TRENDS AND TRAJECTORIES OF GABAPENTINOID USE AND ASSOCIATIONS WITH SUBSEQUENT HEALTH OUTCOMES AND HEALTHCARE EXPENDITURES IN THE UNITED STATES

by

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ABSTRACT

Background: Increasing use of gabapentinoids (i.e., gabapentin and pregabalin), especially in off-label use or concurrent use with opioids, has raised concerns of misuse/abuse of gabapentinoids in the United States (US). Little is known about the patient and prescriber characteristics most associated with gabapentinoid use, as well as utilization patterns of gabapentinoids and their associations with subsequent adverse health outcomes and healthcare expenditures in the US.

Objectives: This dissertation aimed to examine (1) trends, patient and prescriber characteristics, and potential off-label use of gabapentinoids among the US ambulatory care visits, (2) dual-trajectories of opioid and gabapentinoid use and risk of adverse health outcomes among US Medicare beneficiaries, and (3) association between dual-trajectories of opioid and gabapentinoid use and healthcare expenditures in US Medicare.

Methods: This dissertation included the data source from (1) National Ambulatory Medical Care Survey (NAMCS) data from 2003-2015 and (2) 5% national representative sample of Medicare data from 2011-2016. A multivariable logistic regression, group-based multi-trajectory models along with inverse probability of treatment weighted multivariable Cox proportional hazard model and inverse probability of treatment weighted multivariable generalized linear regression, with log link and gamma distribution, were used to examine the three objectives of this dissertation, respectively.

Results: This dissertation yielded three important insights into the patterns of gabapentinoid use. First, we found that the ambulatory visits involving gabapentinoids

quadrupled from 2003-2015 in US ambulatory settings. Half of the gabapentinoid visits had concurrent opioids and/or benzodiazepine use. Gabapentinoids were mainly prescribed by primary care physicians, and potential off-label use of gabapentinoids was overwhelmingly high. Second, we identified ten distinct dual-trajectories of opioid and gabapentinoid use among fee-for-service Medicare beneficiaries with fibromyalgia, low back pain, neuropathy, or osteoarthritis. Consistent high-dose opioid-only users and all consistent opioid and gabapentinoid users (regardless of doses) were associated with more than doubled risk of drug overdose, compared to opioid-only early discontinuers. Third, they also had higher concurrent healthcare expenditures among the identified distinct opioid and gabapentinoid trajectories among Medicare beneficiaries.

Conclusions: The increasing trend and extensive off-label use of gabapentinoids, especially concurrent use with opioids identified from NAMCS data, highlight the greater need for an understanding of long-term safety of gabapentinoid use. The distinct opioid and gabapentinoid dose and duration patterns among fee-for-service Medicare beneficiaries were associated with different risk of adverse health outcomes and healthcare expenditures. High-dose opioid-only users and all consistent opioid and gabapentinoid users (regardless of doses) were associated with a higher risk of adverse health outcomes and healthcare expenditures, compared to opioid-only early discontinuers. Healthcare providers should consider carefully when prescribing the concurrent opioid and gabapentinoid use in clinical practice. When the co-administration is necessary, patients should be monitored closely and assessed the benefit-risk profiles on a regular basis.

Keywords: Gabapentinoids; trends; opioid; trajectories; health outcomes; healthcare expenditures; Medicare; NAMCS

CHAPTER 1. INTRODUCTION OF GABAPENTINOIDS

1.1. OVERVIEW OF GABAPENTIN AND PREGABALIN USE

1.1.1. Indications and Off-label Use

Gabapentinoids, including gabapentin and pregabalin, have been approved by the United States (US) Food and Drug Administration (FDA) for treatment of partial seizures, postherpetic neuralgia, diabetic peripheral neuropathy (pregabalin only), fibromyalgia (pregabalin only), neuropathic pain associated with spinal cord injury (pregabalin only), and restless legs syndrome in adults (gabapentin only).[1-3] Since the initial approval of gabapentin in December 1993 and pregabalin in December 2004, gabapentinoids have been increasingly off-label used for a variety of pain conditions and anxiety disorders, such as postoperative pain and social anxiety disorder, although with limited evidence supporting these uses (**Table 1.1**).[3-10] It is estimated that over 80% of gabapentin prescriptions are off-label used for over 40 conditions.[5-7,11,12] The US manufacturer of gabapentin and pregabalin were fined a large scale of money to settle civil and criminal allegations for illegal marketing of gabapentin ($420 million in 2004) and pregabalin and other three medications ($2.3 billion in 2009).[13,14]

1.1.2. Pharmacological Mechanisms and Pharmacokinetics

The exact mechanisms of analgesic and anticonvulsant effects of gabapentinoids are not fully understood. Gabapentinoids are 3-substitued derivatives of ɣ-aminobutyric acids (GABA), which are neurotransmitter inhibitors in the human cerebral cortex and

play an important role in controlling the excitability of neurons. Unlike some addictive substances (e.g., benzodiazepines and alcohol), gabapentinoids don't bind to GABA receptors.[15-17] Instead, gabapentinoids are inhibitors of α2δ-subunit-containing voltage-dependent calcium channels (VGCC).[18,19] Gabapentinoids inhibit the influx of α2δ-subunit complex to the plasma membrane, and thus restrain the excitatory neurotransmitters, glutamate and norepinephrine, without dopamine projection in the brain.[20,21] Pregabalin is a stronger VGCC inhibitor than gabapentin.[22,23] Research have also found that gabapentinoid use was associated with a modest increase of GABA concentration in the brain, which could drive the feelings of relaxation and euphoria for a person.[23,24]

Pharmacokinetically, pregabalin is absorbed more rapidly than gabapentin, reaching maximum blood concentration within 1.5 vs 2 hours after oral intake.[4] The absorption of gabapentin has a saturation process (i.e., a non-linear relationship with increasing dose).[22,23] Pregabalin has a higher bioavailability than gabapentin (>90% vs. 27%-60%).[4] Both pregabalin and gabapentin rarely bind to protein in the plasma (<3%) and are not metabolized in the liver and excreted unchanged from the body.[4,22,23] Overall, they have few drug-drug interactions with other drugs, except with other anticonvulsants (major severity) and morphine (moderate severity).[4] In addition, patients with chronic kidney diseases (e.g., end-stage renal diseases) are required for dose reduction due to that gabapentinoids were mainly eliminated through kidney.[23]

1.1.3. Recommended Daily Dose and Side Effects

The adult dosing of gabapentin varies by indications, ranging from 300 milligrams (mg) to 3,600 mg per day.[4] The most common side effects of gabapentin are dizziness (28%) and somnolence (21%), due to its action on the central nervous system (CNS). The adult dosing of pregabalin varies from 150 mg to 660 mg per day depending on the indications.[4] Common side effects of pregabalin include dizziness (17% to 32%), somnolence (11.4% to 35.7%), and other neurologic and psychiatric symptoms such as disturbance in thinking (2% to 8%), euphoria (2% to 6%), and even suicidal thoughts (rare). Due to concerns about the addiction potential of pregabalin and its neurologic and psychiatric side effects, pregabalin is listed as a Schedule V Controlled Substance (low addiction potential) by the US Drug Enforcement Administration (DEA).[25] The American Geriatric Society's Beers Criteria also recommends to avoid or reduce dose of gabapentinoids in the elderly population due to its CNS effects, especially for those with a history of falls or fractures.[26]

Gabapentinoids have a wide therapeutic dosage range and use is considered as generally safe.[4] A case report of a woman who developed only mild symptoms without further clinical intervention after ingesting 91 grams (g) gabapentin (25 times more than FDA recommended maximum dose).[27] The most severe non-fatal pregabalin use was from a hospitalized male after taking 11.5 g pregabalin (17 times more than FDA recommended maximum dose). There are no antidotes currently available for gabapentinoid overdose. The wide and relative safe therapeutic dose range with multiple potential pharmacological mechanisms may contribute to the extensive off-label use of gabapentinoids.

1.2. TRENDS IN GABAPENTINOID USE IN THE UNITED STATES

The off-label use of gabapentinoids accompanies an increasing trend in gabapentinoid use in the US in the last decade.[28-30] According to the IMS Health national prescription data, gabapentin ranked 10th in the most dispensed medications in 2016 (a total of 64 million prescriptions compared to 39 million in 2012).[28] Updated GoodRx® data showed that gabapentin ranked as the 7th most prescribed medication in 2017.[3] The sales for pregabalin reached to $4.4 billion in 2016, more than double of the amount in 2012.[28] Another study using the Medical Expenditure Panel Survey (MEPS) data also found an increasing trend in gabapentinoid use in US.[29] Individuals using gabapentinoids increased from 1.2% in 2002 to 3.9% in 2015 among the US adults. This increase was mainly driven by the escalating use of gabapentin over time; while pregabalin use remained stable over time. However, no studies to date have further examined patient and prescriber characteristics associated with gabapentinoid use, especially in the ambulatory care settings where chronic pain is primarily managed.

Additionally, gabapentin use has also increased substantially among individuals with a history of substance use disorders (e.g., opioids, cocaine, and cannabis). One study found that 15% of the 503 adults reporting current non-medical use of prescription opioids in Kentucky reported using gabapentin to get “high” in the past 6 months in 2015 (compared to 6% in 2014 and 0.5% in 2008).[30] Data from the National Drug Diversion Program of the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) documented that rates of gabapentin diversion, defined as unauthorized selling or sharing of prescription medications across persons, have increased from zero case in the first quarter of 2002 to 0.0027 cases per 100,000 population in the fourth

quarter of 2015.[31] Furthermore, the number of fatalities involving gabapentin use quadrupled from 11 cases in 2005 to 51 cases in 2016 based on the national poison data from the American Association of Poison Control Center, while the deaths involving pregabalin were consistent over time (8-10 cases each year).[32-43]

1.3. EVIDENCE ON MISUSE, ABUSE, DEPENDENCE, ADDICTION, AND OVERDOSE OF GABAPENTINOIDS

A substantial increase use in gabapentinoids in the US, especially among individuals with substance use disorders, raises public concerns about the potential for misuse, abuse, dependence, addiction, and overdose risk of gabapentinoids.[3,28,44,45] Based on interviews with individuals non-medically using and abusing gabapentin, their experiences and feelings resulting from gabapentin use included muscle relaxation, pain relief, improved sociability, euphoria, a marijuana-like “high”, hallucinations, and feeling drunk and “high”.[46,47] Gabapentin use has become more popular among drug abusers due to its stimulating drug “high”, low price, and easy to access or obtain from physicians.[46] Given the concerns of increasing use, misuse and abuse of gabapentin, states including Minnesota, Ohio, Virginia, Kentucky, Wyoming, Massachusetts, and North Dakota have mandated the reporting of gabapentin prescriptions in their Prescription Drug Monitoring Programs (PMDPs) as of December 2017.[48,49]

Using PubMed and Embase databases, we have updated a systematic literature search (as of 03/31/2019) based on two published systematic reviews that examined the characteristics and potentials of misuse, abuse, dependence, addiction, and overdose of gabapentinoids.[44,45] The searching strategy in PubMed used was

"(((((((((misuse) OR abuse) OR addiction) OR overdose) OR death) OR fatality) OR non-medical use) OR dependence OR diversion) AND ((((gabapentin) OR pregabalin) OR gabapentinoids) OR gabapentinoid)". **Tables 1.2 to 1.4** and **Sections 1.3.1 to 1.3.4** summarized the prior studies examining misuse, abuse, dependence, addiction and overdose of gabapentinoids.

1.3.1. Misuse and Abuse

Misuse refers to individuals using a drug not as prescribed or instructed (e.g., including taking another person's drug or taking a higher dose than recommended, injecting or inhaling a drug rather than taking it orally).[50] Abuse indicates the consistent use of a drug despite a consciousness of harmful consequences.[50] There are 14 epidemiological studies examining the misuse and/or abuse of gabapentinoids among the general and addicted populations (**Table 1.2**).[30,51-63] In the two studies conducted in the general population, the life-time prevalence of misuse of gabapentin was up to 1.1% and 0.5% for pregabalin.[54,57] The prevalence of misuse and/or abuse of gabapentin and pregabalin ranged from 15% to 22% and 3% to 26%, respectively, among individuals with a history of substance use disorders.[30,52,53,55,58,61,62] Overall, persons with a history of substance use disorders are more likely to misuse and/or abuse gabapentinoids.

1.3.2. Dependence

Based on the World Health Organization (WHO) 10th revision of the International Classification of Diseases (ICD-10) diagnostic criteria for substance dependence, five criteria are used to evaluate whether one person has developed dependence on a drug

or other addicted substance, including: (1) a strong desire of sense of compulsion to take the substance, (2) a physiological withdrawal state when substance use is reduced or ceased, (3) evidence of tolerance to the effects of the substance, (4) preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use, or a great deal of time being spent in activities necessary to obtain the substance, and (5) persistent use of the substance despite a consciousness of harmful consequences of using the substance.[64] If one individual manifests three or more of the five symptoms for at least one month within a 12-month period, then he/she is considered to have developed substance use dependence.[64] Among the 23 case reports of gabapentin dependence, five cases fulfilled the ICD-10 criteria of substance use dependence, and four out of the five cases had prior substance use disorders (**Table 1.3**).[65-84] Among the 15 cases related to pregabalin dependence, ten cases developed pregabalin dependence based on ICD-10 criteria, and seven of them had other substance use disorders such as opioids, benzodiazepines, and cannabis (**Table 1.3**).[85-98] Individuals with prior substance use experience are more likely to develop gabapentinoid dependence compared to those without a history.

1.3.3. Addiction

Addiction is defined as individuals showing a psychological wanting or addictive behaviors or symptoms for a drug (e.g., craving and loss of self-control), rather than having physical symptoms like drug tolerance or withdrawal that more indicate the drug dependence.[99-101] Although both gabapentin and pregabalin have a low addiction

potential compared to opioids and other substances, pregabalin appears to be more addictive than gabapentin. Persons abusing gabapentin may have feelings “high” and euphoria like taking opioids. The low addiction characteristic but inducing “high” feelings could be driven and explained by that different neurological areas control different feelings. Based on the Incentive Sensitization Theory of Addiction, the “wanting” for a drug (e.g., craving and loss of self-control) is mediated by a robust brain system including dopamine projection, whereas the “liking” for the drug (abusing potential) is mediated by a restricted brain system of small hedonic hotspots.[102] Gabapentinoid use is not associated with dopamine projection, but have reactions (“liking”) in the restricted brain system. Furthermore, prior research showed that the feeling of “wanting” increased but the “liking” feeling dropped down as time goes by. Therefore, gabapentinoids may be more likely to become addictive among individuals with a history of substance use disorder. Medications with similar characteristics include bupropion (an antidepressant), tianeptine (an antidepressant), quetiapine (an antipsychotic drug), and flupirtine (an analgesic drug).[79,103-105]

Nineteen studies have examined the addiction potentials of gabapentinoids.[106-124] Eight animal studies in rats, mice, and monkeys found that gabapentin use did not induce self-administration behaviors (even at the daily dose of 3,200 mg).[108-112,117,119,121] The three human studies also showed that gabapentin did not influence the cocaine self-administration or seeking behavior among cocaine abusers.[113-115] The findings on addiction to pregabalin were controversial. Three of six animal studies showed that animals developed drug self-administration behaviors when receiving the

pregabalin.[106,107,116,120,122-124] However, two human studies examining addiction characteristics of pregabalin did not find such behaviors.[120,124]

1.3.4. Overdose

There were 18 case reports or case series studies examining non-fatal, intentional or non-intentional gabapentinoid overdose (**Table 1.4**).[27,120,125-140] The dose taken in these cases varied from 1.8 g to 91 g for gabapentin and 4.2 g to 11.5 g for pregabalin (FDA recommended maximum daily dose, gabapentin: 3.6 g/d, pregabalin: 0.66 g/d). The clinical symptoms of these overdose cases included sedation, coma, dizziness, somnolence, confusion, cardiovascular problems, and respiratory depression. These studies suggested a relative good tolerance with mild toxicities of gabapentin. In US, 29 case studies or pharmacovigilance database reports documented overdose fatalities involving gabapentinoid use and most of these cases had concurrent use with opioids, benzodiazepines, or antidepressants.[32-43,141-155] A similar increasing trend in gabapentinoid-related overdose deaths was detected in the United Kingdom (UK) (12 cases in 2012 vs 170 cases in 2016) as in US (40 cases in 2012 vs 61 cases in 2016).[143] This increasing trend of gabapentinoid-related overdose deaths were seen in both gabapentin (8 cases vs 59 cases) and pregabalin (4 cases vs 111 cases) as pregabalin is not a controlled substance in UK.

