling was also used to evaluate the association between co-reports of abuse and other potential indicators of abuse and gabapentin, which were compared to a positive and negative control (pregabalin and duloxetine, respectively).

Summary of findings

Chapter two helped to characterize and explain gabapentin misuse within two substance abuse populations in Appalachian Kentucky. A correlation between gabapentin misuse and nonmedical prescription opioid use was found; a finding supported by other recently published studies.[15,32,34,42] Among focus group participants, gabapentin initiation typically followed receiving a prescription from their doctor for an off-label use (e.g., treatment of non-herpetic pain), which could be a factor in facilitating its misuse. Additionally, several long-term drug users noted that younger people were misusing gabapentin. Though no information was gathered on whether young drug users were initiating drug use with gabapentin, this could be a likely possibility since many providers are unaware of its widespread misuse and are willing to prescribe it. This is an important area for further examination.

Chapter three estimated and described the prevalence and effects of, motivations behind, and risk factors for gabapentin misuse, abuse, and diversion

through a systematic review of peer-reviewed published literature. Thirty-three papers were included in the study, consisting of 23 case studies and 11 epidemiological reports from seven countries. Population prevalence of gabapentin misuse was reported to be approximately 1%, though the prevalence is much higher within populations of people who abuse opioids (15-22%). Between 40-65% of individuals who misuse gabapentin have a prescription. The review identified an array of subjective experiences reminiscent of opioids, benzodiazepines, and psychedelics were reported over a range of doses, including those with clinical recommendations. Gabapentin was misused primarily for recreational purposes, self-medication, or intentional self-harm and was misused alone or in combination with other substances, especially opioids, benzodiazepines, and/or alcohol. Individuals with histories of drug abuse were most often involved in its misuse.

Chapter four performed a post-marketing pharmacovigilance assessment of FAERS data from 2005 to 2015. Abuse-related signals were identified for gabapentin, pregabalin, and duloxetine. The strongest gabapentin-AE signals were found with ataxia, drug tolerance, and feeling drunk; these signals occurred with pregabalin as well. Examination of the co-reporting of an abuse-specific AE (AS-AE; e.g., substance abuse) and a possible abuse indicator AE (e.g., euphoria) revealed that co-endorsement of an AS-AE and drug withdrawal syndrome, AS-AE and auditory hallucinations, AS-AE and delusions, and AS-AE with euphoric mood occurred with significantly higher odds for both gabapentin and pregabalin independently, compared to duloxetine. The presence of abuse-related signals for gabapentin is important for regulatory policy and providers prescribing gabapentin.

Limitations

The findings from this dissertation should be considered in light of several limitations, described in detail within the corresponding chapter(s), but highlighted for posterity here. Results from chapter two were derived solely from self-report, either through a survey or through conversation in the focus groups. Chapter three excluded grey literature from review, which may have contained greater detail about risk factors for and results of gabapentin misuse. Lastly, chapter four utilized the FAERS publicly available database, which has a very low spontaneous reporting rate and may not reflect experiences from the larger population.

Conclusions

In spite of limitations, this dissertation fills a critical gap in the literature, given the abundance of case and anecdotal reports of widespread gabapentin abuse, but no rigorous assessment of these abuses. Further, there has been limited understanding of what may contribute to gabapentin misuse, abuse, and diversion, as well as identification of its risk factors. Gabapentin, when used appropriately, is effective for its indicated uses and may be a valuable alternative to more problematic opioid analgesics;[43] however, we must first understand the abuse potential of gabapentin and for whom it may be counter-effective.

It is clear that gabapentin is misused for a variety of reasons throughout the United States and internationally. It is also clear that due to continuous claims that gabapentin has no abuse potential, providers have comfortably prescribed gabapentin off label for many disorders, including those of pain and drug and alcohol abuse. While gabapentin may be effective for certain non-approved usages,

widespread off-label prescribing of gabapentin has flooded the market thereby facilitating its diversion. Findings from the studies included in this dissertation provide definitive evidence of the following: (1) that gabapentin should be prescribed with caution, especially for individuals with a history of substance abuse, and providers should be aware that it is abused; (2) controlled pharmacological experiments are needed to better understand and characterize gabapentin psychopharmacology and the risks associated with gabapentin misuse; and (3) a critical reexamination of gabapentin's abuse liability and regulation are warranted.

APPENDIX A

Systematic review search queries

PubMed
(Gabapentin[supplementary concept] OR
Gabapentin OR
Gralise OR
Neurontin OR
Horizant OR
Fanatrex)

AND

(Prescription drug misuse[MeSH] OR
Misuse OR
Abuse OR
Substance-related Disorders [MeSH] OR
Drug Overdose[MeSH] OR
Overdose OR
Addict* OR
Dependen* OR
withdrawal)

Web of Science
(Gabapentin OR
Gralise OR
Neurontin OR
Horizant OR
Fanatrex)

AND

(Misuse OR
Abuse OR
Overdose OR
Addict* OR
Dependen* OR
withdrawal)

CINAHL
((MH "Gabapentin") OR
gabapentin OR
Gralise OR
Neurontin OR
Horizant OR

Fanatrex)

AND

((MH “Substance Abuse”) OR
“substance abuse” OR
“misuse” OR
“abuse” OR
(MH “Overdose” OR)
“overdose” OR
Addict* OR
Dependen* OR
withdrawal)

PsycINFO
(“Gabapentin” OR
“Gralise” OR
“Neurontin” OR
“Horizant” OR
“Fanatrex”)

AND

(DE “Drug Abuse” OR
DE “Drug Abuse Prevention” OR
DE “Drug Overdoses” OR
“Abuse” OR
“Misuse” OR
“Overdose” OR
Addict* OR
Dependen* OR
withdrawal)

Cochrane
(gabapentin OR
Gralise OR
Neurontin OR
Horizant)

AND

(misuse OR
abuse OR
overdose OR
addict* OR
dependen* OR

withdrawal)

REFERENCES

1. Mack A. Examination of the evidence for off-label use of gabapentin. *Journal of managed care pharmacy : JMCP.* 2003;9(6):559-568.
2. Maneuf YP, Gonzalez MI, Sutton KS, Chung FZ, Pinnock RD, Lee K. Cellular and molecular action of the putative GABA-mimetic, gabapentin. *Cellular and molecular life sciences : CMLS.* 2003;60(4):742-750.
3. Dougherty JA, Rhoney DH. Gabapentin: a unique anti-epileptic agent. *Neurological research.* 2001;23(8):821-829.
4. Petroff OA, Hyder F, Rothman DL, Mattson RH. Effects of gabapentin on brain GABA, homocarnosine, and pyrrolidinone in epilepsy patients. *Epilepsia.* 2000;41(6):675-680.
5. Compton P, Kehoe P, Sinha K, Torrington MA, Ling W. Gabapentin improves cold-pressor pain responses in methadone-maintained patients. *Drug and alcohol dependence.* 2010;109(1-3):213-219.
6. Hamer AM, Haxby DG, McFarland BH, Ketchum K. Gabapentin use in a managed medicaid population. *Journal of managed care pharmacy : JMCP.* 2002;8(4):266-271.
7. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med.* 2006;166(9):1021-1026.
8. Newman M. Bitter pills for drug companies. *BMJ (Clinical research ed).* 2010;341:c5095.

9. Bonnet U, Banger M, Leweke FM, Maschke M, Kowalski T, Gastpar M. Treatment of alcohol withdrawal syndrome with gabapentin. *Pharmacopsychiatry.* 1999;32(3):107-109.

10. Lavigne JE, Heckler C, Mathews JL, et al. A randomized, controlled, double-blinded clinical trial of gabapentin 300 versus 900 mg versus placebo for anxiety symptoms in breast cancer survivors. *Breast cancer research and treatment.* 2012;136(2):479-486.

11. Myrick H, Malcolm R, Brady KT. Gabapentin treatment of alcohol withdrawal. *The American journal of psychiatry.* 1998;155(11):1632.

12. Nunes EV. Gabapentin: a new addition to the armamentarium for alcohol dependence? *JAMA internal medicine.* 2014;174(1):78-79.

13. Voris J, Smith NL, Rao SM, Thorne DL, Flowers QJ. Gabapentin for the treatment of ethanol withdrawal. *Substance abuse.* 2003;24(2):129-132.

14. The Henry J. Kaiser Family Foundation. Medicaid Benefits: Prescription Drugs. 2012; http://kff.org/medicaid/state-indicator/prescription-drugs/. Accessed August 24, 2015.

15. Smith RV, Lofwall MR, Havens JR. Abuse and diversion of gabapentin among nonmedical prescription opioid users in Appalachian Kentucky. *The American journal of psychiatry.* 2015;172(5):487-488.

16. Drug Enforcement Administration Department of Justice. Schedules of controlled substances: placement of pregabalin into schedule V. Final rule. *Federal register.* 2005;70(144):43633-43635.

17. Papazisis G, Tzachanis D. Pregabalin's abuse potential: a mini review focusing on the pharmacological profile. *International journal of clinical pharmacology and therapeutics.* 2014;52(8):709-716.

18. Sills GJ. The mechanisms of action of gabapentin and pregabalin. *Current opinion in pharmacology.* 2006;6(1):108-113.

19. Njie-Carr V. Violence experiences among HIV-infected women and perceptions of male perpetrators' roles: a concurrent mixed method study. *The Journal of the Association of Nurses in AIDS Care : JANAC.* 2014;25(5):376-391.

20. Dixon BE, Grannis SJ, Revere D. Measuring the impact of a health information exchange intervention on provider-based notifiable disease reporting using mixed methods: a study protocol. *BMC medical informatics and decision making.* 2013;13:121.

21. Eastwood JG, Jalaludin BB, Kemp LA. Realist explanatory theory building method for social epidemiology: a protocol for a mixed method multilevel study of neighbourhood context and postnatal depression. *SpringerPlus.* 2014;3:12.

22. Koorts H, Gillison F. Mixed method evaluation of a community-based physical activity program using the RE-AIM framework: practical application in a real-world setting. *BMC public health.* 2015;15:1102.