1.4. RISK OF CONCURRENT USE OF OPIOIDS AND GABAPENTINOIDS

Based on prior literatures, individuals with a history of substance use disorders are more likely to develop misuse, abuse, dependence, addiction, and overdose of

gabapentinoids. However, concurrent use of opioids and gabapentinoids is quite common in the US.[12,29,40-42] One study using MEPS data showed that over half (52.6%) of gabapentinoid users concurrently had opioid prescriptions in 2015.[29] In another study of 838,365 commercially insured beneficiaries having ≥120 days of gabapentinoid use during a 12-month period between 2013 and 2015, 22% of the gabapentin users and 26% of the pregabalin users had a long-term concurrent opioid use (≥120 days).[12] In addition, 36 out of 59 (61%) and 29 out of 61 (48%) gabapentinoid related overdose deaths involved both opioid and gabapentinoid use in the US in 2015 and 2016, respectively.[40,41] From the pharmacological perspective, opioids and gabapentinoids both work on one's CNS and thus, cause an additive respiratory depression effect. There is also a drug-drug-interaction between morphine and gabapentin, demonstrated as morphine could increase gabapentin absorption by 44%. Therefore, the co-administration of opioids and gabapentinoids may increase the risk of adverse outcomes (e.g., sedation, confusion, and overdose), especially among older adults without dosage adjustment.[156] These increased risks of adverse outcomes (e.g., overdose) have raised safety concerns discerning concurrent use of opioids and gabapentinoids.[157-162]

To date, four studies have examined the association between concurrent use of opioids and gabapentinoids and the risk of adverse health outcomes (**Table 1.5**).[163-166] In a retrospective cohort study using the commercial insurance claims data from 2013-2015, Peckham et al. examined the risks of hospitalizations, emergency department (ED) visits, and diagnosis-based respiratory depression and other drug related adverse effects (e.g., altered mental status, detoxification, ataxia, and blurred vision) among

individuals using gabapentin only, opioids only, and both gabapentin and opioids.[165] The authors defined gabapentin overuse as the average daily dose higher than FDA maximum adult dosing (3,600 mg/d). Individuals with sustained overuse (three or more rolling calendar quarters with a dosage per calendar day exceeding FDA maximum adult dosing) of gabapentin and opioids (three or more rolling calendar quarters with a dosage per calendar day >50 morphine milligram equivalent) had an odds ratio (OR) of 4.08 [95% confidence interval (CI)=2.58-6.55] in the risk of all-cause hospitalization, compared to those only using gabapentin within FDA suggested dose. Similar associations were also found in other outcomes including all-cause ED visit (OR=2.94, 95% CI=1.97-4.40) and respiratory depression (OR=4.11, 95% CI=1.75-9.62). There are several limitations in this study. First, simply applying the FDA recommended maximum daily dose (3,600 mg) as a cutoff point to identify overuse may not well stratify patients' risk of adverse outcomes within normal dose. Second, only gabapentin was included and pregabalin was not studied. Third, limiting to chronic gabapentin or opioid users (i.e., ≥120 days of cumulative use during a 12-month period) may miss some other distinct utilization patterns such as short-term use. Lastly, this study limited to non-elderly population aged 16-64 years and thereby, the findings may not be generalized to older populations who need dose adjustment and are more susceptible to drug-related adverse events according to the Beers Criteria.[26]

In two case-control studies, Gomes et al. used the insurance claims data of residents in Ontario, Canada from 1997-2013.[164,166] Cases were those with opioid-related deaths, and controls were those opioid users who were alive during the study period. The proportions of individuals having gabapentin and pregabalin use,

respectively, within 120 days before the index date (dates of death for cases and randomly assigned dates according to the distribution of index dates of cases for controls) were examined. Concurrent use of opioids and gabapentin had an OR of 1.49 (95% CI=1.18-1.88) in opioid-related deaths compared to those using opioids only, but there was no significant gabapentin dose-dependent association (moderate dose: OR=1.56, 95% CI=1.06-2.28; high dose: OR=1.58, 95% CI=1.09-2.27).[164] Concurrent use of opioids and pregabalin was also associated with higher risk of opioid-related death, compared to those using opioids only (OR=1.68, 95% CI=1.19-2.36).[166] One limitation is that the case-control study design may not accurately estimate the risk of outcomes. Furthermore, although these two studies have examined dose effect, the impact of duration effect was not examined.

In a recent retrospective cohort study of individuals who were receiving opioid maintenance treatment (with prior opioid use disorders) in Sweden between 2005 and 2012, Abrahamsson et al. examined the mortality risk (overdose, non-overdose, and all-cause) among periods with pregabalin use vs periods without pregabalin use (time-dependent exposure status).[163] Periods with pregabalin use were associated with a 182% and 101% increased risk of overdose death and all-cause mortality, respectively, (overdose death: hazard ratio [HR]=2.82, 95% CI=1.79-4.43; all-cause mortality: HR=2.01, 95% CI=1.38-2.91), compared to periods without pregabalin use. This increased risk was not observed for the non-overdose death outcome. This study did not examine any dose-dependent effects in terms of duration and dose on the outcomes of interest.

1.5. SUMMARY OF LITERATURE REVIEWS

In summary, gabapentinoid use (primarily gabapentin) has increased dramatically during the last decade in the US. Although pregabalin appears to be more addictive than gabapentin, the listing of pregabalin as a Schedule V Controlled Substance may result in its steady utilization over time. Interviews with drug abusers suggested that gabapentin has become a common drug for misuse and abuse due to its low cost, easy access from physicians or black market, and ability to potentiate opioid-like “high” feeling. Moreover, concurrent use of opioids and gabapentinoids is common (>50%) among the general population in the US. Concurrent use of opioids and gabapentinoids may increase the risk of adverse health outcomes such as hospitalizations, ED visits, and overdose mortality, especially for older population.

1.6. RESEARCH GAP AND STUDY OBJECTIVES

Two major limitations and gaps were identified based on prior research. First, little is known regarding the patient and prescriber characteristics (e.g., disease conditions or prescriber specialties) to better inform target interventions. Findings on the extent of potentially off-label use and utilization patterns may shed a light to guide the FDA and payers for improvement of drug safety and patient care (e.g., requesting more studies examining the efficacy and safety of gabapentinoids in off-label use).[167] Second, there is a lack of comprehensive studies identifying distinct utilization patterns that incorporate dynamic changes in dose and duration of gabapentinoid use over time. Identifying trajectories of opioid and gabapentinoid use at high risk of adverse outcomes and high health care expenditures will also inform opioid- and gabapentinoid-related

policies and interventions (e.g., prior authorization). Therefore, this dissertation developed three objectives as follows:

Objective 1: To examine the trends, patient and prescriber characteristics, and the extent of potential off-label use of gabapentinoids in the US ambulatory care settings.

Objective 2: To identify distinct utilization trajectories of opioids and gabapentinoids and examine their associations with subsequent adverse health outcomes (e.g., drug overdose) among Medicare beneficiaries.

Objective 3: To examine the association between distinct utilization trajectories of opioids and gabapentinoids and healthcare expenditures (e.g., annual direct medical costs) among Medicare beneficiaries.

1.7. CONCEPTUAL FRAMEWORK

The conceptual framework for this dissertation was adapted from the Andersen behavioral model of health services use.[168] The goal of Andersen behavior model is to understand the multi-dimensional factors that facilitate or hurdle the access to health care. The Andersen behavioral model comprises three components as a function of individual access to health care including (1) contextual characteristics, (2) individual characteristics, and (3) health behaviors (**Figure 1.1**). Each domain includes several factors that can have an impact on the health service use.

The contextual characteristics include three components, predisposing, enabling, and need factors measured at aggregated community level. Contextual predisposing factors include demographics (e.g., age, sex, and marital status), social (e.g.,

composition of education, race, and employment in the community), and health belief determinants (e.g., how health services should be organized or financed). Contextual enabling factors include health policy (e.g., Affordable Care Act), financing (e.g., income per capita), and organization determinants (e.g., number of health service facilities) within the community. The contextual needing factors include environmental determinants (e.g., quality of air) and population health indices (e.g., life expectancy).

The individual characteristics share the similar components with the contextual characteristics, but more focus on the individual-level measures, such as person's demographics, health beliefs, and health conditions. In addition to the contextual and individual characteristics, the Andersen model considers health behaviors' influence on health status and health outcomes as well. Health behavior characteristics are comprised of personal health practice (e.g., diet, exercises, and tobacco and alcohol use), process of medical care (e.g., patients counseling and education, prescribing patterns, and quality of provide-patient communication), and use of personal health services (e.g., number of physician visits, hospitalizations, and dental services).

Based on the Andersen health behavior model, health outcomes including self-rated health status, professionally evaluated health status, patient satisfaction, and quality of life and the contextual, individual, and health behavior characteristics are mutually influenced by each other. The contextual, individual, and health behavior characteristics can determine the health status of one person, on the contrary, the health outcomes can also have an impact on the contextual, individual, and health behavior characteristics of one person. For example, if one person lives with healthy diet, regular exercises, and good insurance coverage, then he has a higher likelihood of

being healthy. Since this person enjoys the benefits of being healthy, he would be more likely to insist on his current lifestyle.

In summary, the Andersen behavior model suggests that one's health outcomes are influenced by multiple dimensions of access to medical care, including the contextual, individual, and health behavior characteristics. In order to more accurately evaluate the risk of opioid and gabapentinoid use using real-world data, the Andersen behavior model was serve as a basis to address and include potential confounding factors.

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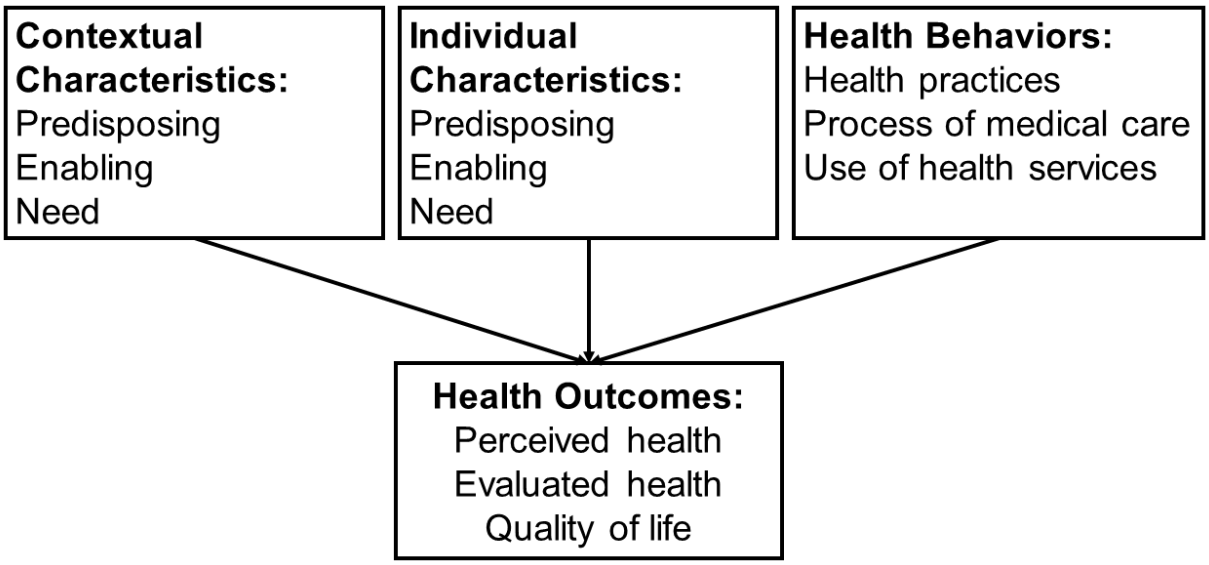
1.9. FIGURE



1.1. Adapted Andersen Behavior Model of Health Services Use

1.10. TABLES

1.1. FDA Indications and Off-label Uses for Gabapentinoids

Drug	FDA indication (approved year)	Common Off-label use
Gabapentin	Partial seizures (1993), postherpetic neuralgia (2002), restless legs syndrome in adults (2011).	Diabetic peripheral neuropathy, fibromyalgia, hemodialysis-associated pruritus, hot sweats, postoperative pain (acute), alcohol dependence, alcohol withdrawal, neuropathic pain, social anxiety disorder
Pregabalin	Diabetic peripheral neuropathy (2004), postherpetic neuralgia (2004), partial seizures (2005), fibromyalgia (2007), neuropathic pain associated with spinal cord injury (2012)	Familial dysautonomia, generalized anxiety disorder, postoperative pain, restless legs syndrome, hot flashes, social anxiety disorder

1.2. Summary of Epidemiological Studies Examining Gabapentinoid Misuse and/or Abuse

Author (year)	Country or region	Samples	Methods	Results	History of other substance use disorder
In general population					
Kapil et al. (2014)[57]	England and Wales	n=1,500 aged 16-59 years old	Online survey about the recreational substance use	Life-time prevalence: gabapentin 1.1% (n=17); pregabalin 0.5% (n=8)	Unknown
Cossmann et al. (2016)[54]	Germany	n=400 aged ≥65 years old	Interview on use of psychoactive substance	12-month prevalence: 0% for gabapentin and pregabalin; life-time prevalence: gabapentin 0.25% (n=1); pregabalin 0% (n=0)	The one with misuse of gabapentin was dependent on opioid
In addicted population					
Piralishvili et al. (2013)[60]	US	n=506 adults in opioid substitution programs	Self-reported questionnaire of psychoactive substance	8.22% reported using pregabalin for non-medical use	Dependent on opioids
Grosshans et al. (2013)[55]	Germany	n=124 aged 20-55 years old in opioid substitution program vs n=111 treated for non-opioid addiction, mostly alcohol	Pregabalin urine screen	12.1% with non-medical pregabalin use in opioid substitution program vs 2.7% with non-medical pregabalin use in non-opioid addiction group	Dependent on other substance like opioids and alcohol
Baird et al. (2013)[52]	Scotland	n=129 adults in 6 detoxification clinics	Self-reported questionnaire about psychoactive substance use	19% with non-medical use of gabapentin; 3% with non-medical use of pregabalin	Dependent on opioids at least
McNamara et al. (2015)[58]	Ireland	n=440 adults aged 21-61 years old in 6 opioid substitution programs	Pregabalin urine screen	7% with non-medical pregabalin use	Dependent on opioids at least
Smith et al. (2015)[30]	US	n=503 adults with non-medical prescription opioid use	Self-reported questionnaire of psychoactive substance use	6-month prevalence of non-medical gabapentin use: 15%	Dependent on opioids
Wilens et al. (2015)[62]	US	n=162 adults in one Massachusetts general hospital	Self-reported questionnaire of psychoactive substance use	22% and 7% reported using gabapentin and pregabalin in higher dosing than prescribed, respectively	Dependent on opioids

1.2. (Continued)

Author (year)	Country or region	Samples	Methods	Results	History of other substance use disorder
Bastiaens et al. (2016)[53]	US	n=250 adults in a correctional community center, Pittsburgh	Self-reported questionnaire of psychoactive substance use	Among n=145 individuals with opioid use disorder (OUD), 26% reported misused gabapentin; among n=105 individuals without (OUD), 4% reported misused gabapentin	All individuals had further substance use disorders.
Alblooshi et al. (2016)[51]	United Arab Emirates	n=250 aged 18-62 years old at the National Rehabilitation Center	Interview about substance use	41% with non-medical use of pregabalin together with other prescription drugs; 27% with non-medical use of pregabalin alone	Dependent on other substances
Heikman et al. (2016)[56]	Finland	n=82 adults in a methadone substitution program	Gabapentin and pregabalin urine screen	Gabapentin and pregabalin were detected in 0.5% and 4% of the 200 urine samples	Dependent on other substances
Mutschler et al. (2016)[59]	Switzerland	n=109 adults aged between 18 and 64 years with opioid substitution therapy	Self-reported pregabalin use and hair toxicity analyses	Zero case reported using pregabalin in the past 3-month	Dependent on opioids at least
Snellgrove et al. (2017)[61]	Germany	n=253 adults in one detoxification ward	Interview and pregabalin urine screen	1-month prevalence: 26%; life time prevalence: 56%.	Dependent on other substances, mostly opioids and benzodiazepines

1.3. Summary of Case Reports Examining Gabapentinoid Dependence

Author (year)	Country or region	Drug	Craving	Seeking behavior	Tolerance	Withdrawal symptoms	Abuse	No. of fulfilled criteria	History of substance use disorder
Markowitz et al. (1997)[74]	US	Gabapentin	U	U	N	N	U	0	Cocaine
Cora-Locatelli et al. (1998)[67]	US	Gabapentin	U	U	U	Y	U	1	None
Rosebush et al. (1999)[80]	Canada	Gabapentin	U	U	U	Y	U	1	None
Norton (2001)[75]	US	Gabapentin	U	U	U	Y	U	1	None
	US	Gabapentin	U	U	U	Y	U	1	None
	US	Gabapentin	U	U	U	Y	U	1	None
Barrueto et al. (2002)[65]	US	Gabapentin	U	U	Y	Y	Y	3	None
Drabkin et al. (2003)[69]	Canada	Gabapentin	U	U	Y	U	U	1	None
Reccoppa et al. (2004)[77]	US	Gabapentin	U	U	U	U	U	0	Cocaine
Tran et al. (2005)[83]	US	Gabapentin	U	U	U	Y	U	1	None
Victorri-Vigneau et al. (2007)[84]	France	Gabapentin	U	Y	Y	Y	U	3	Alcohol
Pittenger et al. (2007)[76]	US	Gabapentin	U	U	U	Y	U	1	Alcohol, cocaine, and opioids
	US	Gabapentin	U	U	Y	Y	Y	3	Alcohol
Kruszewski et al. (2009)[72]	US	Gabapentin	Y	U	Y	Y	Y	4	Alcohol
Hellwig et al. (2010)[71]	US	Gabapentin	U	U	U	Y	U	1	Alcohol
Finch et al. (2010)[70]	US	Gabapentin	U	U	U	Y	U	1	Unknown
See et al. (2011)[82]	US	Gabapentin	U	U	U	Y	U	1	None
Di Fabio et al. (2013)[68]	Italy	Gabapentin	U	U	U	Y	U	1	None
Mah et al. (2013)[73]	Canada	Gabapentin	U	U	U	Y	U	1	None
Reeves et al. (2014)[78]	US	Gabapentin	U	U	U	U	Y	1	Cannabis, cocaine
Reeves et al. (2014)[79]	US	Gabapentin	U	U	U	U	U	0	Opioids
Satish et al. (2015)[81]	India	Gabapentin	Y	Y	Y	Y	U	4	Opioids
Bonnet et al. (2016)[66]	Germany	Gabapentin	N	N	Y	Y	N	2	None
Oaklander et al. (2005)[94]	US	Pregabalin	U	U	U	Y	U	1	None
Grosshans et al. (2010)[92]	Germany	Pregabalin	U	Y	Y	Y	U	3	Alcohol, cannabis, and heroin

1.3. (Continued)

Author (year)	Country or region	Drug	Craving	Seeking behavior	Tolerance	Withdrawal symptoms	Abuse	No. of fulfilled criteria	History of substance use disorder
Filipetto et al. (2010)[89]	US	Pregabalin	U	Y	Y	Y	U	3	Opioids
Karosin et al. (2012)[98]	Austria	Pregabalin	U	U	U	Y	U	1	None
Carrus et al. (2012)[87]	South Europe	Pregabalin	U	U	Y	Y	U	2	Benzodiazepines cocaine, and cannabis
	South Europe	Pregabalin	Y	U	U	Y	Y	3	Ecstasy, alcohol, and cannabis
Papazisis et al. (2013)[95]	Greece	Pregabalin	U	Y	Y	U	U	2	Cannabis and alcohol
Gahr et al. (2013)[90]	Germany	Pregabalin	U	Y	U	Y	U	2	Alcohol
Barrett et al. (2015)[86]	US	Pregabalin	Y	U	U	Y	Y	3	Opioids
Ashwini et al. (2015)[85]	India	Pregabalin	U	Y	Y	Y	Y	4	None
Yazdi et al. (2015)[96]	Austria	Pregabalin	Y	Y	Y	Y	Y	5	Benzodiazepines, alcohol, and tramadol
Gahr et al. (2015)[91]	Germany	Pregabalin	Y	Y	Y	U	U	3	Benzodiazepines
Halaby et al. (2015)[93]	Lebanon	Pregabalin	Y	U	Y	Y	Y	4	None
Driot et al. (2016)[88]	France	Pregabalin	Y	Y	Y	Y	U	4	None
Lupi et al. (2018)[97]	Italy	Pregabalin	Y	Y	Y	U	Y	4	Opioids