23. Carpiano RM, Daley DM. A guide and glossary on post-positivist theory building for population health. *Journal of epidemiology and community health.* 2006;60(7):564-570.

24. O'Campo P. Invited commentary: Advancing theory and methods for multilevel models of residential neighborhoods and health. *American journal of epidemiology.* 2003;157(1):9-13.

25. Tashakkori A, Teddlie C. Handbook on mixed methods in the behavioral and social sciences. Thousand Oaks, CA: Sage; 2003.

26. World Health Organization. Lexicon of alcohol and drug terms published by the World Health Organization. 2015; http://www.who.int/substance_abuse/terminology/who_lexicon/en/. Accessed August 14, 2015.

27. Inciardi JA, Surratt HL, Kurtz SP, Burke JJ. The diversion of prescription drugs by health care workers in Cincinnati, Ohio. *Substance use & misuse.* 2006;41(2):255-264.

28. Larance B, Degenhardt L, Lintzeris N, Winstock A, Mattick R. Definitions related to the use of pharmaceutical opioids: extramedical use, diversion, non-adherence and aberrant medication-related behaviours. *Drug and alcohol review.* 2011;30(3):236-245.

29. Morse JM. Approaches to qualitative-quantitative methodological triangulation. *Nursing research.* 1991;40(2):120-123.

30. Patton M. Sampling and triangulation. *Qualiative Evaluation and Research Methods Newbury Park: Sage Publications.* 1990:165-198.

31. Creswell JW. Designing and conducting mixed methods research. 2007.

32. Baird CR, Fox P, Colvin LA. Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers. *European addiction research.* 2014;20(3):115-118.

33. Kapil V, Green JL, Le Lait MC, Wood DM, Dargan PI. Misuse of the gamma-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. *British journal of clinical pharmacology.* 2014;78(1):190-191.

34. Wilens T, Zulauf C, Ryland D, Carrellas N, Catalina-Wellington I. Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions.* 2015;24(2):173-177.

35. Reeves RR, Ladner ME. Potentiation of the effect of buprenorphine/naloxone with gabapentin or quetiapine. *The American journal of psychiatry.* 2014;171(6):691.

36. Schifano F, D'Offizi S, Piccione M, et al. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. *Psychotherapy and psychosomatics.* 2011;80(2):118-122.

37. Peterson BL. Prevalence of gabapentin in impaired driving cases in Washington State in 2003-2007. *Journal of analytical toxicology.* 2009;33(8):545-549.

38. Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse and diversion: a systematic review. *Addiction.* 2016;111(7):1160-1174.

39. Havens JR, Lofwall MR, Frost SD, Oser CB, Leukefeld CG, Crosby RA. Individual and network factors associated with prevalent hepatitis C infection among rural Appalachian injection drug users. *American journal of public health.* 2013;103(1):e44-52.

40. Staton-Tindall M, Harp KL, Minieri A, et al. An exploratory study of mental health and HIV risk behavior among drug-using rural women in jail. *Psychiatric rehabilitation journal.* 2015;38(1):45-54.

41. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qualitative health research.* 2005;15(9):1277-1288.

42. Bastiaens L, Galus J, Mazur C. Abuse of Gabapentin is Associated with Opioid Addiction. *The Psychiatric quarterly.* 2016;87(4):763-767.

43. Dowell D, Haegerich TM, Chou R. *CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016.* 2016.

44. Kruszewski SP, Paczynski RP, Kahn DA. Gabapentin-induced delirium and dependence. *Journal of psychiatric practice.* 2009;15(4):314-319.

45. Salehi M, Kheirabadi GR, Maracy MR, Ranjkesh M. Importance of gabapentin dose in treatment of opioid withdrawal. *Journal of clinical psychopharmacology.* 2011;31(5):593-596.

46. Crockford D, White WD, Campbell B. Gabapentin use in benzodiazepine dependence and detoxification. *Canadian journal of psychiatry Revue canadienne de psychiatrie.* 2001;46(3):287.

47. Smithson J. Using and analysing focus groups: limitations and possibilities. *International journal of social research methodology.* 2000;3(2):103-119.

48. Mersfelder TL, Nichols WH. Gabapentin: Abuse, Dependence, and Withdrawal. *The Annals of pharmacotherapy.* 2016;50(3):229-233.

49. Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse and diversion: a systematic review. *Addiction (Abingdon, England).* 2016;111(7):1160-1174.

50. Suman-Chauhan N, Webdale L, Hill DR, Woodruff GN. Characterisation of [3H]gabapentin binding to a novel site in rat brain: homogenate binding studies. *European journal of pharmacology.* 1993;244(3):293-301.

51. Thurlow RJ, Brown JP, Gee NS, Hill DR, Woodruff GN. [3H]gabapentin may label a system-L-like neutral amino acid carrier in brain. *European journal of pharmacology.* 1993;247(3):341-345.

52. Gee NS, Brown JP, Dissanayake VU, Offord J, Thurlow R, Woodruff GN. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. *The Journal of biological chemistry.* 1996;271(10):5768-5776.

53. European Medicines Agency. *Summary information on referral opinion pursuant to Article 30 of Council Directive 2001/83/EC for Neurontin and associated names (see Annex I) International Non-Proprietary Name (INN): Gabapentin: Background information.* 2006.

54. National Institute for Health and Clinical Excellence. *Neuropathic pain in adults: pharmacological management in non-specialist settings.* 2013.

55. European Medicines Agency. *Annex III: Summary of Product Characteristics, Labelling, and Package Leaflet.* June 9, 2006 2006.

56. Pfizer. Neurontin U.S. Physician Prescribing Information. 2014.

57. Hart CL, Ward AS, Collins ED, Haney M, Foltin RW. Gabapentin maintenance decreases smoked cocaine-related subjective effects, but not self-administration by humans. *Drug and alcohol dependence.* 2004;73(3):279-287.

58. Lile JA, Kelly T, Hays L. Separate and combined effects of gabapentin and Δ 9-THC doses in cannabis users discriminating Δ 9-THC. College on Problems of Drug Dependence; June, 2013; San Diego, California.

59. Bisaga A, Evans SM. The acute effects of gabapentin in combination with alcohol in heavy drinkers. *Drug and alcohol dependence.* 2006;83(1):25-32.

60. Cantrell FL, Mena O, Gary RD, McIntyre IM. An acute gabapentin fatality: a case report with postmortem concentrations. *International journal of legal medicine.* 2015;129(4):771-775.

61. Fischer JH, Barr AN, Rogers SL, Fischer PA, Trudeau VL. Lack of serious toxicity following gabapentin overdose. *Neurology.* 1994;44(5):982-983.

62. Howland RH. Gabapentin: can it be misused? *Journal of psychosocial nursing and mental health services.* 2014;52(1):12-15.

63. Markowitz JS, Finkenbine R, Myrick H, King L, Carson WH. Gabapentin abuse in a cocaine user: implications for treatment? *Journal of clinical psychopharmacology.* 1997;17(5):423-424.

64. Pittenger C, Desan PH. Gabapentin abuse, and delirium tremens upon gabapentin withdrawal. *The Journal of clinical psychiatry.* 2007;68(3):483-484.

65. Reccoppa L, Malcolm R, Ware M. Gabapentin abuse in inmates with prior history of cocaine dependence. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions.* 2004;13(3):321-323.

66. Reeves RR, Burke RS. Abuse of combinations of gabapentin and quetiapine. *The primary care companion for CNS disorders.* 2014;16(5):16.

67. Roberge RJ, Francis EH, 3rd. Use of naloxone in valproic acid overdose: case report and review. *The Journal of emergency medicine.* 2002;22(1):67-70.

68. Rohman L, Hebron A. Acute dystonic reaction caused by gabapentin. *The Journal of emergency medicine.* 2014;46(3):e89.

69. Satish R, Kandasamy A, Jayarajan D, Benegal V. Gabapentin dependence in a patient with opioid dependence syndrome. *The Journal of neuropsychiatry and clinical neurosciences.* 2015;27(1):e64.

70. Victorri-Vigneau C, Guerlais M, Jolliet P. Abuse, dependency and withdrawal with gabapentin: a first case report. *Pharmacopsychiatry.* 2007;40(1):43-44.

71. Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness R. In: Eden J, Levit L, Berg A, Morton S, eds. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington (DC): National Academies Press (US) Copyright 2011 by the National Academy of Sciences. All rights reserved.; 2011.

72. Smith BH, Higgins C, Baldacchino A, Kidd B, Bannister J. Substance misuse of gabapentin. *The British journal of general practice : the journal of the Royal College of General Practitioners.* 2012;62(601):406-407.

73. Hakkinen M, Vuori E, Kalso E, Gergov M, Ojanpera I. Profiles of pregabalin and gabapentin abuse by postmortem toxicology. *Forensic science international.* 2014;241:1-6.

74. Wills B, Reynolds P, Chu E, et al. Clinical outcomes in newer anticonvulsant overdose: a poison center observational study. *Journal of medical toxicology : official journal of the American College of Medical Toxicology.* 2014;10(3):254-260.

75. Klein-Schwartz W, Shepherd JG, Gorman S, Dahl B. Characterization of gabapentin overdose using a poison center case series. *Journal of toxicology Clinical toxicology.* 2003;41(1):11-15.

76. Seale JP, Dittmer T, Sigman EJ, Clemons H, Johnson JA. Combined abuse of clonidine and amitriptyline in a patient on buprenorphine maintenance treatment. *Journal of addiction medicine.* 2014;8(6):476-478.

77. Barrueto F, Jr., Green J, Howland MA, Hoffman RS, Nelson LS. Gabapentin withdrawal presenting as status epilepticus. *Journal of toxicology Clinical toxicology.* 2002;40(7):925-928.

78. Fernandez MC, Walter FG, Petersen LR, Walkotte SM. Gabapentin, valproic acid, and ethanol intoxication: elevated blood levels with mild clinical effects. *Journal of toxicology Clinical toxicology.* 1996;34(4):437-439.

79. Rasimas JJ, Burkhart KK. Cardiac conduction disturbances after an overdose of nefazodone and gabapentin. *The American journal of emergency medicine.* 2006;24(7):886-888.