1.4. Summary of Gabapentinoid Related Fatal and Non-Fatal Drug Overdose

Author (year)	Country or region	Samples	Methods	Results	Addiction history
Non-fatal overdosing					
Fischer et al. (1994)[129]	US	16-year old male swallowed 50g gabapentin	Case report	Non-fatal	Cocaine
Fernandez et al. (1996)[27]	US	31-year old male self-poisoning gabapentin	Case report	Non-fatal	None
Fernandez et al. (1996)[128]		32-year old male self-poisoning 92g gabapentin	Case report	Non-fatal	Unknown
Stopforth (1997)[137]	South Africa	17-year old female swallowed 40g gabapentin	Case report	Non-fatal	None
Verma et al. (1999)[138]	US	30-year old female was treated with 1800 mg/d gabapentin	Case report	Non-fatal	None
Klein-Schwartz et al. (2003)[130]	US	20 individuals with gabapentin intoxications, with doses ranging from 50mg (child) to 35g	Case series	Non-fatal	Unknown
FDA (2004)[125]	US	6 patients took pregabalin from 1500mg to 8000mg	Premarketing medical review	Non-fatal	Unknown
Spiller et al. (2002)[136]	US	61-year old female self-poisoning with gabapentin	Case report	Non-fatal	Unknown
Rasimas et al. (2006)[134]	US	44-year old female	Case report	Non-fatal	Alcohol, cannabis
Braga et al. (2007)[126]	UK	29-year old male self-poisoning with 11.5g pregabalin	Case report	Non-fatal	None
Wood et al. (2010)[140]	UK	54-year old male self-poisoning with 8.4g pregabalin	Case report	Non-fatal	Unknown
Zacny et al. (2012)[120]	US	Healthy volunteers	Double-blinded, randomized cross-over control study. Participants were exposed to 75 and 150mg pregabalin, 10mg oxycodone, and 75mg pregabalin +10mg oxycodone	Respiration rate was lower in pregabalin 75mg group (10.3±0.7) and 150gm group (10.6±0.8), oxychodone 10mg group (10.5±0.7), and 75mg pregabalin +10mg oxycodone group (9.6±0.5), compared to placebo group (12.9±0.6)	15 participants reported use of cannabis

1.4. (Continued)

Author (year)	Country or region	Samples	Methods	Results	Addiction history
Schauer et al. (2013)[135]	US	59-year old self-poisoning 90g gabapentin	Case report	Non-fatal	Unknown
Millar et al. (2013)[133]	UK	10 adults presented to emergency department following recreational pregabalin abuse, with dose from 0.5g to 1.4g	Case series	Non-fatal	Unknown
Koschny et al. (2014)[131]	Germany	21-year old female intoxication with 16g gabapentin	Case report	Non-fatal	Unknown
Kriikku et al. (2014)[132]	Finland	206 pregabalin use positive drivers	Case series	Non-fatal	Benzodiazepines, cannabis, opioids, amphetamines, and alcohol
Wills et al. (2014)[139]	US	94 cases with gabapentin overdoses and 18 cases with pregabalin overdoses identified from poison center data	Pharmacovigilance case report	Non-fatal	Unknown
Daly et al. (2017)[127]	Ireland	Intentional drug overdose presentations to emergency department between 2007 and 2015.	Registry study	Non-fatal	Unknown
Fatal overdosing					
Moore et al. (2005)[155]	US	54-year old female self-poisoning gabapentin	Case report	Fatal	Unknown
Button et al. (2010)[144]	UK	49-year old female and 50-year old male self-poisoning with pregabalin	Case report	Fatal	Benzodiazepines, Z-drugs, opioids, and antidepressants
Launiainen et al. (2011)[145]	Finland	1,623 deceased young adults	Registry study	68 cases with pregabalin positive	Unknown
Middleton (2011)[146]	US	82-year old female self-poisoning gabapentin	Case report	Fatal	Unknown
Lottner-Nau et al. (2013)[147]	Germany	982 autopsies of drug-related deaths	Registry study	43 (4.4%) cases were pregabalin positive	Opioids, benzodiazepines, neuroleptics, and alcohol

1.4. (Continued)

Author (year)	Country or region	Samples	Methods	Results	Addiction history
Launiainen et al. (2014)[145]	Finland	57,903 autopsy cases, with 135 and 380 autopsy cases related to gabapentin and pregabalin	Registry study	Main cause of death in 8 of the 135 (6%) cases was attributed to gabapentin, which value was 12 of 380 (3.2%) in pregabalin users	Unknown
Priez-Barallon et al. (2014)[148]	France	18 cases of death related to pregabalin	Case series	Fatal	Unknown
Hakkinen et al. (2014)[149]	Finland	43 and 316 deaths were found in postmortem toxicology	Registry study	Fatal	Positive addiction history was found in 48.1% of pregabalin and 18.6% of gabapentin cases
		31-year old male with non-medical use of pregabalin	Case report	Fatal	Unknown
		26-year old male with non-medical use of pregabalin	Case report	Fatal	Buprenorphine and amphetamine
Cantrell et al. (2015)[150]	US	47-year old female ingested 15.6g gabapentin	Case report	Fatal	None
Ojanpera et al. (2016)[151]	Finland	Among 19,670 drug-related deaths, 39 and 6 fatalities were related to pregabalin and gabapentin use	Registry study	Fatal	Unknown
Eastwood et al. (2016)[152]	UK	70 cases of postmortem toxicology analysis, most related to pregabalin	Registry study	Fatal	13% heroin, 28% morphine, 19% methadone, 20% cocaine, 55% diazepam, 24% alcohol
Chiappini et al. (2016)[153]	Europe	410 gabapentin and 1,315 pregabalin misuse reported in EudraVigilance database	Database review	86 (21%) fatalities among 410 gabapentin misuse cases; 27 (2%) fatalities among 1,315 pregabalin misuse cases	Unknown

1.4. (Continued)

Author (year)	Country or region	Samples	Methods	Results	Addiction history
Office for National Statistics (2016)[143]	England and Wales	Drug-related poisoning deaths	Registry study	Gabapentin related deaths: 2011 (n=4), 2012 (n=8), 2013 (n=9), 2014 (n=26), and 2015 (n=49) Pregabalin related deaths: 2011 (n=4), 2012 (n=4), 2013 (n=33), 2014 (n=38), and 2015 (n=90)	Unknown
Lai et al. (2006)[43]	US	1,261 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	11 fatalities were involved with gabapentin use and 0 fatalities were involved with pregabalin use	Unknown
Bronstein et al. (2007)[32]	US	1,229 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	19 fatalities were involved with gabapentin use and 10 fatalities were involved with pregabalin use	Unknown
Bronstein et al. (2008)[33]	US	1,239 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	21 fatalities were involved with gabapentin use and 9 fatalities were involved with pregabalin use	Unknown
Bronstein et al. (2009)[34]	US	1,315 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	12 fatalities were involved with gabapentin use and 14 fatalities were involved with pregabalin use	Unknown
Bronstein et al. (2010)[35]	US	1,158 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	19 fatalities were involved with gabapentin use and 4 fatalities were involved with pregabalin use	Unknown
Bronstein et al. (2011)[36]	US	1,146 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	31 fatalities were involved with gabapentin use and 9 fatalities were involved with pregabalin use	Unknown
Bronstein et al. (2012)[37]	US	1,158 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	34 fatalities were involved with gabapentin use and 5 fatalities were involved with pregabalin use	Unknown

1.4. (Continued)

Author (year)	Country or region	Samples	Methods	Results	Addiction history
Mowry et al. (2013)[38]	US	1,190 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	32 fatalities were involved with gabapentin use and 8 fatalities were involved with pregabalin use	Unknown
Mowry et al. (2014)[39]	US	1,218 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	33 fatalities were involved with gabapentin use and 7 fatalities were involved with pregabalin use	Unknown
Mowry et al. (2015)[40]	US	1,173 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	31 fatalities were involved with gabapentin use and 11 fatalities were involved with pregabalin use	Unknown
Mowry et al. (2016)[41]	US	1,256 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	51 fatalities were involved with gabapentin use and 8 fatalities were involved with pregabalin use	Unknown
Gummin et al. (2017)[42]	US	1,415 nonpharmacological and pharmacological related fatalities reported to the nation's poison center	Registry study	51 fatalities were involved with gabapentin use and 10 fatalities were involved with pregabalin use	Unknown
Abrahamsson et al. (2017)[163]	Sweden	4,501 individuals in opioid maintenance program	Registry study	356 individuals died. Z-drugs and pregabalin were associated with overdose death	Opioids at least
Elliott et al. (2017)[154]	UK	9 fatalities attributed to pregabalin abuse	Case series	Fatal	Opioids, benzodiazepines, antidepressants

1.5. Summary of Studies Examining the Risk of Concurrent Use of Opioids and Gabapentinoids

Author (year)	Peckham et al. (2018)[165]	Gomes et al. (2017, 2018)[164,166]	Abrahamsson et al. (2017)[163]
Data source	Truven Health MarketScan® Commercial Claims and Encounters database, 2013-2015	Insurance claims data of residents in Ontario, Canada from 1997-2013	Swedish national registers from July 1, 2005 to December 31, 2012
Study design	Retrospective cohort study	Case-control study	Retrospective cohort study
Study cohort	(1) Subjects with ≥120 days of gabapentin only; (2) subjects with ≥120 days of opioids only; (3) subjects with concurrent use of gabapentin and opioids ≥120 days during a 12-month period	Cases were those with opioid-related deaths, and controls were those opioid users who were alive during the study period. The index dates for cases were the dates of deaths and randomly assigned dates according to the distribution of index dates of cases for controls	Subjects receiving methadone or buprenorphine for opioid maintenance treatment
Exposures	Within each cohort: (1) no evidence of overuse, defined as zero or one claim exceeding FDA maximum dosage per day (3,600 mg/d); (2) mild overuse, defined as two or more claims or one or two calendar quarters average daily dose (January-March, February-April) exceeding FDA maximum dosing; (3) sustained overuse, defined as three or more rolling calendar quarters average daily dose exceeding FDA maximum dosing; (4) sustained overuse and top 1%, defined as meeting the sustained overuse criterion and among the top 1% of users.	Concurrent use of gabapentin and pregabalin, respectively, within 120 days before the index date. In addition, the gabapentin dose was categorized into low dose (<900 mg/d), moderate dose (900 to 1,799 mg/d), and high dose (≥1,800 mg/d) group. Pregabalin dose was categorizrd into low or moderate dose (≤300 mg/d) and high dose (>300 mg/d).	Concurrent use with pregabalin during the study period
Outcomes	(1) All-cause hospitalization, (2) all-cause ED visit, (3) drug-related adverse events such as altered mental status, detoxification, and respiratory depression in the 6-month period	Opioid-related deaths.	Mortality (overdose, non-overdose, and all-cause)
Covariates	Injury, pain, neuropathic pain, postherpetic neuralgia, hot flashes, seizure disorder, restless leg syndrome, concurrent benzodiazepine or Z-hypnotic use, and sex.	Age, medication use (pregabalin, antidepressants, benzodiazepines, and other psychotropic drugs), number of drugs dispensed in the past 6 months, diagnosis of alcohol use disorder, Charlson comorbidity index, chronic lung disease, diabetes, and number of pharmacies used	Sex, age, previous non-fatal overdose, previous psychiatric inpatient treatment, previous suicide attempt, and OMT status.

1.5. (Continued)

Author (year)	Peckham et al. (2018)[165]	Gomes et al. (2017, 2018)[164,166]	Abrahamsson et al. (2017)[163]
Statistical analyses	Multivariable logistic regression	Conditional multivariable logistic regression	Extended Cox regression with treatment as time-varying variable
Main results	Sustained overuse of gabapentin and opioids had an OR of 4.08 (95% CI=2.58-6.46) in all-cause hospitalization compared to gabapentin only, no overuse. Significant associations were also found in all-cause ED visit (OR=2.94, 95%CI=1.97-4.40) and respiratory depression (OR=4.11, 95%CI=1.75-9.62)	Concurrent use of gabapentin and opioids had an OR of 1.49 (95% CI=1.18-1.88) in opioid-related death compared to using opioids alone. There was no significant dose-dependent association (moderate dose: OR=1.56, 95%CI=1.06-2.28; high dose: OR=1.58, 95%CI=1.09-2.27). Concurrent use of pregabalin and opioids had an OR of 1.68 (95%CI=1.19-2.36). There was dose-dependent association (low or moderate dose: OR=1.52, 95% CI=1.04-2.22; high dose: OR=2.51, 95% CI=1.24-5.06)	Periods with pregabalin use was associated with 182% and 101% increased risk of overdose death and all-cause mortality, respectively (overdose death: HR=2.82, 95% CI=1.79-4.43; all-cause mortality: HR=2.01, 95% CI=1.38-2.91), compared to periods without pregabalin use. The increased risk was not observed for the non-overdose death outcome.
Limitations	(1) Simply apply FDA maximum daily dose (3,600 mg/d) as a cutoff point to identify overuse; (2) only gabapentin was examined; (3) limit to chronic gabapentin or opioid users (≥120 days); (4) non-elderly population aged 16-64 years.	(1) case-control study design may not accurately estimate the risk of outcome; (2) did not examine the impact of duration effect; and (3) did not reflect the clinical practice of US	(1) Focus on pregabalin only; (2) did not examine the dose-dependent effects in terms of duration and dose on the outcomes of interest; (3) limit study participants with prior opioid use disorders.

CHAPTER 2. TRENDS, PATIENT AND PRESCRIBER CHARACTERISTICS AND OFF-LABEL USE OF GABAPENTINOIDS AMONG UNITED STATES AMBULATORY CARE VISITS FROM 2003-2015

2.1. ABSTRACT

Objectives: Increasing use of gabapentinoids (i.e., gabapentin and pregabalin) has raised concerns of misuse and abuse of gabapentinoids in the United States (US). Yet, little is known about the patient and prescriber characteristics of gabapentinoid use. This information may be valuable to better inform target interventions in the general clinical practice, where chronic pain is primarily managed. We aimed to examine the trends, utilization characteristics, and the extent of off-label use of gabapentinoids among the US ambulatory care visits.

Methods: This cross-sectional study used the National Ambulatory Medical Survey data from 2003-2015. Among all the adult ambulatory care visits (≥18 years), we first estimated the annual national number of visits and proportions for gabapentinoids, opioids, and benzodiazepines, respectively. We used multivariable logistic regression to test the trend significance of the annual proportion of gabapentinoid visits, adjusting for patient and prescribe characteristics. We then examined the patient and prescriber characteristics of gabapentinoid visits.

Results: From 2003-2015, the visits involving gabapentinoids (7.4-30.4 million), opioids (9.9-91.3 million), and benzodiazepines (27.7-62.2 million) increased substantially. The

trend of adjusted proportion of gabapentinoid visits more than tripled (9.1-33.1 per 1,000 visits; P_{trend}<0.0001), mainly driven by gabapentin. Among 233.1 million gabapentinoid visits from 2003-2015 (age <65 years=61.8%; female=61.9%; white=86.2%), 52.4% were from individuals having a governmental insurance, and 60.3% were from those with ≥2 chronic conditions. Half of the gabapentinoid visits had concurrent use with opioids (31.6%), benzodiazepines (14.9%), or both (5.8%). Nearly two-thirds of gabapentinoid visits were seen by primary care physicians (44.8%), neurologists (8.4%), surgeons (6.2%), and psychiatrists (5.1%). Off-label use was substantially high (gabapentin: 98.3% vs pregabalin: 89.8%). Over 80% of gabapentinoid visits were continuous use vs new initiation of gabapentinoids.

Conclusions: Gabapentinoid use has increased substantially in the US ambulatory care settings over time. High proportions of off-label use and concurrent opioid/benzodiazepine use highlight the needs to evaluate for inappropriate gabapentinoid use.

Keywords: Gabapentinoids; trends; patient and prescriber characteristics; NAMCS

2.2. INTRODUCTION

Approximately one-third of adults in the United States (US) have at least one chronic pain condition and seek health care primarily in the ambulatory care settings.[1,2] In response to the misuse and addiction to prescription opioids in the US, states, payers, and healthcare systems have implemented numerous laws, regulations, and policies to combat this opioid epidemic in the past few years.[3] However, using non-opioid analgesics or multimodal analgesia to ensure appropriate pain management while minimizing the risk or adverse outcomes of medications imposes challenges to healthcare providers.

The US Food and Drug Administration (FDA) approved gabapentinoids including gabapentin in 1993 and pregabalin in 2004 for the treatment of partial seizures and postherpetic neuralgia.[4,5] Gabapentin has also been approved for restless legs syndrome in adults, and pregabalin has additional indications for diabetic peripheral neuropathy, fibromyalgia, and neuropathic pain associated with spinal cord injury.[4,5] Pregabalin is a Schedule V Controlled Substance regulated by the US Drug Enforcement Administration (DEA), while gabapentin is not regulated at the federal level legislation.[6]

Although there is limited evidence supporting for the off-label use, gabapentinoids, especially gabapentin, have been extensively used for various types of pain conditions and anxiety disorders.[4,7-9] According to the IMS Health national prescription data, gabapentin ranked the 10th most dispensed medications in 2016, with a total of 64 million prescriptions, increasing from 39 million prescriptions in 2012.[10] The sales of pregabalin doubled from $1.9 billion in 2012 to $4.4 billion in 2016.[10] A recent

study using the US Medical Expenditure Panel Survey (MEPS) data also found that the proportions of gabapentinoid users more than tripled from 1.2% in 2002 to 3.9% in 2015.[11]

Restrictions on opioid prescribing, perceptions of less addiction liability and relative safety profiles of gabapentinoids, and inappropriate marketing may contribute to the significantly increasing trend in gabapentinoid use in the US in the past decade.[10] However, increasing safety concerns regarding misuse and abuse of gabapentinoids, along with a few small studies reporting the concomitant use of gabapentinoids among individuals with opioid use disorder, necessitate the investigation of gabapentinoid utilization patterns in the US ambulatory care settings where chronic pain is primarily managed.[12] Indeed, prior studies suggest an increased risk of opioid-related death associated with concurrent opioid and gabapentinoid use.[13] In order to better inform target interventions and health policies regarding gabapentinoid use in the general clinical practice, we examined the trends, patient and prescriber characteristics, and extent of potential off-label use of gabapentinoids among the US ambulatory care visits from 2003 to 2015.