80. Spiller HA, Dunaway MD, Cutino L. Massive gabapentin and presumptive quetiapine overdose. *Veterinary and human toxicology.* 2002;44(4):243-244.

81. Stopforth J. Overdose with gabapentin and lamotrigine. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde.* 1997;87(10):1388.

82. Schauer SG, Varney SM. Gabapentin overdose in a military beneficiary. *Military medicine.* 2013;178(1):e133-135.

83. Jones H, Aguila E, Farber HW. Gabapentin toxicity requiring intubation in a patient receiving long-term hemodialysis. *Annals of internal medicine.* 2002;137(1):74.

84. Koschny R, Lutz M, Seckinger J, Schwenger V, Stremmel W, Eisenbach C. Extracorporeal life support and plasmapheresis in a case of severe polyintoxication. *Journal of Emergency Medicine.* 2014;47(5):527-531.

85. Middleton O. Suicide by gabapentin overdose. *Journal of forensic sciences.* 2011;56(5):1373-1375.

86. Smith RV, Lofwall MR, Havens JR. Gabapentin focus groups among illicit drug users. Unpublished.

87. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clinical pharmacokinetics.* 2010;49(10):661-669.

88. United Nations Office on Drugs and Crime. *World Drug Report.* 2012.

89. Ministry of Health Singapore. Drug Subsidies. 2015; https://www.moh.gov.sg/content/moh_web/home/costs_and_financing/schemes_subsidies/drug_subsidies.html. Accessed December 26, 2015.

90. Australian Government Department of Health The Pharmacy Benefits Scheme. Gabapentin. 2016; http://www.pbs.gov.au/medicine/item/4591P-8505P. Accessed December 26, 2015.

91. Smith N, Quansah K, Chelak K, Fitzsimmons H. *Narcotics, Benzodiazepines, Stimulants, and Gabapentin: Policies, Initiatives, and Practices Across Canada, 2014.* Ottawa: Canadian Agency for Drugs and Technologies in Health;2014.

92. Drug Enforcement Administration Department of Justice. Controlled Substances. 2015; http://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf. Accessed December 26, 2015.

93. Public Health England and NHS England. *Advice for prescribers on the risk of the misuse of pregabalin and gabapentin.* 2014.

94. EMCDDA-Europol. *Annual Report on the implementation of Council Decision 2005/387/JHA; Annex 2 - New psychoactive substances reported to the EMCDDA and Europol for the first time in 209 underf the term of Council.* 2009.

95. Cora-Locatelli G, Greenberg BD, Martin JD, Murphy DL. Rebound psychiatric and physical symptoms after gabapentin discontinuation. *The Journal of clinical psychiatry.* 1998;59(3):131.

96. Finch CK, Eason J, Usery JB. Gabapentin withdrawal syndrome in a post-liver transplant patient. *Journal of pain & palliative care pharmacotherapy.* 2010;24(3):236-238.

97. Hellwig TR, Hammerquist R, Termaat J. Withdrawal symptoms after gabapentin discontinuation. *American journal of health-system pharmacy :*

AJHP : official journal of the American Society of Health-System Pharmacists. 2010;67(11):910-912.

98. Norton JW. Gabapentin withdrawal syndrome. *Clinical neuropharmacology.* 2001;24(4):245-246.

99. Rosebush PI, MacQueen GM, Mazurek MF. Catatonia following gabapentin withdrawal. *Journal of clinical psychopharmacology.* 1999;19(2):188-189.

100. Tran KT, Hranicky D, Lark T, Jacob N. Gabapentin withdrawal syndrome in the presence of a taper. *Bipolar disorders.* 2005;7(3):302-304.

101. Mah L, Hart M. Gabapentin withdrawal: case report in an older adult and review of the literature. *Journal of the American Geriatrics Society.* 2013;61(9):1635-1637.

102. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA.* 2016;315(15):1624-1645.

103. U.S. Food and Drug Administration. *Center for Drug Evaluation and Research 2015-2016 Drug Safety Priorities: Initiatives and Innovation.* 2016.

104. U.S. Food and Drug Administration. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). 2016; http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/. Accessed April 12, 2016.

105. Poluzzi E, Piccinni C, Raschi E, De Ponti F. *Data Mining Techniques in Pharmacovigilance: Analysis of the Publicly Accessible FDA Adverse Event Reporting System (AERS).* INTECH Open Access Publisher Rijeka; 2012.

106. World Health Organization. Pharmacovigilance. 2016; http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/. Accessed April 12, 2016.

107. World Health Organization. Safety monitoring of medicinal products: reporting system for the general public. *Geneva: WHO.* 2012.

108. Bate A, Lindquist M, Edwards I, et al. A Bayesian neural network method for adverse drug reaction signal generation. *European journal of clinical pharmacology.* 1998;54(4):315-321.

109. Evans S, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiology and drug safety.* 2001;10(6):483-486.

110. Szarfman A, Machado SG, O'neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug safety.* 2002;25(6):381-392.

111. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiology and drug safety.* 2002;11(1):3-10.

112. U.S. Food and Drug Administration. FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files. 2016; http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm. Accessed April 12, 2016.