2.3. METHODS

2.3.1. Data Source

This cross-sectional study used the National Ambulatory Medical Care Survey (NAMCS) data from 2003 to 2015. The National Center for Health Statistics administers NAMCS to collect information related to the health care delivery in the US ambulatory health care settings, on average at annual basis (1973-1981, 1985 and 1989 to present).[14] NAMCS collects data from a nationally representative sample of non-federally employed, office-based physicians who are included in the American Medical Association and American Osteopathic Association master files, except anesthesiologists, pathologists, and radiologists.[15] These selected physicians are asked to provide information from medical records for a random selection of patient visits in a random week in a given year.[15] Requested information includes patient demographics, diagnoses, services and lab tests ordered, prescriptions or over-the-counter (OTC) medications prescribed or used, physician specialties, and reimbursements.

NAMCS uses a multistage probability stage design from 2003 to 2011 and a stratified two-stage sample design since 2012 to ensure collecting the representativeness of patient visits in the US ambulatory care settings.[15,16] The multistage probability stage design identifies geographic areas (primary sampling units) first, practicing physicians next, and then patient visits.[16] The stratified two-stage sampling design involves physicians selected in the first stage and visits selected in the second stage.[15] The number of visits varied from 25,665 to 76,330 during the period of 2003 to 2015, with physician response ranging from 46% to 67%.

2.3.2. Study Cohort

The analytical sample included the adult patient visits involving gabapentin or pregabalin prescribed or used from 2003 to 2015. The numbers of medications recorded in NAMCS have increased over time, from eight medications collected before 2011, ten medications between 2012 and 2013, and up to 30 medications since 2014. In order to make sure the findings were comparable across years, we only included the first eight medications listed each year, similar to the approaches used in prior literatures.[17-19] We used the Multum Lexicon Plus® system to identify medications of interest based on generic ingredients (**eTable 2.1**).[20] This study of using public-available de-identified data was deemed human subjects exempt from review by the University of Arizona Institutional Review Board.

2.3.3. Patient Characteristics

We examined patient characteristics including age (<65 years vs ≥65 years), sex, race/ethnicity (white vs non-white), smoking status (current vs former or non-smoker), insurance coverage status (government insurance, commercial insurance, vs others), and the major visit reason (chronic problems/routine check-up vs others). Given that up to 14 chronic conditions (arthritis, asthma, cancer, cerebrovascular disease/history of stroke or transient ischemic attack, chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, depression, diabetes, hyperlipidemia, hypertension, ischemic heart disease, obesity, and osteoporosis) and variable of overweight or obese

were collected starting 2005, number of chronic conditions and overweight or obese were calculated for each patient visit from 2005 to 2015.

Visits with concurrent use of gabapentinoids with opioids and benzodiazepines were identified (concurrent use with opioids, concurrent use with benzodiazepines, vs concurrent use with both opioids and benzodiazepines). Prescription opioids included buprenorphine, butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, propoxyphene, and tramadol. Prescription benzodiazepines included alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, oxazepam, prazepam, quazepam, temazepam, and triazolam.

2.3.4. Prescriber Characteristics

Variables of prescriber characteristics included physician specialty, geographic region (northwest, midwest, south vs west), and urbanicity (metropolitan vs non-metropolitan) of practice locations. Physician specialties are categorized into 14 categories in NAMCS data (general and family practice, internal medicine, pediatrics, general surgery, obstetrics and gynecology, orthopedic surgery, cardiovascular diseases, dermatology, urology, psychiatry, neurology, ophthalmology, otolaryngology, and others). Based on the data distribution and clinical knowledge of specialties most commonly prescribing gabapentinoids, we created a physician specialty indicator (primary care including general/family practice and internal medicine, surgery including general surgery and orthopedic surgery, psychiatry, neurology, vs others).

2.3.5. Gabapentinoid Utilization Characteristics

NAMCS collects up to three diagnosis codes using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* for each patient visit. We identified visits involving gabapentinoids with a FDA-approved indication including partial seizures, postherpetic neuralgia, restless legs syndrome (gabapentin only), diabetic peripheral neuropathy (pregabalin only), fibromyalgia (pregabalin only), and neuropathic pain associated with spinal cord injury (pregabalin only). Patient visits without any FDA approval indication were considered as off-label use. **eTable 2.2** includes the detailed *ICD-9-CM* codes for each FDA indication. We further examined whether the patient visit was the new initiation or continuous use of gabapentinoids.

2.3.6. Main Statistical Analysis

Our analyses included two steps. First, among all the ambulatory care visits from adults aged ≥18 years, we estimated the national annual number of visits and proportions among all visits for gabapentinoids (overall, and by gabapentin and pregabalin), as well as for opioids and benzodiazepines, respectively. When the unweighted number was less than 30 or the relative standard error was greater than 30%, we only reported unweighted numbers due to reliability concerns based on NAMCS' recommendation.[21] We then estimated the adjusted annual proportion of gabapentinoid visits and tested their significance of trend using multivariable logistic regression, adjusting for patient and prescriber characteristics, with indicator "year" as

the categorical variable. Similarly, the adjusted annual proportion of gabapentin and pregabalin visits over time were estimated.

Second, among all ambulatory visits with gabapentinoids, we examined their patient and prescriber characteristics and the extent of potential off-label use. We then compared the characteristics differences between gabapentin and pregabalin visits using the standardized mean difference (SMD). SMD >0.1 was considered as having non-negligible difference between the groups.[22] All analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA).

2.3.7. Stratification and Sensitivity Analysis

In order to improve the reliability of our findings, we conducted subgroup analyses by combining years into two-year intervals (e.g., 2003-2004, 2005-2006, ..., 2015) as recommended by NAMCS. We examined the trends in gabapentinoid use over years stratified by the patient and prescriber characteristics described previously. Furthermore, given that only including the first eight medications collected in NAMCS data may result in an underestimate of gabapentin use, we conducted a sensitivity analysis by including all medication collected in NAMCS each year.

2.4. RESULTS

From 2003 to 2015, substantial increases in the US ambulatory care visits involving prescription gabapentinoids (7.4 to 30.4 million), opioids (9.9 to 91.3 million), and benzodiazepines (27.7 to 62.2 million) were observed (**Figure 2.1**). The trend of adjusted proportions of gabapentinoid visits more than tripled from 2003 to 2015 (9.1 to 33.1 per 1,000 visits; $P_{trend}<0.0001$; **Figure 2.2**). The increasing trend in gabapentinoid use was mainly driven by gabapentin while pregabalin use remained stable over time (**eFigures 2.1-2.3**).

Characteristics of gabapentinoid use in the ambulatory care settings were similar across years. Among the 233.1 million gabapentinoid visits from 2003 to 2015 (age <65 years: 61.8%; female: 61.9%; white: 86.2%), 52.4% were from individuals having a governmental insurance and 60.3% were from those with ≥2 chronic conditions (**Table 2.1**). Half of the gabapentinoid visits had concurrent use with opioids (31.6%), benzodiazepines (14.9%), or both (5.8%). Two-thirds of gabapentinoid visits were prescribed by primary care physicians (44.8%), neurologists (8.4%), surgeons (14.5%), and psychiatrists (5.1%). Off-label use was higher for gabapentin than for pregabalin (98.3% vs 89.8%). Over 80% of gabapentinoid visits were continuous use of gabapentinoids.

Stratification analyses showed that ambulatory care visits from individuals aged ≥65 years, having governmental insurance, with ≥2 chronic conditions, with concurrent opioid or benzodiazepine use, and visiting neurologists were more likely to use

gabapentinoids (**eFigures 2.4-2.6**). Including all available medications collected showed 39.7 million ambulatory visits with gabapentinoids in 2015 (**eFigure 2.7**).

2.5. DISCUSSION

Using the NAMCS data, our study found that the visits involving gabapentinoids quadrupled from 2003 to 2015. Potential off-label use of gabapentinoids was overwhelmingly high (98% vs 83% for gabapentin in 2001 reported by Radley et al.[9]). Similar to the Johansen's MEPS study, gabapentinoid visits were more likely to be from older age, females, and those with more chronic conditions. Half of the gabapentinoid visits had concurrent opioid and/or benzodiazepine use. Notably, we additionally identified other characteristics associated to gabapentinoid use: white race, having a governmental insurance, primary care physicians, physician practices located in metropolitan and south regions, and continuous use of gabapentinoids.

Current initiatives implemented in part of the US health systems to reduce high-risk gabapentinoid use included prior authorization and step therapy for pregabalin, mandatory reporting of gabapentin use to the prescription drug monitoring programs in some states (e.g., Ohio, Virginia, and Massachusetts), and classification of gabapentin as a Schedule V Controlled Substance with prescribing quantity limits.[23,24] However, definition for high-risk gabapentinoid use varied. While gabapentinoids are promoted as a key constituent of multimodal analgesia to reduce the opioid dosage in perioperative and other acute pain settings, more evidence is needed to evaluate the safety of opioid-gabapentinoid interactions with respect to dose, duration, and interactions given increasing awareness of adverse outcomes.[25] Our study underscores the need for safety evaluation regarding gabapentinoid use in the US ambulatory care setting,

especially with the substantially high prevalence of concurrent opioid and gabapentinoid use and off-label use of gabapentinoids.

Our study had several limitations. First, gabapentinoid use and FDA-approved indications may be underestimated because only eight medications and three *ICD-9-CM* codes were available in NAMCS (~18-23% underestimate of medication use based on our sensitivity analyses using 30 medications in 2014 and 2015; ~10-15% overestimate off-label use compared to prior studies[9]). Second, NAMCS data lack of duration and dose information of medication use. Third, our findings represent visit-level data rather than patient-level. Nonetheless, variations of gabapentinoid use in different patient and prescriber characteristics highlight the needs for effectiveness and safety of gabapentinoid studies and routine monitoring systems for individuals at high risk of drug abuse/misuse.

2.6. CONCLUSION

Gabapentinoid use has increased substantially in the US ambulatory care over time. High proportions of off-label use and concurrent opioid/benzodiazepine use highlight the needs to evaluate for inappropriate gabapentinoid use.

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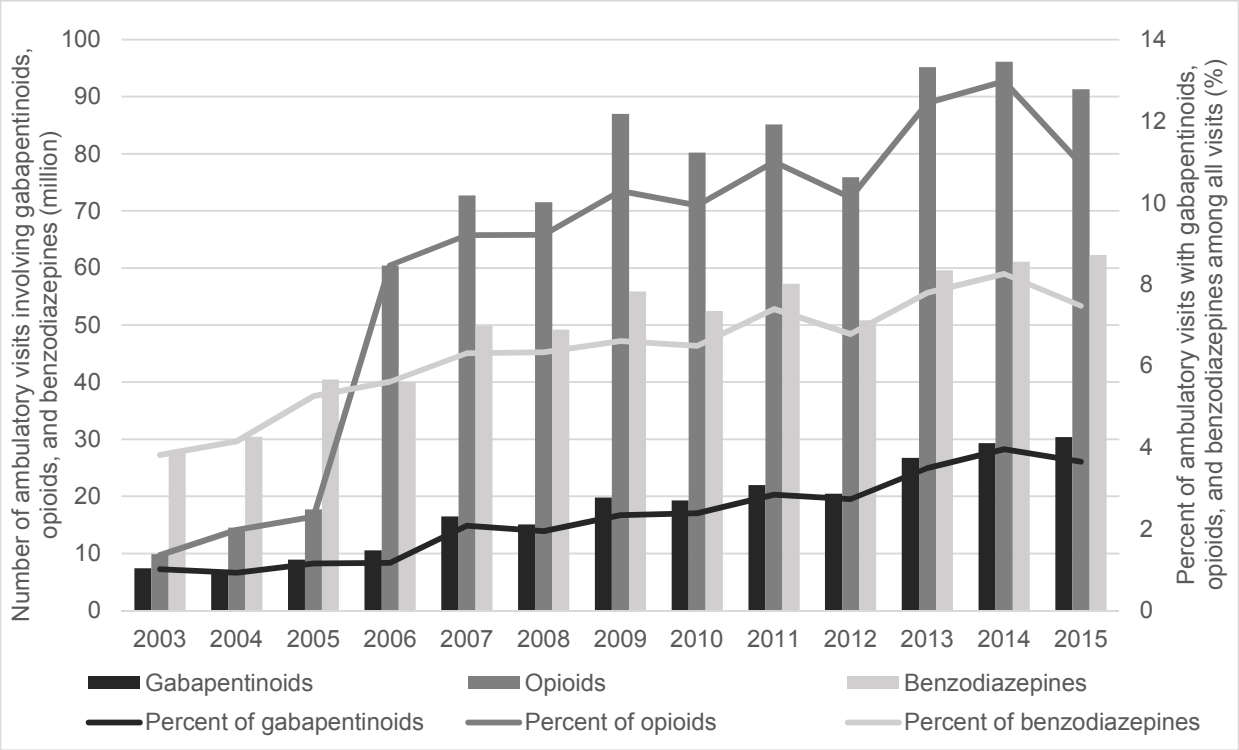
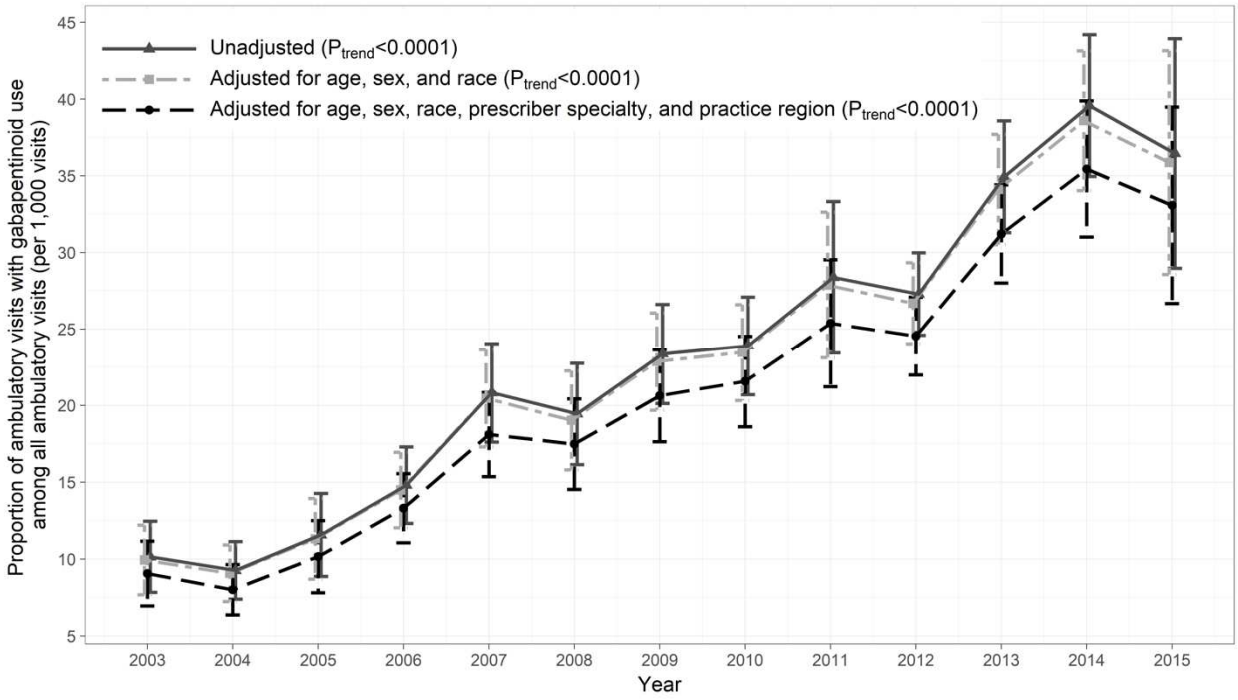
2.8. FIGURES



2.1. Trends in the Use of Gabapentinoids, Opioids, and Benzodiazepines in the US Ambulatory Settings: 2003-2015 National Ambulatory Medical Care Survey (NAMCS)



2.2. Trends in Proportion of Ambulatory Care Visits with Gabapentinoid Use among US Ambulatory Care Visits: 2003-2015 National Ambulatory Medical Care Survey (NAMCS)

2.9. TABLE

2.1. Characteristics of Patients, Prescribers, and Utilizations of Gabapentinoid Use in the US Ambulatory Settings: 2003-2015 National Ambulatory Medical Care Survey (NAMCS)

	Gabapentinoids[1]		Gabapentin[1]		Pregabalin[1]		
Characteristics	Wt. No. Visits[2]	Wt. %	Wt. No. Visits[2]	Wt. %	Wt. No Visits[2]	Wt. %	SMD[3]
Patient Characteristics							
≥65 years	89.0	38.2	72.4	39.2	17.3	34.1	0.11
Female	144.4	61.9	114.2	61.8	31.7	62.6	0.02
Race/ethnicity[4]							0.03
White	201.0	86.2	159.1	86.1	44.1	87.1	
Non-white	32.1	13.8	25.8	13.9	6.6	12.9	
Current smoker	43.1	18.5	34.6	18.7	8.9	17.6	0.03
Insurance type[5]							0.19
Governmental[6]	122.1	52.4	99.5	53.8	23.6	46.5	
Commercial	89.4	38.4	67.5	36.5	23.2	46.0	
Others	11.3	4.9	9.3	5.0	2.0	4.0	
Major visit reason due to chronic problems[5]	145.8	62.6	115.6	62.5	3.2	63.0	0.01
Concurrent use with							
Opioids	73.6	31.6	55.0	29.7	19.4	38.2	0.18
Benzodiazepines	34.8	14.9	28.2	15.3	6.9	13.5	0.05
Both opioids and benzodiazepines	13.4	5.8	10.1	5.5	3.4	6.7	0.05
≥2 chronic conditions[7]	132.0	60.3	104.5	61.3	29.2	57.6	0.07
Overweight/obese[7,8]	98.2	44.9	78.1	45.7	21.3	42.0	0.07
Prescriber Characteristics							
Specialty							0.22
Primary care[9]	104.3	44.8	82.5	44.6	22.6	44.6	
Neurology	19.7	8.4	15.9	8.6	4.5	8.8	
Surgery[10]	14.5	6.2	10.7	5.8	4.0	7.9	
Psychiatry	11.9	5.1	10.9	5.9	1.1	2.1	
Others	82.7	35.5	64.9	35.1	18.5	36.6	
Geographic region							0.21
Northwest	37.0	15.9	30.2	16.3	7.5	14.8	
Midwest	48.4	20.7	37.9	20.5	10.9	21.4	
South	96.5	41.4	73.5	39.8	24.0	47.4	
West	51.2	22.0	43.3	23.4	8.3	16.4	
Metropolitan area	202.6	86.9	161.0	87.1	43.8	86.4	0.02
Gabapentinoid utilization							
Potential off-label use[11]	225.0	96.5	181.8	98.3	45.5	89.8	0.37
Continuous use[5,7,12]	183.4	83.8	144.0	84.4	41.0	80.9	0.08

SMD = standardized mean difference; Wt = weighted.

[1] National estimates of ambulatory visits involving gabapentinoids, gabapentin, and pregabalin were 233.1, 184.9, and 50.7 million, accounting for 1.9%, 1.5%, and 0.4% of all adult ambulatory visits,

respectively. Among the total 233.1 million ambulatory visits involving gabapentinoids, 2.5 million used both gabapentin and pregabalin.
[2] Number of weighted ambulatory visits (i.e., national estimates) was represented in units of millions.
[3] SMD=0.2, 0.5, and 0.8 were considered as small, medium, and large differences between gabapentin and pregabalin visits.
[4] Racial groups other than white and African American only accounted for 3.0% of all gabapentinoid visits. Therefore, African American and other racial groups were combined as non-white.
[5] Percent of missing data for insurance type, major visit reason due to chronic problems, and new initiation vs. continuous use of medications was 4.3%, 1.9%, and 2.6%, respectively.
[6] Governmental insurance included Medicare, Medicaid, children's health insurance program, or other state-based programs.
[7] Variables of chronic condition, overweight/obese, and new initiation vs. continuous use of medications were available starting in 2005. The weighted proportions were calculated based on the overall gabapentinoid visits from 2005 to 2015 (219.0 million).
[8] Overweight/obese condition was measured as body mass index ≥25.
[9] Primary care included general/family practice and internal medicine.
[10] Surgery included general surgery and orthopedic surgery.
[11] Potential off-label use was defined as gabapentinoid visits without any FDA-approved indications including partial seizures and postherpetic neuralgia for both gabapentin and pregabalin. Other FDA-approval indications include restless legs syndrome (gabapentin only), diabetic peripheral neuropathy (pregabalin only), fibromyalgia (pregabalin only), and neuropathic pain associated with spinal cord injury (pregabalin only).
[12] Among all the gabapentinoid visits from 2005 to 2015, 0.4% of visits had both new and continuous use of gabapentinoids (0.2% and 0.02% for gabapentin and pregabalin visits, respectively).

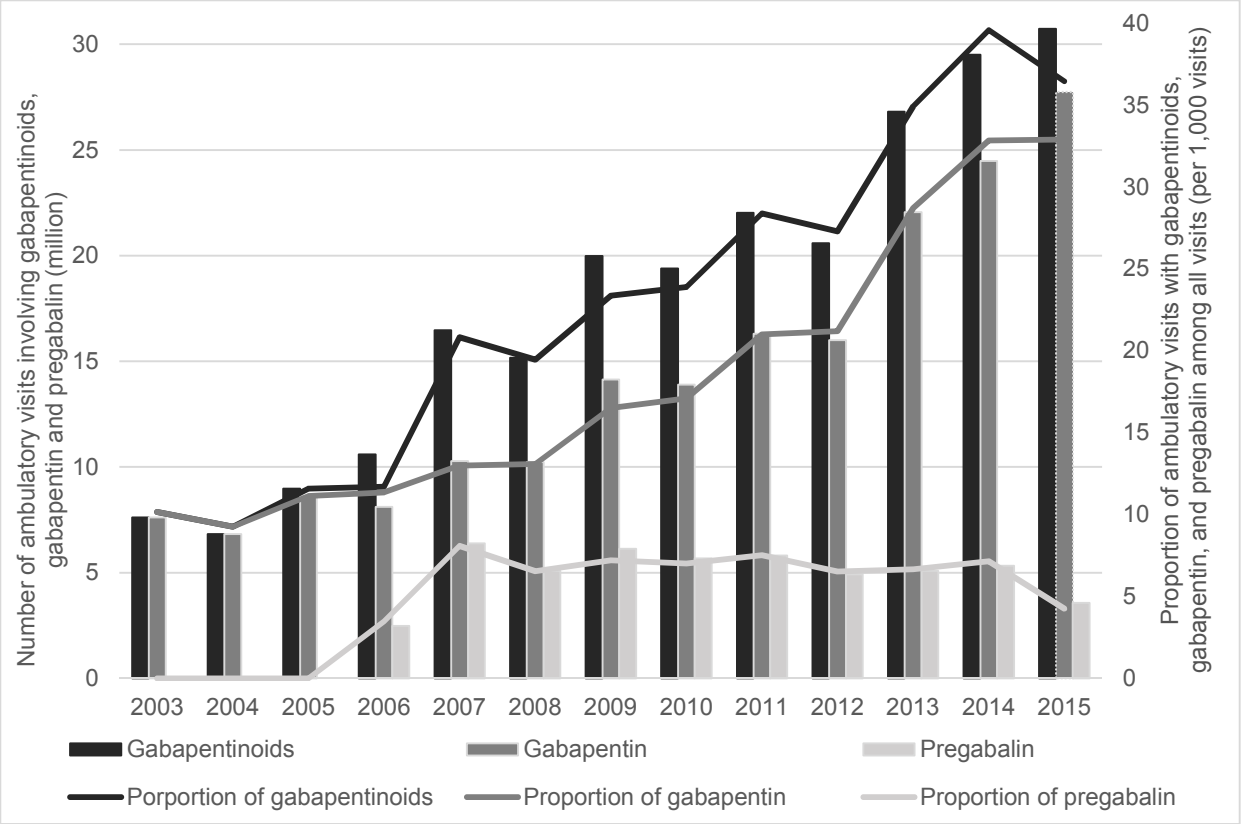
2.10. SUPPLEMENTAL DATA

eTable 2.1. Generic Codes Used to Identify Gabapentinoids, Opioids, and Benzodiazepines

Medication class and drugs	Lexi or Multum's Generic codes
Gabapentinoids	
Gabapentin	d03182
Pregabalin	d05508
Opioids	
Buprenorphine	d00840, d04819
Butorphanol	d00838
Codeine	a11076, d00012, d03357, d03364, d03393, d03394, d03398, d03423, d03426, n08029
Dihydrocodeine	d03168
Fentanyl	d00233
Hydrocodone	a10897, a10956, a11768, d03075, d03340, d03356, d03361, d03396, d03428, d03915, d04225
Hydromorphone	d00255
Meperidine	d00017, d03433
Methadone	d00050
Morphine	d00308
Oxycodone	d00329, d03431, d03432
Oxymorphone	d00833
Pentazocine	d00334
Propoxyphene	d00360, d03434
Tramadol	d03826, d04766
Benzodiazepines	
Alprazolam	d00168
Chlordiazepoxide	d00189, d03462, d03492
Clonazepam	d00197
Clorazepate	d00198
Diazepam	d00148
Estazolam	d00915
Flurazepam	d00238
Halazepam	d00904
Lorazepam	d00149, n15002
Midazolam	d00301
Oxazepam	d00040
Prazepam	a54760
Quazepam	d00917
Temazepam	d00384
Triazolam	d00397

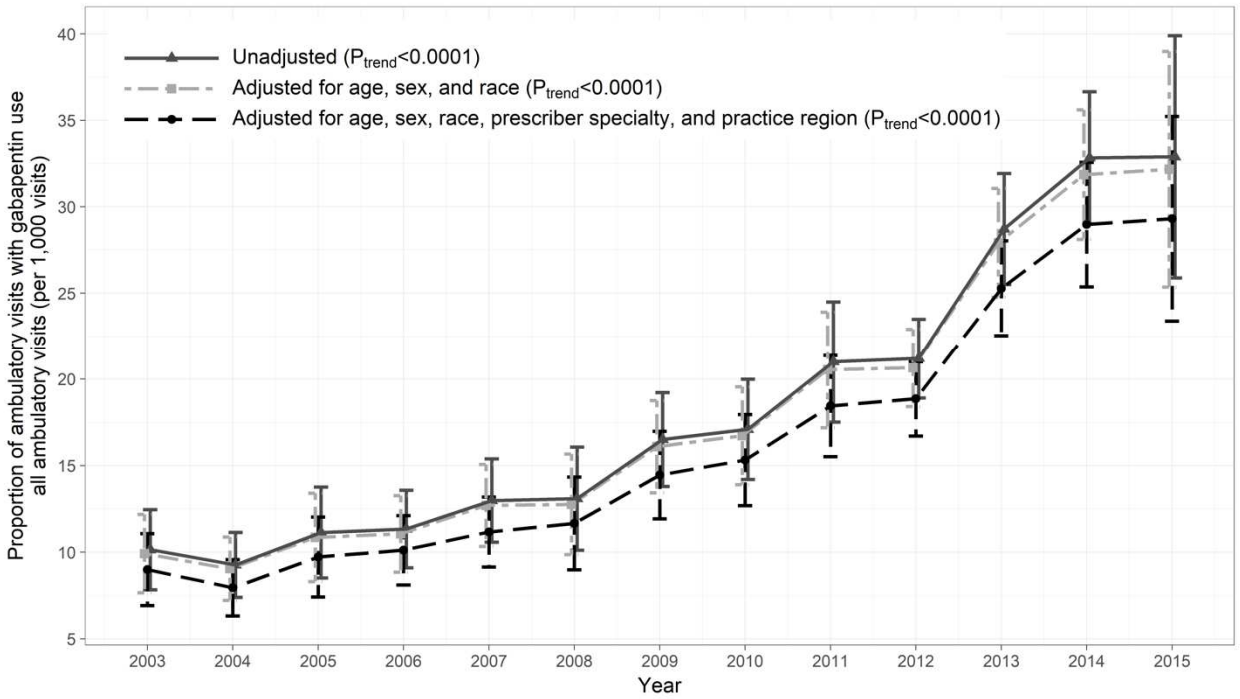
eTable 2.2. ICD-9-CM Codes of Diseases Included in the Study

Diseases/Conditions	ICD-9-CM
Partial seizures[6]	780.31, 780.32, 780.33, 780.39
Postherpetic neuralgia[185,186]	053.10, 053.11, 053.12, 053.13, 053.14, 053.19
Restless legs syndrome[183]	333.94
Diabetic peripheral neuropathy[183,187]	250.60, 250.61, 250.62, 250.63, 357.2
Fibromyalgia[188,189]	729.1
Neuropathic pain associated with spinal cord injury[190]	344.0x, 344.1x, 344.6x, 806.xx, 952.xx (spinal cord injury) with 338.0 (central pain syndrome)

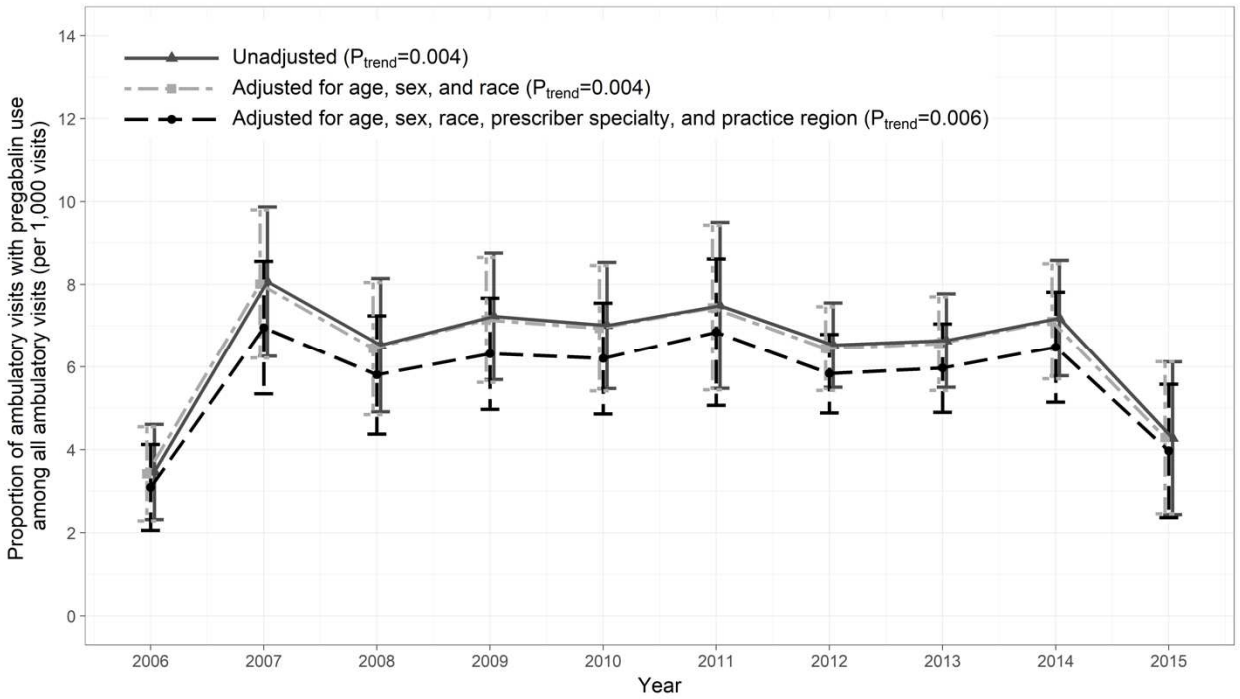


eFigure 2.1. Trends in the Use of Gabapentinoids, Gabapentin, and Pregabalin in the US Ambulatory Settings: 2003-2015 National Ambulatory Medical Care Survey (NAMCS)

National estimates of ambulatory visits involving pregabalin in 2005 was not reported due to the unweighted number less than 30, which yielded unreliable national estimates based on NAMCS's recommendation.

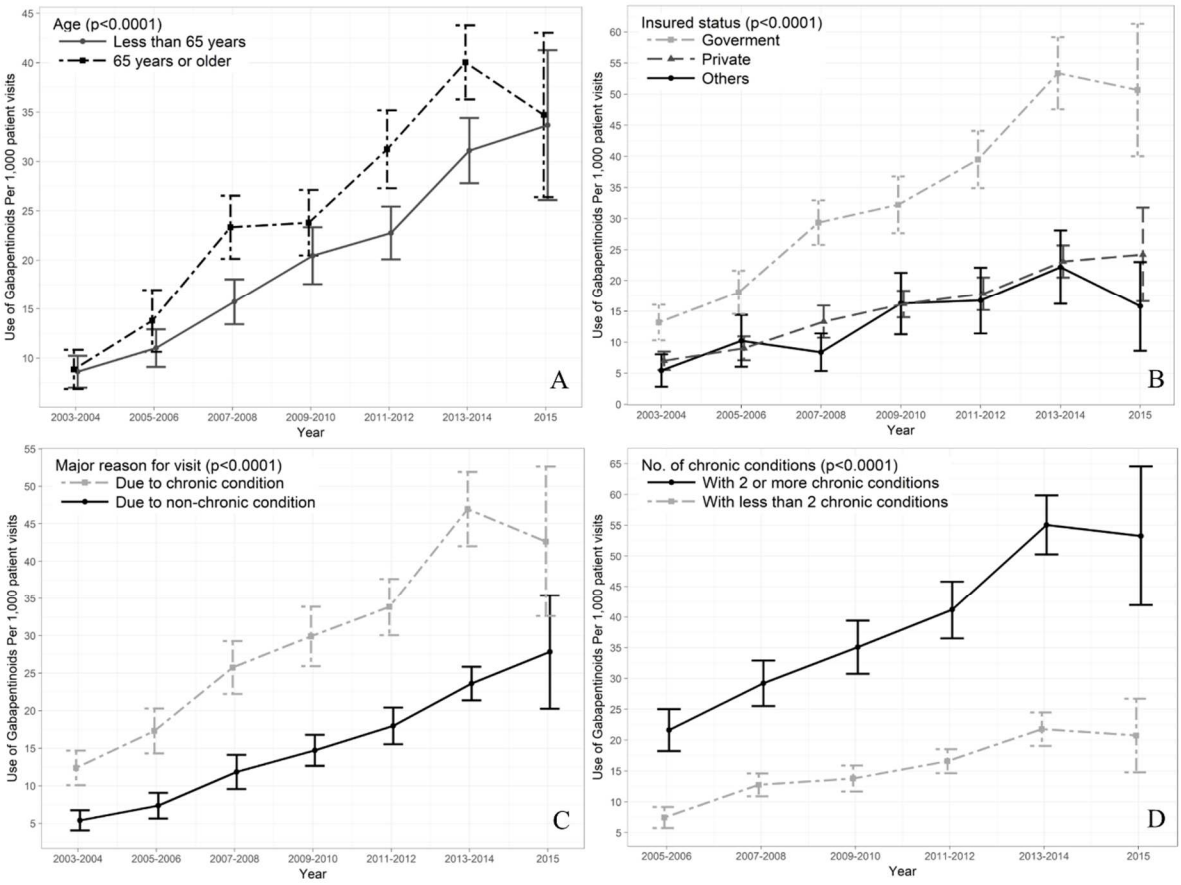


eFigure 2.2. Trends in the Proportion of Ambulatory Care Visits with Gabapentin Use among all US Ambulatory Care Visits: 2003-2015 National Ambulatory Medical Care Survey (NAMCS)

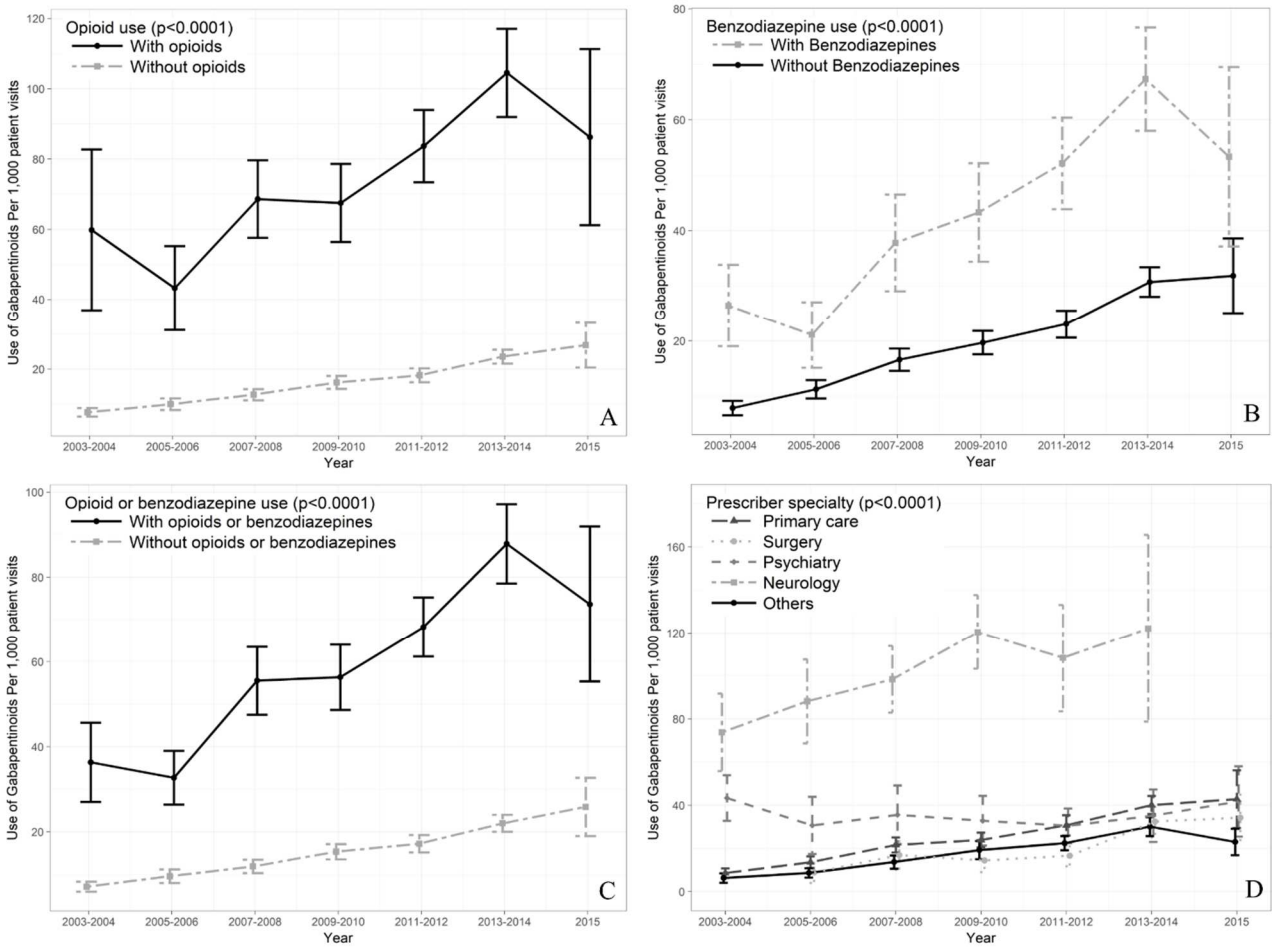


eFigure 2.3. Trends in the Proportion of Ambulatory Care Visits with Pregabalin Use among all US Ambulatory Care Visits: 2003-2015 National Ambulatory Medical Care Survey (NAMCS)

When only including the data from 2007 to 2014, P_{trend} for unadjusted model, model adjusting for age, sex, and race, and model adjusting for age, sex, race, prescriber specialty, and practice region was 0.78, 0.76, and 0.83, respectively.