113. U.S. Food and Drug Administration. Drug Approval Package: Lyrica (Pregabalin) Capsules. 2005; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021446_LyricaTOC.cfm. Accessed November 19, 2016.

114. MedDRA. http://www.meddra.org. Accessed April 12, 2016.

115. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology. *"ASC_NTS.DOC" file for the Quarterly Data Extract (QDE) from the FDA Adverse Event Reporting System (FAERS).* 2015.

116. Moore N, Kreft‐Jais C, Haramburu F, et al. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non‐case study in the French pharmacovigilance system database. *British journal of clinical pharmacology.* 1997;44(5):513-518.

117. European Medicines Agency. *Overview of comments received on draft guideline on the use of statistical signal detection methods in the EudraVigilance data analysis system (EMEA/106464/2006).* London, United Kingdom2008.

118. Bannister W. Matching without unique identifiers—Fuzzy matching applications with SAS® software. *Cary, NC: SAS® Institute.* 2004.

119. Fan Z, Westat R. Matching character variables by sound: a closer look at Soundex function and sounds-like operator. *SAS® Users Group Institute, Paper.* 2004:072-029.

120. Patridge C. The fuzzy feeling SAS provides: Electronic matching of records without common keys. Paper presented at: Proceedings of the 22nd Annual SAS Users Group International Conference1997.

121. Banda JM, Evans L, Vanguri RS, Tatonetti NP, Ryan PB, Shah NH. A curated and standardized adverse drug event resource to accelerate drug safety research. *Scientific data.* 2016;3:160026.

122. Zhang Z, Infante A, Meit M, English N, Dunn M, Bowers K. An analysis of mental health and substance abuse disparities & access to treatment services in the Appalachian region. *Final report Washington: Appalachian Regional Commission.* 2008.

123. Schwan S, Sundstrom A, Stjernberg E, Hallberg E, Hallberg P. A signal for an abuse liability for pregabalin--results from the Swedish spontaneous adverse drug reaction reporting system. *Eur J Clin Pharmacol.* 2010;66(9):947-953.

124. Smith SM, Dart RC, Katz NP, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. *Pain.* 2013;154(11):2287-2296.

125. Ahmed I, Poncet A. PhViD: an R package for pharmacovigilance signal detection. *R package version.* 2013;1(6).

126. Diener HC, Dichgans J, Bacher M, Hulser J, Liebich H. Mechanisms of postural ataxia after intake of alcohol. *Zeitschrift fur Rechtsmedizin Journal of legal medicine.* 1983;90(3):159-165.

127. Roehrs T, Roth T. Sleep, sleepiness, sleep disorders and alcohol use and abuse. *Sleep medicine reviews.* 2001;5(4):287-297.

128. Chiappini S, Schifano F. A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. *CNS drugs.* 2016;30(7):647-654.

129. Zhang M, Sproule B. Problematic pregabalin and gabapentin use: Results from the Canada Vigilance Adverse Reaction Online Database. *Drug and alcohol dependence.* 2015(156):e244.

130. Hazell L, Shakir SA. Under-reporting of adverse drug reactions : a systematic review. *Drug safety.* 2006;29(5):385-396.

131. Rodriguez EM, Staffa JA, Graham DJ. The role of databases in drug postmarketing surveillance. *Pharmacoepidemiology and drug safety.* 2001;10(5):407-410.

132. de Boer A. When to publish measures of disproportionality derived from spontaneous reporting databases? *British journal of clinical pharmacology.* 2011;72(6):909-911.

133. Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. *British journal of clinical pharmacology.* 2011;72(6):905-908.

134. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. *Drug safety.* 2007;30(10):891-898.

135. Hartnell NR, Wilson JP. Replication of the Weber effect using postmarketing adverse event reports voluntarily submitted to the United States Food and Drug Administration. *Pharmacotherapy.* 2004;24(6):743-749.

136. Hochberg AM, Hauben M, Pearson RK, O'Hara DJ, Reisinger SJ. Systematic investigation of time windows for adverse event data mining for recently approved drugs. *Journal of clinical pharmacology.* 2009;49(6):626-633.

137. Wang HW, Hochberg AM, Pearson RK, Hauben M. An experimental investigation of masking in the US FDA adverse event reporting system database. *Drug safety.* 2010;33(12):1117-1133.

VITA

EDUCATION

2012 – present *University of Kentucky College of Public Health*
Ph.D., Departments of Epidemiology and Biostatistics
Advisor: Jennifer R. Havens, PhD, MPH
Dissertation: "Exploration of the misuse, abuse, and diversion of gabapentin."

2008 – 2012 *University of Kentucky College of Public Health*
Master of Public Health, Department of Health Services Management
Advisor: Julia F. Costich, JD, PhD
Capstone: "Rural-urban comparison of collaborations for service provision in decentralized rural and urban local health departments."