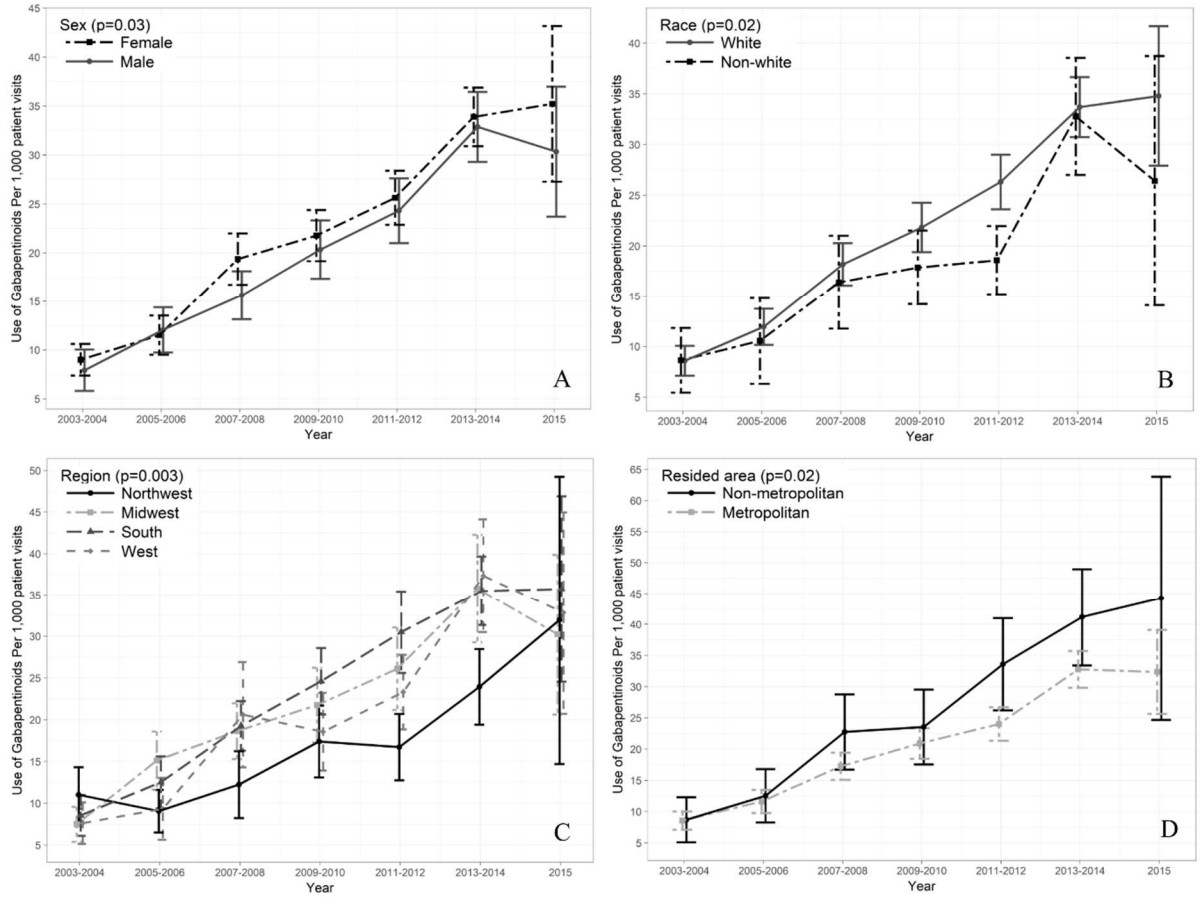


eFigure 2.4. Trends in the Proportion of Ambulatory Care Visits with Gabapentinoid Use among all US Ambulatory Care Visits, Stratified by Age, Insured Status, Major Visit Reason, and Number of Chronic Conditions: 2003-2015 National Ambulatory Medical Care Survey (NAMCS)

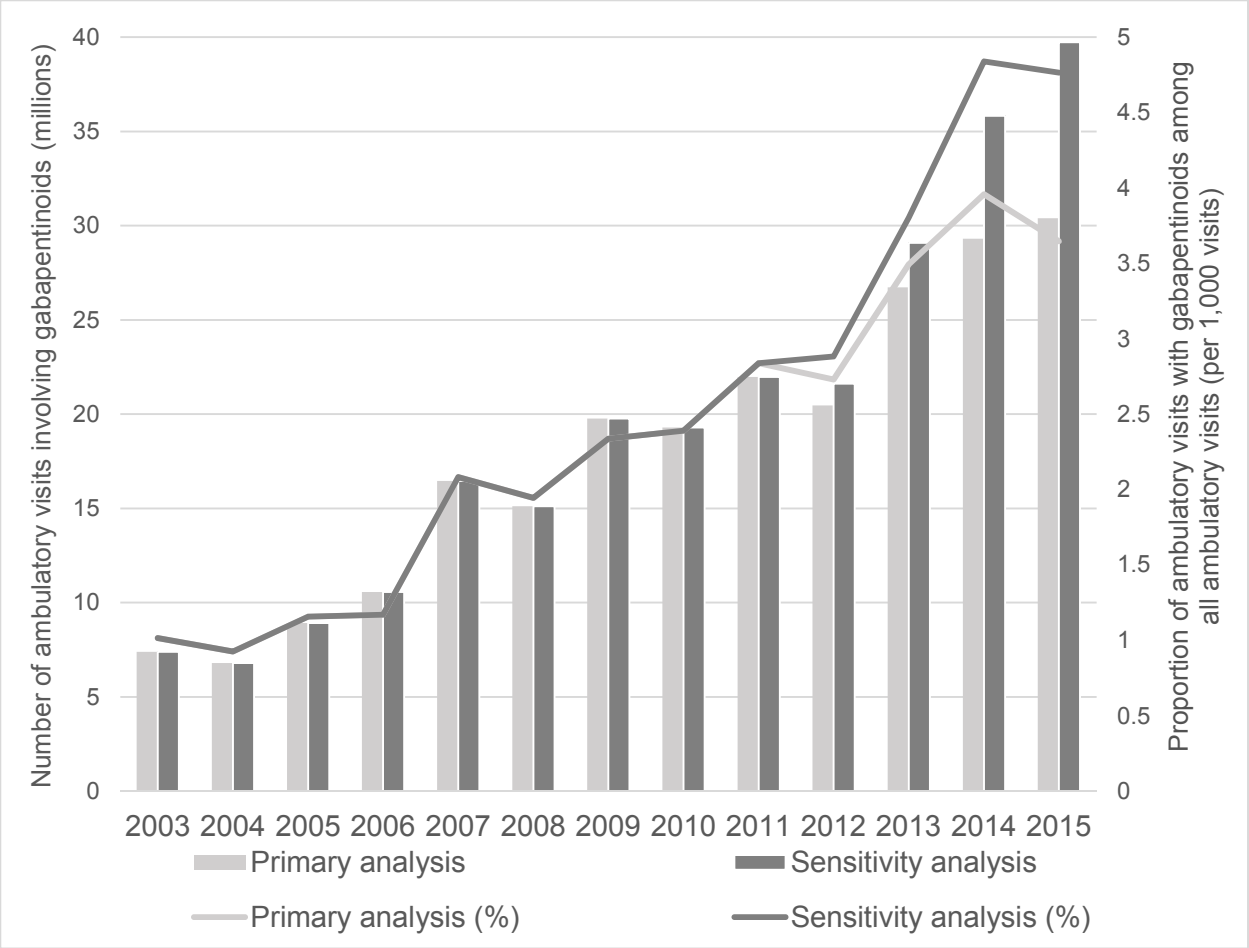


eFigure 2.5. Trends in the Proportion of Ambulatory Care Visits with Gabapentinoid Use among all US Ambulatory Care Visits, Stratified by Concurrent Use of Opioids and Benzodiazepines and Prescriber Specialty: 2003-2015 National Ambulatory Medical Care Survey (NAMCS)

National estimates of gabapentinoid visits prescribed by surgery between 2003 and 2014 were not reported because its unweighted number was less than 30, so was the gabapentinoid visits prescribed by a neurologist in 2015, which relative standard error was greater than 30%



eFigure 2.6. Trends in the Proportion of Ambulatory Care Visits with Gabapentinoid Use among all US Ambulatory Care Visits, Stratified Sex, Race/Ethnicity, and Prescriber Geographic Region and Urbanity: 2003-2015 National Ambulatory Medical Care Survey (NAMCS)



eFigure 2.7. Trends in the Use of Gabapentinoids in the US Ambulatory Care Settings, by Including First Eight Medications and All Medications Available Each Year: 2003-2015 National Ambulatory Medical Care Survey (NAMCS)

CHAPTER 3. DUAL-TRAJECTORIES OF OPIOID AND GABAPENTINOID USE AND RISK OF SUBSEQUENT ADVERSE HEALTH OUTCOMES IN UNITED STATES MEDICARE

3.1. ABSTRACT

Objectives: Increasing gabapentinoid (GABA) use, along with concurrent prescription opioid (OPI) use, has raised safety concerns of misuse/abuse of GABAs in the United States. Little is known about the patterns of concurrent OPI and GABA use (hereafter OPI-GABA) most associated with the risk of adverse health outcomes. We examined the association between OPI-GABA dose and duration trajectories and subsequent drug overdose risk among Medicare beneficiaries.

Methods: This retrospective cohort study included fee-for-service Medicare beneficiaries with fibromyalgia, low back pain, neuropathy, and/or osteoarthritis who newly initiated OPI and/or GABA from 2011-2016. During the first year of OPI and/or GABA initiation (i.e., index-year), we used group-based multi-trajectory models to identify distinct OPI-GABA use patterns, based on standardized daily dose (i.e., morphine milligram equivalent for OPIs and minimum effective daily dose for GABAs). We used inverse probability of treatment weighted multivariable Cox proportional hazards model to estimate the risk of time to the first drug overdose diagnosis within 12 months following the index-year, adjusting for socio-demographics and health factors.

Results: Among 71,005 beneficiaries (mean age ± SD= 65.5 ± 14.5 years, female=68.1%, white=76.8%), ten distinct trajectories were identified (3 OPI-only

trajectories, 3 GABA-only trajectories, and 4 OPI-GABA trajectories). Compared with OPI-only early discontinuers (40.6% of the cohort), the subsequent 1-year drug overdose risk varied by trajectory group: consistent low-dose OPI-only users (16.6%; HR=1.47, 95%CI=1.19-1.82), consistent high-dose OPI-only users (1.8%; HR=4.57, 95%CI=2.99-6.98), GABA-only early discontinuers (12.5%; HR=1.39, 95%CI=1.09-1.77), consistent low-dose GABA-only users (11.0%; HR=1.44, 95%CI=1.12-1.85), consistent high-dose GABA-only users (3.1%; HR=1.43, 95%CI=0.94-2.17), early discontinuation of OPIs and consistent low-dose GABA users (6.9%; HR=1.24, 95%CI=0.90-1.69), consistent low-dose OPI-GABA users (3.4%; HR=2.49, 95%CI=1.76-3.52), consistent low-dose OPI and high-dose GABA users (3.2%; HR=2.46, 95%CI=1.71-3.53), and consistent high-dose OPI and moderate-dose GABA users (0.9%; HR=7.22, 95%CI=4.46-11.69).

Conclusions: Subsequent risk of drug overdose varied substantially by different OPI-GABA trajectories among Medicare beneficiaries. High-dose OPI-only users and all consistent OPI-GABA users (regardless of doses) were associated with more than doubled subsequent drug overdose risk.

Keywords: Gabapentinoids; opioids; trajectories; overdose; Medicare

3.2. INTRODUCTION

The United States (US) Food and Drug Administration (FDA) has approved gabapentinoids (GABAs), including gabapentin and pregabalin, for the treatment of partial seizures and postherpetic neuralgia.[1,2] Gabapentin is also approved for restless legs syndrome in adults, while pregabalin has indications for diabetic peripheral neuropathy, fibromyalgia, and neuropathic pain associated with spinal cord injury.[1,2] The use of GABAs, primarily gabapentin, tripled from 1.2% in 2002 to 3.9% in 2015 among US adults.[3] Off-label use of gabapentin accounts for over 80% of gabapentin prescriptions.[4-8]

Substantial off-label use of GABAs for a variety of acute and chronic pain conditions has raised concerns discerning potential misuse, abuse, dependence, and overdose risk of GABAs, especially among individuals with concurrent opioid (OPI) use.[9-12] Four observational studies showed that the use of GABAs alone or with OPIs was associated with an increased risk of adverse outcomes (e.g., hospitalizations, OPI-related deaths).[13-16] Nevertheless, concurrent OPI and GABA (hereafter OPIs-GABAs) use is common in the US. According to the Medical Expenditure Panel Survey data, 52.6% of adults using GABAs reported OPI-GABA use in 2015.[3] In a study of US commercial insurers, a quarter of individuals using GABAs had long-term concurrent OPI use (≥120 days) in a one year period between 2013 and 2015.[7] There is a lack of evidence or consensus in clinical practice on the duration and dose patterns of OPI-GABA use that are most associated with an increased risk of adverse health outcomes.

Patterns of OPI-GABA use change over time and vary across patient sub-groups due to multiple reasons (e.g., pain conditions, insurance restrictions). However, previous studies have used arbitrary single-value cutoff points on dose and duration (e.g., having any 120 cumulative days of concurrent OPI and gabapentin use in a year), which limit the ability to identify heterogeneous utilization patterns over time. Identifying distinct refill patterns that incorporate both OPI and GABA dose and duration changes over time may provide important implications and guidance in clinical practice.

The objective of this study was to apply group-based multi-trajectory models to account for the dynamic nature of OPI-GABA use simultaneously and to examine their associations with subsequent risk of drug overdose, opioid use disorder (OUD), and non-opioid substance use disorders (SUDs) among Medicare beneficiaries receiving at least one OPI or GABA prescription. We chose Medicare because of the high prevalence of prescription OPI and GABA use and availability of national claims data, and because the Part D plans will soon be required for specific interventions targeting individuals at high risk for opioid-related morbidity.[3,17-19]

3.3. METHODS

3.3.1. Data Source

This study used a 5% nationally representative sample of Medicare beneficiaries from 2011 to 2016 (~3.8 million unique beneficiaries). Medicare is the US government health insurance program for individuals aged ≥65 years as well as for those aged <65 years with certain disabilities or end-stage renal diseases (ESRD). Medicare beneficiaries can be covered under the fee-for-service (FFS) or Medicare Advantage plans. The FFS program, also called traditional Medicare, includes the Part A (hospital), Part B (medical) insurance and Part D (prescription drug coverage). Medicare Advantage plans, also referred as Part C insurance, are the Medicare-approved private health plans, including health plans such as health maintenance organizations, preferred provider organizations, and Medicare medical savings account plans. Given that submission of medical claims data to the Centers for Medicare and Medicaid (CMS) for beneficiaries enrolled in the Medicare Advantage plans varies across plans and thus may not be complete, we limited to the FFS beneficiaries.

The data source included Medicare master beneficiary summary files, medical claims of inpatient, outpatient, carrier, skilled nursing facility, home health, hospice, and durable medical equipment, and part D drug event (PDE) files. We also linked the Medicare data to the Area Health Resource File (AHRF) through beneficiary's state and county code. AHRF is a publicly available dataset provided by the Health Resource and Services Administration (HRSA) and include the county-level information on health care providers (e.g., number of physicians), hospital and health facilities (e.g., number of

hospitals), and census-based demographic information (e.g., education and income levels, metropolitan/non-metropolitan county).