2003 – 2007 *Asbury University*
Bachelor of Arts in Chemistry, Minor in Latin

PROFESSIONAL EXPERIENCE

2015 – present **Statistician**
Mental Illness Research, Education and Clinical Centers (MIRECC)
Corporal Michael J. Crescenz VA Medical Center (Philadelphia, PA)

2015 – 2016 **Data Manager**
Department of Health Behavior
University of Kentucky College of Public Health (Lexington, KY)

2015 **Student Researcher**
University of Kentucky College of Public Health (Lexington, KY)
*Project in Mayasandra, India

2013 – 2016 **Research Assistant**
Center on Drug and Alcohol Research, Department of Behavioral Science
University of Kentucky College of Medicine (Lexington, KY)

2013 **Data Analyst**
Department of Health Behavior

University of Kentucky College of Public Health (Lexington, KY)

2012 – 2013 **Research Assistant**
Department of Gerontology
University of Kentucky College of Public Health (Lexington, KY)

2011 – 2012 **Clinical Research Coordinator**
Department of Cardiology
Gill Heart Institute at University of Kentucky (Lexington, KY)

2011 **Community Health Intern**
University of Kentucky College of Public Health (Lexington, KY)
*Project in Bomet, Kenya

2009 – 2011 **Data Manager**
Department of Health Behavior
University of Kentucky College of Public Health (Lexington, KY)

2008 – 2009 **Teaching Assistant**
Department of Chemistry
University of Kentucky College of Arts and Sciences (Lexington, KY)

2007 **Laboratory Technician**
Department of Pharmaceutical Sciences
University of Kentucky College of Pharmacy (Lexington, KY)

2006 – 2007 **Certified Nursing Assistant**
Wesley Village (Wilmore, KY)

AWARDS and HONORS

2015 Academic Enhancement Scholarship
University of Kentucky College of Public Health

2015 Student Travel Award
University of Kentucky Graduate School

2014 Outstanding Presentation Award
University of Kentucky College of Public Health

2012 CPH Exam Scholarship
University of Kentucky College of Public Health

2003 – 2007 Dean's List
Asbury University

2003 – 2007 Presidential Scholar
Asbury University

2002 Kentucky Governor's Scholar

CERTIFICATES

2012 Certificate in Public Health, *National Board of Public Health Examiner*

RESEARCH/GRANT SUPPORT (from present)

Inactive

Pilot Grant Program Smith (PI) 1/7/15-6/30/15
University of Kentucky College of Medicine
Exploration of gabapentin as an emerging drug of abuse
The primary goal is to investigate the experience of gabapentin abuse among people who daily abuse the drug in Appalachian Kentucky.
Role: Principal Investigator

NIH/NIMH R01 MH083621 Crosby (PI) 5/1/13-9/1/13
A Brief, Clinic-Based, HIV Prevention Program for African American Teen Males
This study is a randomized controlled trial to test the efficacy of a brief, clinic-based intervention designed to prevent STI acquisition among African American males aged 18-25.
Role: Data Analyst

NIH/NIDA K01 DA031764 Zanjani (PI) 8/15/12-8/30/13

Community Intervention Research on Prescription Drug Safety in Older Rural Adults
The purpose of this study is to examine prescription drug safety in older adults using a community-based health intervention for reducing alcohol consumption.
Role: Research Assistant

NIH/NIAID R01 AI068119 Crosby (PI) 3/1/09-2/1/11
Do Condoms Protect from Non-Viral Sexually Transmitted Infections?
The purpose of this study is to determine condom effectiveness against penile-vaginal acquisition of non-viral STIs using Personal Digital Assistants as an innovative approach for collecting data on sexual behaviors.
Role: Data Manager

PUBLICATIONS (from present)

1. Mark KP, **Smith RV**, Young AM, Crosby R. (2016) Comparing 3-month recall to daily reporting of sexual behaviors. *Sexually Transmitted Infections*, epub ahead of print, doi: 10.1136/sextrans-2016-052556.
2. Zanjani F, Crook L, **Smith R**, Antimisiaris D, Schoenberg N, Martin C, Clayton R. (2016) Community pharmacy staff perspectives on programming to prevent alcohol and medication interactions in older adults. *Journal of the American Pharmacists Association* 56(5): 544-8.

3. **Smith RV**, Young AM, Mullins UB, Havens JR. (2016) Individual and network correlates of antisocial personality disorder among rural nonmedical prescription opioid users: individual and network correlates of ASPD. *Journal of Rural Health*, epub ahead of print, doi: 10.1111/jrh.12184.
4. Zanjani FJ, **Smith RV**, Slavova S, Charnigo RJ, Schoenberg N, Martin C, Clayton R. (2016) Concurrent alcohol and medication poisoning hospital admissions among older rural and urban residents. *American Journal of Drug and Alcohol Abuse* 42(4):422-30.
5. **Smith RV**, Havens JR, Walsh SL. (2016) Gabapentin misuse, abuse, and diversion: a systematic review. *Addiction* 111(7):1160-74.
6. **Smith RV**, Lofwall MR, Havens JR. (2015) Abuse and diversion of gabapentin among nonmedical prescription opioid users in Appalachian Kentucky. *American Journal of Psychiatry* 172(5): 487-8.
7. Crosby RA, Charnigo RJ, Salazar LF, Pasternak R, Terrell I, Ricks J, **Smith RV**, Taylor S. (2014) Enhancing condom use among young black males: a randomized controlled trial. *American Journal of Public Health* 104(11): 2219-25.

PUBLICATIONS UNDER REVIEW

1. Hershenberg R, **Smith RV**, Goodson J. (Under review) Activating Veterans toward sources of reward: a pilot report on development, feasibility, and clinical outcomes of a 12-week BA-informed group treatment. *Cognitive and Behavioral Practice*.
2. Goodson JT, Helstrom AW, Marino E, **Smith RV**. (Under review) The impact of service-connected disability and therapist experience on outcomes from prolonged exposure therapy with Veterans. *Psychological Trauma: Theory, Research, Practice, and Policy*.
3. Boland EM, Rao H, **Smith RV**, Basner M, Detre J, Dinges D, Goel N, Sheline Y, Thase ME, Gehrman PR. (Under review) Antidepressant effects of acute sleep deprivation: an updated meta-analysis. *Journal of Clinical Psychiatry*.

PRESENTATIONS (from present)

Presentations at Scholarly Meetings (Peer-Reviewed)

1. Mark K, **Smith R**, Young A, Crosby R. Understanding misclassification bias in sex research: comparing three-month recall to daily reporting of sexual behaviors. The Society for the Scientific Study of Sexuality. November 2015. (Albuquerque, NM)

2. **Smith RV**, Lofwall MR, Walsh S, Havens JR. Diverted Buprenorphine Use Among Appalachian People Who Use Drugs. College on Drug and Alcohol Dependence. June 2015. (Phoenix, AZ)
3. Zanjani F, **Smith R**, Crook L, Clayton R, Schoenberg N, Martin C. Preventing Alcohol and Medication Interactions: Pharmacist Interviews. The Gerontological Society of America Annual Scientific Meeting. November 2014. (Washington, DC)
4. Zanjani F, **Smith R**, Clayton R, Schoenberg N, Martin C. Preventing Alcohol and Medication Interactions in Collaboration with Pharmacists. 35th Annual Meeting and Scientific Sessions of the Society of Behavioral Medicine. April 2014. (Philadelphia, PA)
5. **Smith, RV,** Young AM, Mullins UB, Havens JR. Individual and Network Correlates of Antisocial Personality Disorder among Rural Nonmedical Prescription Opioid Users. University of Kentucky Center for Clinical and Translational Science Public Health Research Day. March 2014. (Lexington, KY)
6. Zanjani F, **Smith R**, Clayton R, Martin C, Schoenberg NE. Preventing Alcohol and Medication Interactions: Pharmacist Viewpoint. The Gerontological Society of America Annual Scientific Meeting. November 2013. (New Orleans, LA)
7. **Smith, RV**, Johnson AJ, Charnigo R, Costich J. Collaborative Service Provision in Rural and Urban Health Departments. University of Kentucky Center for Clinical and Translational Science Public Health Research Day. April 2013. (Lexington, KY)
8. Crosby RA, Shrier L, Charnigo R, **Vickers RA**. Reducing Misclassification Bias in Sex Research Through the Use of Personal Digital Assistants. Third Youth Annual Conference on Youth and Technology & Sexual Health. February 2010. (San Francisco, CA)
9. **Vickers, RA**, Pospisil, K, Dwoskin L. Nicotine Stimulation of the Nitrosylation of Tyrosine Residues in Rat Striatum, in vivo. Kentucky Academy of Science Annual Meeting. November 2006. (Morehead, KY)

Guest Lectures

1. **Kentucky Pharmacy Law Review** (Lexington, KY). "Gabapentin as a drug of abuse: What do we know?" April 17, 2015.
2. **Fulbright Global Health Innovations Seminar** (Hosted by the University of Kentucky with funding from the Institute of International Education) (Lexington, KY). Panelist for Global Health Innovations/Trends panel discussion: "Innovative Business Models that Leverage 'Conscious Consumerism': Perspectives on Impact on Global Health and Community Development." February 26, 2015.

SERVICE

University/Academic Service

2016	CPH Exam Content Mapper, *National Board of Public Health Examiners*
2015	Student Assembly Abstract Reviewer, *143rd APHA Annual Meeting and Exposition*
2014 – 2015	Research Committee (Member), *University of Kentucky College of Public Health*
2014	Student Assembly Abstract Reviewer, *142nd APHA Annual Meeting and Exposition*
2013 – 2014	Mentor, *University of Kentucky College of Public Health*

Ad Hoc Journal Review

2016	*Pharmacoepidemiology and Drug Safety*
2016	*The Journal of Rural Health*
2015, 2016	*Clinical Drug Investigation*

Memberships in Professional Societies

2009 – 2015	American Public Health Association
2006 – 2007	Sigma Zeta (Math/Science Honor Society)

Community Service

2015	University of Kentucky Shoulder-to-Shoulder Organization (India)
2013 – 2015	Lexington-Fayette County Medical Reserve Corps
2013 – 2015	Kentucky Public Health Assistance and Support Team (KPHAST)
2011	Volunteer, WGM Kenya (Bomet, Kenya)
2011	Operations Volunteer, Refuge Clinic (Lexington, KY)
2009	University of Kentucky Shoulder-to-Shoulder Organization (Ecuador)
2005	Hurricane Katrina Relief Volunteer (Pass Christian, MS)