3.3.2. Study Design and Cohort

This retrospective cohort study included FFS beneficiaries who were US residents, having ≥1 inpatient or ≥2 other medical claims of fibromyalgia, low back pain, neuropathy (i.e., diabetic peripheral neuropathy, postherpetic neuralgia, and trigeminal neuralgia), or osteoarthritis using the International Classification of Diseases codes (see **eTable 3.1** for ICD-9-CM/ICD-10-CM codes). We focused on these chronic conditions for which OPIs and GABAs are commonly prescribed.[20,21]

The analytical sample was restricted to beneficiaries newly initiating OPIs or GABAs, who had no use of OPI or GABA prescription within 6 months prior to the index date (i.e., first prescription date of either OPIs or GABAs, whichever occurred first, see **eFigure 3.1** for study design diagram). We excluded beneficiaries who: (1) had ESRDs, seizures or epilepsy, and any type of cancer during the study period (except for non-melanoma skin cancer; **eTable 3.1**); (2) did not have continuous enrollment in Parts A, B, and D between 6 months prior to and 12 months post the index date; (3) had a diagnosis of any outcomes of interest, including drug overdose, OUD, and non-opioid SUDs, within 12 months following the index date (in order to establish the temporal associations between the identified trajectories and subsequent outcomes of interest); and (4) filled opioids for acute pain indications, which we defined as 1) filling only one OPI prescription, 2) filling two OPI prescriptions, but on the same day, or 3) filling <15

day opioid supply during the index year.[22] The University of Arizona Institutional Review Board approved the study.

3.3.3. Exposures: Dual-Trajectories of Opioid and Gabapentinoid (OPI-GABA) use

Our exposure of interest was membership in a distinct dual-trajectories of OPI-GABA use by (1) constructing weekly measures of standardized daily dose (SDD) for OPIs and GABAs, respectively, and (2) identifying distinct dose and duration patterns of OPI-GABA use by applying group-based multi-trajectory models with SDD as the outcomes in the model.

First, based on dispensing date and days supplied for each OPI and GABA prescription, we calculated SDD for OPIs using morphine milligram equivalent (MME),[23] and for GABAs using minimum effective daily dose (i.e., 300 mg for gabapentin and 150 mg for pregabalin).[1] We calculated MME for each OPI prescription by multiplying the quantity dispensed by strength in milligrams, dividing days of supply, and then multiplying a conversion factor provided by the Centers for Disease Control and Prevention (CDC).[24] Low-, moderate-, and high-dose opioid use was defined as an average daily dosage of MME <50, 50-90, and >90, respectively.[25] For GABA use, SDD <2, 2-3, and >3 were considered as low-, moderate-, and high-dose use. We created a daily diary of OPI and GABA use for each patient by summing up the total daily SDD for OPIs and GABAs, respectively. For example, the total SDD for GABAs for a day is two if a person had a 300 mg gabapentin prescription overlapped with a 150 mg pregabalin prescription on the same day.

Second, group-based multi-trajectory models were used to identify differential utilization patterns of OPI-GABA use simultaneously over time and to characterize subgroups more likely to follow similar trajectories.[26-30] In order to identify dose most associated with adverse outcomes, we modeled the average daily MME for OPIs and SDD for GABAs as a longitudinal, continuous outcome for each week of the year after initiating OPIs or GABAs, and the time variable as weeks since index date (week 1-52). In each model, we used the most flexible functional form (up to fifth order polynomial function of time) to allow the trajectories to emerge from the data. Outputs of group-based multi-trajectory models include estimated probabilities of group membership for each individual, estimated trajectory curves over time, and proportion of each group trajectory. We selected the final model based on a combination of (1) the Bayesian information criterion (BIC); wherein the largest value indicates the best-fitting model, and (2) application of Nagin's criteria to assess final model adequacy.[28,29,31] Nagin's criteria for a well-performed trajectory model include an average posterior probabilities ≥0.7 for all group, odds of correct classification ≥5.0 for all groups, and narrow confidence intervals for estimated group membership probabilities.[31]

3.3.4. Outcomes: Drug Overdose, Opioid Use Disorder (OUD), and Non-Opioid Substance Use Disorders (SUDs)

The primary outcome was time to the first diagnosis of fatal or non-fatal drug overdose in the 12 months after the first year of OPI or GABA initiation. We identified any occurrence of fatal or non-fatal drug overdose (e.g., prescription opioids, heroin, and other drugs) using the ICD-9-CM/ICD-10-CM codes (**eTable 3.1**). We also

examined two separate secondary outcomes including time to the first diagnosis of OUD and non-opioid SUDs in the 12 months following the first year of OPI or GABA initiation.

3.3.5. Covariates

On the basis of previous studies that examined OPI and GABA utilizations and associated adverse consequences,[14,32-37] our covariates were measured in the six months prior to index date, including individual socio-demographic and health status factors and regional-level factors. We focused on factors measured on or before the initiation of OPIs and GABAs to assess the prediction accuracy of the variables and to avoid including predictor changes in patient health status that may themselves be consequences of use (or non-use) of OPIs and GABAs. Socio-demographic factors included age, sex, race/ethnicity (White, African American, Hispanic, and others), disability status, and receipt of low-income subsidy (LIS) and dual Medicaid eligibility (with LIS and dual eligibility, with LIS or dual eligibility, and no LIS or dual eligibility). Health status factors included patient comorbidity defined by the Elixhauser comorbidity index (excluding metastatic cancers and solid tumors with or without metastasis; range 0 to 27), serious mental health disorders, and anxiety disorders identified by ICD-9-CM/ICD-10-CM codes (**eTable 3.1**), numbers of outpatient visits, numbers of inpatient or emergency department (ED) visits, numbers of prescription fills for benzodiazepines and Z-hypnotics, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, muscle relaxants, and other prescriptions not mentioned above.

We also linked to the Area Health Resources Files (AHRF) to measure county-level factors, including the standardized numbers of hospitals, non-federally employed physicians, hospitals with pain management programs, and physical medicine/rehabilitation centers per 10,000 population as a proxy for access to health care or certain specialties, population profile (metropolitan and non-metropolitan), annual median household income, and annual unemployment rate.

3.3.6. Statistical Analysis

Characteristics of individuals in each OPI-GABA trajectory groups were described with mean and standard deviation (SD) for continuous variables, and frequency and percentage for categorical variables. Given that the identified trajectory groups were likely to be different due to different patient characteristics and disease complexities, we used multinomial logistic regression to estimate the inverse probability of treatment weighting (IPTW), defined as inverse probability of belonging to one trajectory group where an individual was actually placed. Weighting subjects with IPTW would create a synthetic sample in which treatment assignment is independent of measured covariates.[38] We weighted subjects with IPTW in the analyses to minimize confounding across trajectories. We compared the characteristics across trajectory groups before and after weighting subjects with IPTW using the standardized mean difference (SMD), wherein SMD>0.1 was considered as having non-negligible differences.[37] The IPTW-weighted multivariable Cox proportional hazards models were used to compare time-to-event (i.e., drug overdose, OUD, and non-opioid SUDs) within the 12 months following the first year of OPI or GABA initiations across different OPI-

GABA trajectories, adjusting for the covariates with non-negligible differences after IPTW weighting. These models treated beneficiaries switching to Medicare Advantage plans or without any outcomes of interest in the 12 months after the first year of OPI or GABA initiation as censored observations, and deaths in the 12 months after the first year of OPI or GABA initiation as competing events.[39] We assessed the proportional hazard (P-H) assumption including time dependent covariates.[40] If P-H assumption was violated, a stratified Cox model with different baseline hazards in each stratum would be used.[41] The cause-specific hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

3.3.7. Sensitivity Analysis

Finally, we conducted a sensitivity analysis to assess the potential influences of uncontrolled or unmeasured confounding on the study results. We calculated the "E-value", defined as the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates.[41] A large E-value implies that considerable unmeasured confounding would be needed to explain away an effect estimate; whereas, a small E-value implies little unmeasured confounding would be needed to do so.[42]

The group-based multi-trajectory models were estimated using STATA 15.0 (Stata-Corp LP, College Station, TX) and the TRAJ macro (free download at http://www.andrew.cmu.edu/user/bjones). All other statistical analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA).

3.4. RESULTS

3.4.1. Dual-Trajectories of Opioid and Gabapentinoid (OPI-GABA) Use

Among 71,005 eligible beneficiaries initiating OPI or GABA prescriptions, the overall mean MME and SDD in the 12 months after initiating OPIs or GABAs were 16.8 (SD=33.9) for OPIs and 1.3 (SD=2.0) for GABAs, respectively (**eFigure 3.3**). According to a combination of BIC value (largest BIC=-1,176,954) and Nagin's criteria, a model with ten distinct dual-trajectories for OPI-GABA use performed optimally and was selected as the final model (**eTable 3.2**).

Figure 3.1 illustrates the predicted weekly utilization patterns for OPI and GABA use in the 12 months after initiating OPIs or GABAs. Three of the ten trajectories comprised OPIs only (59.0% of the cohort); however, there were distinct groups with respect to dose and duration. Specifically, 40.6% of the cohort (n=28,842) were OPI-only early discontinuers (Group A); 16.6% were consistent low-dose OPI-only users (Group B; MME ≤30); and 1.8% were consistent high-dose OPI-only users (Group C; MME >120). Similarly, three of the ten trajectories comprised GABAs only (26.6% of the cohort): 12.5% were GABA-only early discontinuers (Group D); 11.0% were consistent low-dose GABA-only users (Group E; SDD <2); and 3.1% were consistent high-dose GABA-only users (Group F; SDD ≥3.5). The remaining four trajectories comprised OPIs-GABAs, but with distinct dose and duration profiles: 6.9% had early discontinuation of OPIs and consistent low-dose GABA use (Group G; SDD ≤1); 3.4% were consistent low-dose OPI-GABA users (Group H; MME <40 and SDD <1.5); 3.2% were consistent low-dose OPI and high-dose GABA users (Group I; MME <30 and SDD

≥3); and 0.9% were consistent high-dose OPI and moderate-dose GABA users (Group J; MME >120 and 1.5< SDD ≤3).

3.4.2. Characteristics Overall and by Trajectory Group

Table 3.1 shows a descriptive comparison of characteristics by OPI-GABA trajectory. Among all eligible beneficiaries, the majority had low back pain (78.5%) or osteoarthritis (70.9%); approximately 20% had fibromyalgia or neuropathy. The mean age was 65.5 (SD=14.5) years, 68.1% were female, and 76.8% were white. Nearly 40% had a disability, and 44.1% had both LIS and dual Medicaid eligibility. The average Elixhauser comorbidity index was 2.7 (SD=2.3) and 72.4% resided in metropolitan counties.

The ten identified trajectory groups had significantly different characteristics before including IPTW (**Table 3.1**). For example, consistent high-dose OPI and moderate-dose GABA users were more likely to have low back pain (94.3% vs 78.5%) and fibromyalgia (38.0% vs 20.2%), to be younger (52.3 ± 12.3 years vs 65.5 ± 14.5 years), male (45.9% vs 31.9%), and to be white (85.8% vs 76.8%), and to be on disability (81.9% vs 39.3%), compared to the overall study cohort. Consistent high-dose OPI and moderate-dose GABA users also had fewer prescriptions for antidepressants (0.4 ± 0.8 vs 1.1 ± 3.4) and other medications (3.7 ± 5.9 vs 16.0 ± 15.1). After taking into account of the IPTW for each beneficiary, most characteristics were comparable across trajectories, except for age, Elixhauser comorbidity index, and number of prescriptions for NSAIDs, antidepressants, and all other medications (SMD >0.1). The minimum and maximum SMD across the 45 group comparisons were presented at **eTable 3.3**.

3.4.3. Inverse Probability Treatment Weighted Multivariable Cox Proportional Hazards Model for Drug Overdose, Opioid Use Disorder, Non-Opioid Substance Use Disorders

As shown in **Figure 3.2** (also **eTable 3.4**), compared with OPI-only early discontinuers (crude rate: 0.8 per 100 person-years), all other trajectories were associated with an increased risk of drug overdose (1.39 to 7.22 times), except early discontinuation of OPI and consistent low-dose GABA users (adjusted HR [aHR]=1.24, 95% CI=0.90-1.69) and consistent high-dose GABA-only users (aHR=1.43, 95% CI=0.94-2.17). Specifically, greater than double the risk of drug overdose in the 12 months after the year of initiating OPIs or GABAs was observed among individuals in the following trajectories: consistent high-dose OPI-only users (aHR=4.57, 95% CI=2.99-6.98), consistent low-dose OPI-GABA users (aHR=2.49, 95% CI=1.71-3.52), consistent low-dose OPI and high-dose GABA users (aHR=2.46, 95% CI=1.71-3.53), and consistent high-dose OPI and moderate-dose GABA users (aHR=7.22, 95% CI=4.46-11.69). Similar findings were observed for the risk of OUD and non-opioid SUDs (**Figures 3.3-3.4**, **eTable 3.4**). Compared with OPI-only early discontinuers, consistent high-dose OPI only users (OUD: aHR=8.11, 95% CI=5.85-11.24; non-opioid SUDs: aHR=2.14, 95% CI=1.61-2.86) and consistent high-dose OPI and moderate-dose GABA users (OUD: aHR=10.89, 95% CI=7.43-15.96; non-opioid SUDs: aHR=2.42, 95% CI=1.66-3.53) were associated with the highest risk of OUD and non-opioid SUDs.

In the sensitivity analysis, E-values indicated that the estimated HRs for consistent high-dose OPI-only users and all consistent OPI-GABA users were more robust to the unmeasured confounding (**eTable 3.5**). For example, the observed drug overdose risk (aHR=7.22) for high-dose OPI and moderate-dose GABA users could be explained by an unmeasured confounder that was associated with both this trajectory group and drug overdose by a HR of 13.92-fold each, beyond the current measured confounders, but weaker confounding could not do so.

3.5. DISCUSSION

Our study yielded three important findings with regard to initiates of OPIs or GABAs among fee-for-service Medicare beneficiaries with fibromyalgia, low back pain, neuropathy, or osteoarthritis. First, we identified ten distinct dual-trajectories of OPI-GABA use in the 12 months after initiating OPIs and GABAs. This high variability likely arises from a combination of patient factors (e.g., pain diagnosis/-es; pain chronicity and severity; medication preferences), prescriber factors (e.g., prescribing preferences; actual or perceived level of patient risk), and payer factors (e.g., formulary tiers; co-pays). Second, the vast majority of beneficiaries received monotherapy, with nearly 60% of the beneficiaries using OPIs only, 26.6% using GABAs only, and only 14.4% using OPI and GABA, with distinct dose and duration patterns. Third, trajectories characterized by consistent high-dose OPI-only use (MME >120) and consistent OPI-GABA use (regardless of doses) were associated with more than double the risk of drug overdose compared to OPI-only early discontinuers.

We identified only four studies that examined OPI-GABA use and associated adverse outcomes.[13-16] However, the operational definitions of concurrent use varied substantially among these studies, including (1) any overlapping OPI-GABA use in the 120 days preceding the outcomes (e.g., opioid-related death),[14,15] (2) any pregabalin use during opioid maintenance treatment,[13], and (3) concurrent use ≥120 days in 12 months.[16] Thus, comparisons between studies are problematic and conclusions based on “concurrent use” may lead to overly broad or inappropriate interventions. In reality, treatment needs and sequelae, including OPI-GABA dose(s) and duration(s), vary

according to patient-specific factors. Consequently, it is appropriate to co-prescribe for certain patients, sometimes notwithstanding known risk.

Using single values (e.g., any overlapping day of concurrent use) over a fixed time period provides a gross measure of use patterns that could mask heterogeneity in concurrent use and risk. Applying arbitrary thresholds of OPI-GABA dose or duration to all patients without better understanding or validation imposes challenges in clinical care and policies around OPI-GABA use. Alternatively, group-based multi-trajectory models may be valuable to better characterize concurrent use. The strengths of the models include (1) the ability to account for dynamic medication use and identify subgroups with similar changes over time; (2) the ability to simultaneously examine dose and duration thresholds and other patterns most relevant to outcomes; and (3) the development of intuitive graphical results of trajectories.[43,44]

Our findings are generally consistent with previous studies that suggested an association between concurrent OPI-GABA use and increased risk of adverse health outcomes.[13-16] These risks may derive from pharmacokinetic factors (e.g.., increased gabapentin absorption with concurrent administration of morphine[45]; renal dysfunction), pharmacodynamic factors (i.e., additive respiratory depressant effects[46]), or both. In addition to examining dynamic dose and duration utilization over time, our study also examined the heterogeneity of dosing (rather than focusing only on identifying doses exceeding the FDA's recommended maximum dose), and characterized both short- and long-term OPI-GABA use.

Recently, several clinical trials suggested efficacy of GABA for off-label pain conditions (e.g., chronic sciatica; irritable bowel syndrome) and for reducing acute and chronic postoperative pain and OPI use.[47-52] However, given the safety concerns about GABAs, there have been calls for placing more stringent regulations on gabapentin at the federal level and to include gabapentin monitoring in state prescription drug monitoring programs (PDMPs) to promote safety; our study findings supported these actions. At the state level, several states, including Kentucky, Minnesota, Ohio, and Virginia, have required mandatory reporting for gabapentin dispensing in PDMPs.[53] Kentucky further classified gabapentin as a Schedule V Controlled Substance and restricted prescribing amount of gabapentin.[53] Other targeted interventions suggested for clinical practice include promoting health provider education and awareness of potential risk for OPI-GABA use, auto-alert electronic health systems, and risk-stratification and risk-informed monitoring of individuals with OPI-GABA use. Our trajectory subgroups (e.g., consistent high-dose OPI and moderate-dose GABA use) may be valuable to better guide target interventions.

This study has several limitations. First, we did not include prevalent GABA and/or OPI users. We used the “new drug user” design to avoid the potential prevalent user bias (i.e., the risk of outcomes and covariate characteristics change with the duration of drug use). Second, our claims-based analyses have limited clinical and socio-behavioral information, such as pain severity and pain relief from using the drug. We also could not capture or measure whether beneficiaries obtained OPIs or GABAs from streets, friends, or other sources not in our claims data analysis. Although unmeasured confounding could not be ruled out, our sensitivity analyses showed that

the results are robust to potential unmeasured confounders based on the E-values of HR estimates. Third, our diagnosis-based outcomes are likely to be underestimated due to under-coding issues because of reasons such as stigma in clinical practice. Prior studies showed high specificity but low sensitivity in SUD-related outcomes (e.g., OPI overdose).[54,55] Finally, the study results have limited generalizability to other payers (e.g., Medicaid) and Medicare beneficiaries using OPIs or GABAs for other conditions than the included four chronic diseases in current study.

3.6. CONCLUSION

Risk of drug overdose, OUD, and non-opioid SUDs varied substantially by different OPI-GABA trajectory groups among the fee-for-service Medicare beneficiaries. High-dose OPI use and all consistent OPI-GABA use, especially high-dose OPI and moderate-dose GABA use, were associated with the highest risk of adverse health outcomes. Clinicians should consider relative risks and benefits before prescribing OPIs-GABAs. When the co-administration is medically necessary, patients should be monitored closely and dynamic benefit-risk profiles should be reviewed on a regular basis.

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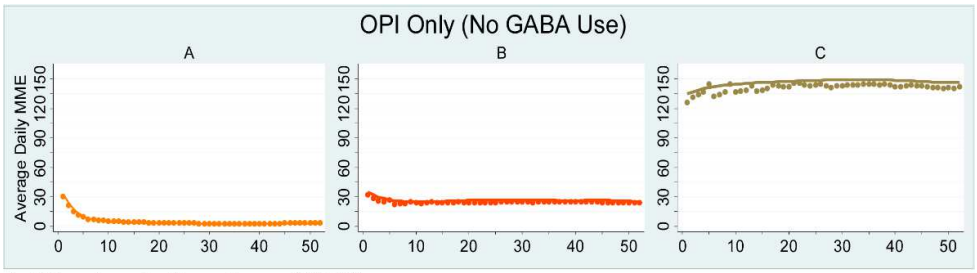
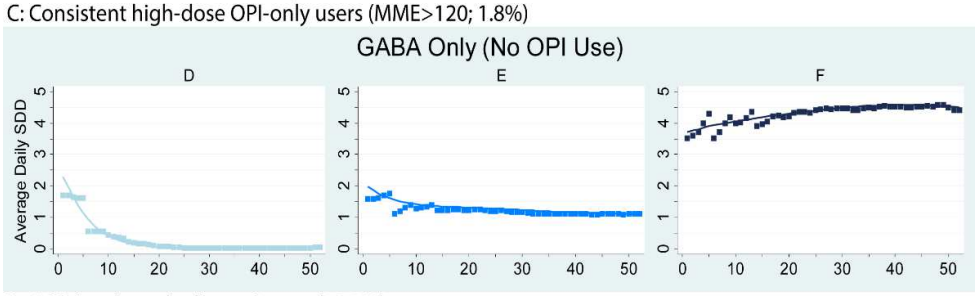
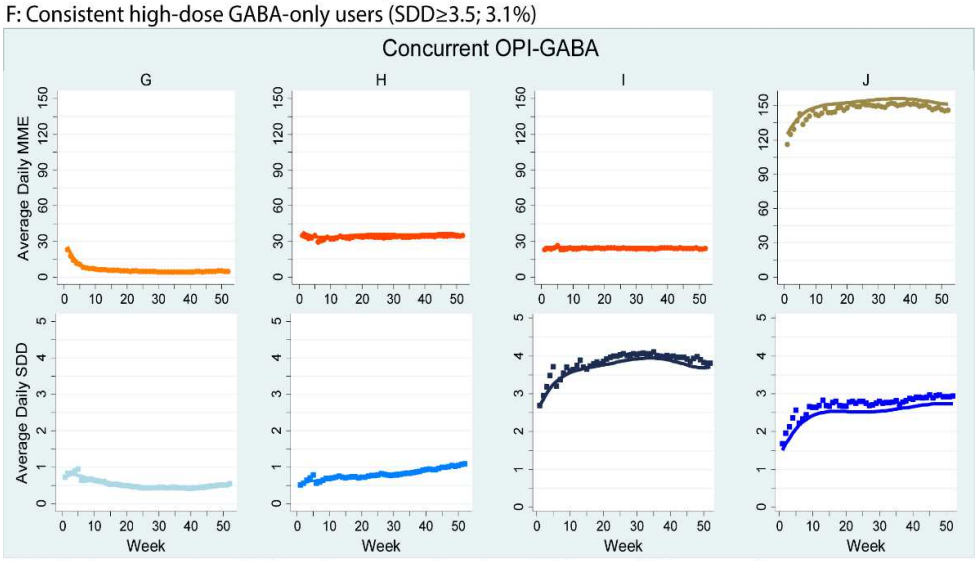
3.8. FIGURES



A: OPI-only early discontinuers (40.6%)
B: Consistent low-dose OPI-only users (MME≤30; 16.6%)
C: Consistent high-dose OPI-only users (MME>120; 1.8%)



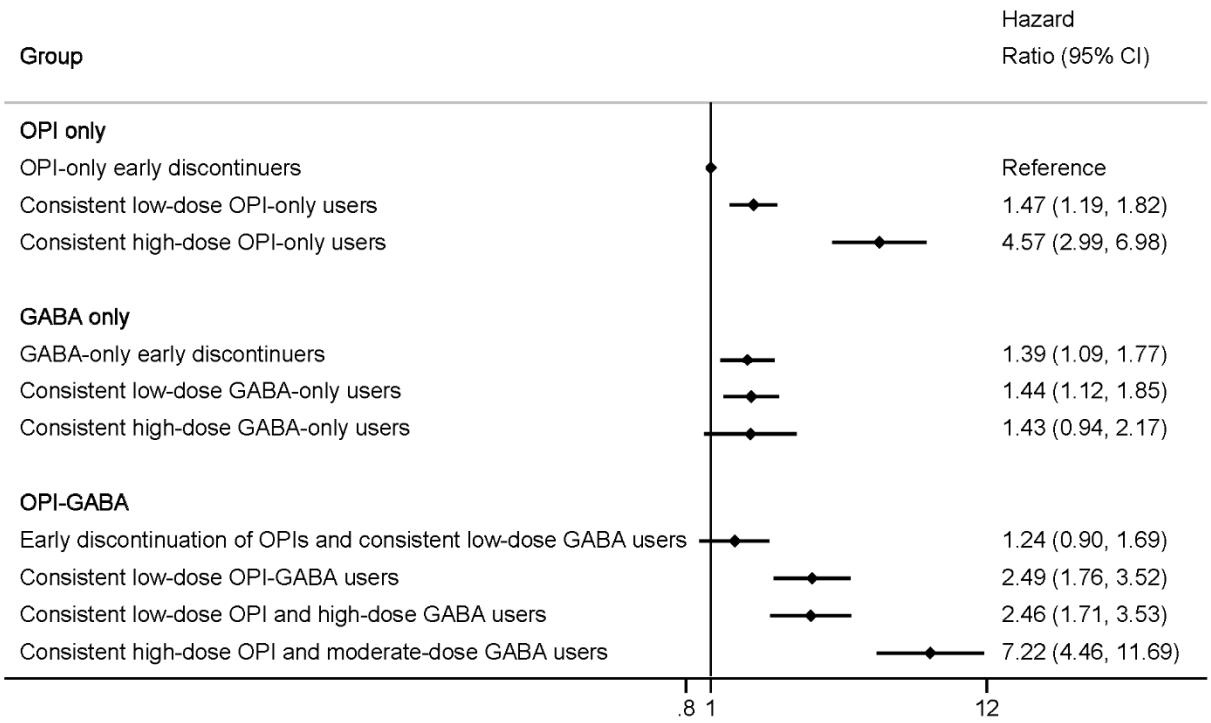
D: GABA-only early discontinuers (12.5%)
E: Consistent low-dose GABA-only users (SDD<2; 11.0%)
F: Consistent high-dose GABA-only users (SDD≥3.5; 3.1%)



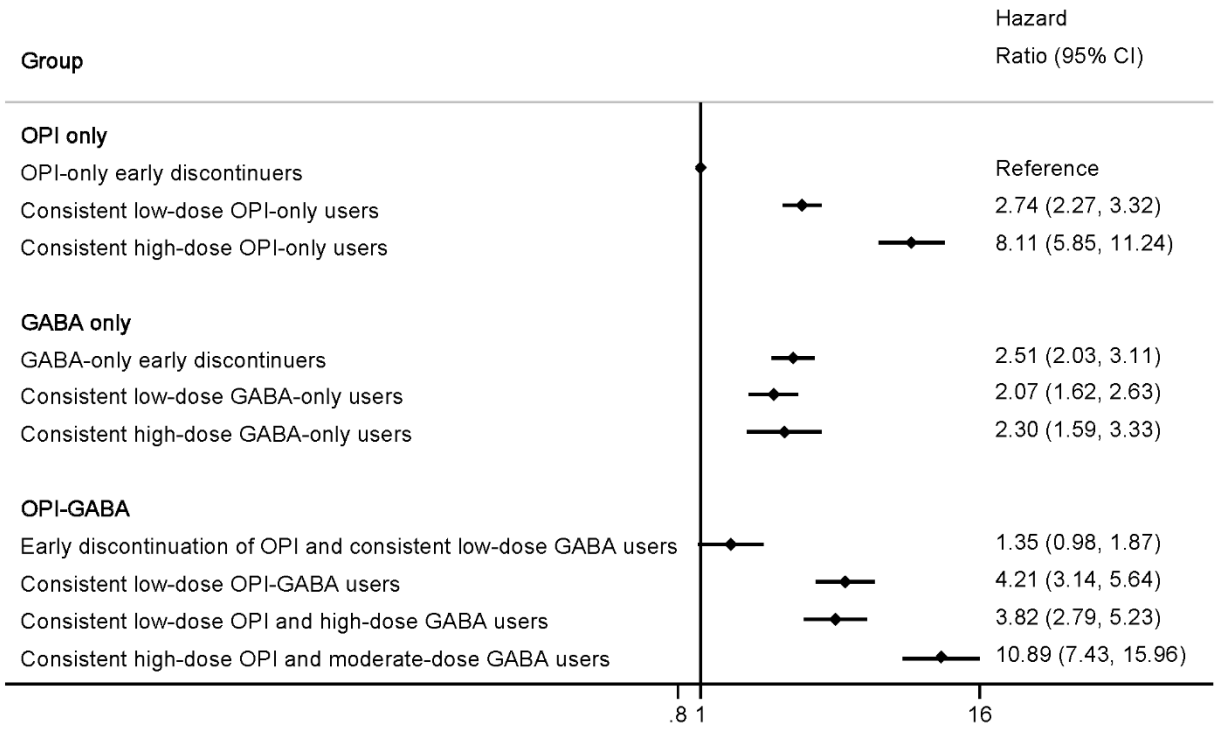
G: Early discontinuation of OPIs and consistent low-dose GABA users (SDD≤1; 6.9%)
H: Consistent low-dose OPI-GABA users (MME<40 and SDD<1.5; 3.4%)
I: Consistent low-dose OPI and high-dose GABA users (MME<30 and SDD≥3; 3.2%)
J: Consistent high-dose OPI and moderate-dose GABA users (MME>120 and 1.5<SDD≤3; 0.9%)

3.1. Dual-Trajectories of Opioid and Gabapentinoid Utilization Patterns among Medicare Beneficiaries

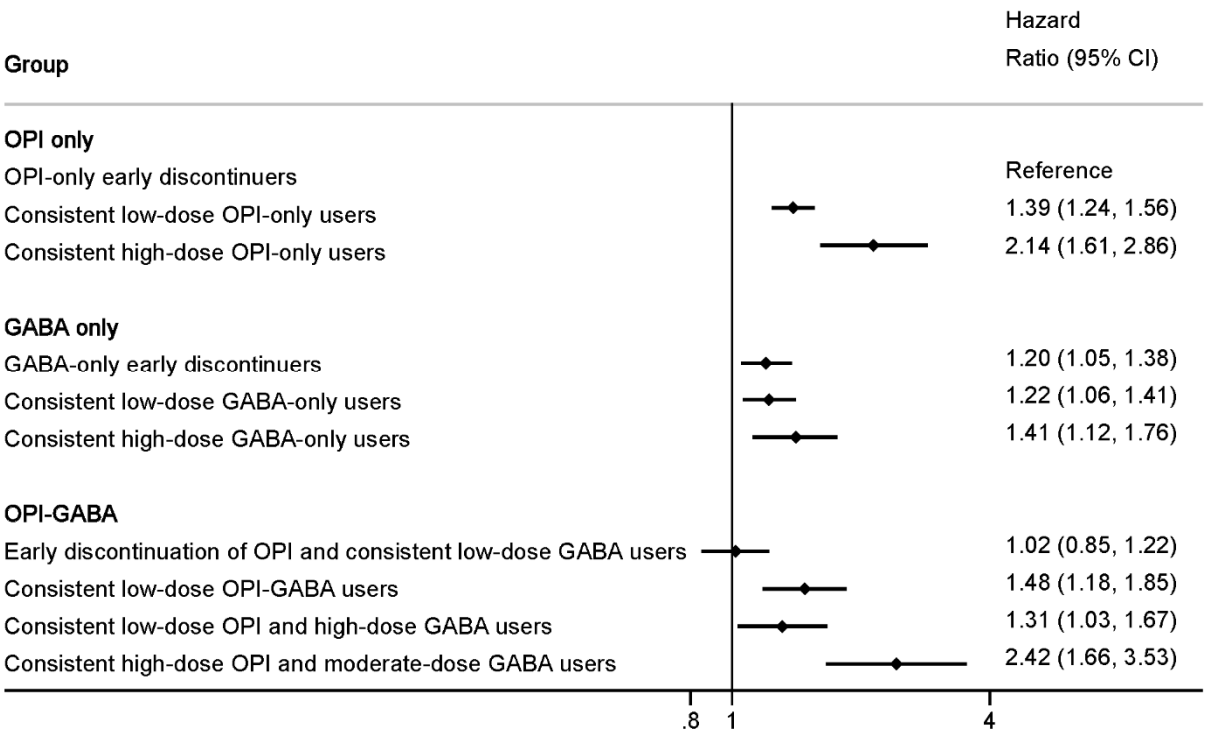
Abbreviations: **GABA**, gabapentinoid; **MME**, morphine milligram equivalent; **OPI**, opioid; **SDD**, standardized daily dose



3.2. Dual-Trajectories of Opioid and Gabapentinoid Use and Risk of Drug Overdose among Medicare Beneficiaries



3.3. Dual-Trajectories of Opioid and Gabapentinoid Use and Risk of Opioid Use Disorder among Medicare Beneficiaries



3.4. Dual-Trajectories of Opioid and Gabapentinoid Use and Risk of Non-Opioid Substance Use Disorders among Medicare Beneficiaries

3.9. TABLE

3.1. Characteristics of Medicare Beneficiaries Initiating Opioids or Gabapentinoids and by Trajectory Group

Characteristics	Overall	OPI Only			GABA only			OPI-GABA				SMD[b] before IPTW	SMD[b] after IPTW
		A[a]	B[a]	C[a]	D[a]	E[a]	F[a]	G[a]	H[a]	I[a]	J[a]		
No. beneficiaries	71,005	28,842	11,793	1,284	8,854	7,802	2,179	4,786	2,408	2,303	664		
% of the overall cohort	100	40.6	16.6	1.8	12.5	11.0	3.1	6.9	3.4	3.2	0.9		
Disease status, %													
Any low back pain	78.5	73.6	79.5	91.7	81.2	79.5	82.2	82.0	90.2	85.8	94.3	0.22	0.08
Any osteoarthritis	70.9	73.4	73.0	55.3	68.7	70.4	62.1	69.8	67.8	65.5	61.0	0.15	0.07
Any fibromyalgia	20.2	14.4	18.7	31.1	24.5	25.1	28.7	22.7	32.1	31.0	38.0	0.20	0.04
Any neuropathy	19.7	13.9	13.1	10.3	24.2	34.5	32.6	27.3	22.8	31.9	21.2	0.26	0.06
Socio-demographics													
Age, mean (SD)	65.5 (14.5)	68.3 (13.8)	64.0 (14.6)	54.1 (3.2)	65.6 (14.8)	65.6 (13.9)	59.8 (13.7)	66.0 (13.8)	59.1 (14.5)	58.9 (13.4)	52.3 (12.3)	0.48	0.19
Female, %	68.1	69.9	64.7	52.0	69.9	70.3	61.6	71.0	64.8	65.4	54.1	0.16	0.07
Race/ethnicity, %												0.20	0.09
White	76.8	76.4	80.2	87.7	72.4	73.8	82.9	73.1	78.5	82.5	85.8		
African American	13.5	13.5	13.5	8.6	14.4	14.1	10.1	14.4	15.4	106	8.3		
Hispanic	3.8	4.0	2.5	1.4	5.3	5.1	2.4	5.0	2.2	2.1	2.3		
Others	5.9	6.1	3.8	2.3	8.0	6.9	4.5	7.6	4.0	4.9	3.6		
Disability status, %	39.3	28.9	43.8	75.3	42.5	44.3	58.0	34.0	57.6	56.9	81.9	0.44	0.08
LIS/dual eligibility, %												0.14	0.06
LIS and dual eligibility	44.1	38.9	44.4	41.8	50.0	53.9	50.3	41.9	47.9	45.8	45.0		
LIS or dual eligibility	6.6	5.9	6.7	8.1	7.5	7.4	8.2	7.5	7.1	7.1	8.1		
No LIS/dual eligibility	49.3	55.1	49.0	50.1	42.4	38.7	41.5	44.7	44.7	47.1	46.8		
Health services use and health status factors													
Elixhauser index, mean (SD)	2.7 (2.3)	2.7 (2.2)	2.5 (2.4)	1.4 (1.9)	2.9 (2.3)	2.9 (2.5)	2.9 (2.5)	2.7 (2.3)	2.3 (2.3)	2.4 (2.5)	1.7 (2.2)	0.31	0.16
Mental disorders, %	4.5	3.9	4.5	2.8	5.3	5.6	8.1	3.4	3.2	3.3	4.2	0.08	0.03
Anxiety, %	12.6	10.4	12.5	13.5	15.7	16.3	18.8	10.9	15.0	11.9	14.6	0.09	0.03
No. outpatient visits, mean (SD)	2.5 (3.5)	2.5 (3.3)	2.1 (3.2)	1.4 (3.0)	2.9 (3.9)	3.1 (4.0)	3.0 (4.0)	2.3 (3.0)	2.1 (3.3)	2.0 (3.3)	1.5 (2.9)	0.22	0.10
No. inpatient/ED visits, mean (SD)	0.6 (1.1)	0.6 (1.0)	0.5 (1.0)	0.3 (1.0)	0.6 (1.4)	0.6 (1.2)	0.6 (1.2)	0.5 (1.0)	0.5 (1.0)	0.5 (1.1)	0.4 (0.9)	0.14	0.06
No. benzodiazepines or Z-hypnotics, mean (SD)	0.5 (3.7)	0.4 (3.4)	0.4 (3.4)	0.1 (1.2)	0.7 (1.3)	0.8 (4.9)	0.8 (4.9)	0.5 (3.4)	0.1 (2.4)	0.2 (1.8)	0.1 (0.6)	0.11	0.07

3.1. (Continued)

Characteristics	Overall	OPI Only			GABA only			OPI-GABA				SMD[b] before IPTW	SMD[b] after IPTW
		A[a]	B[a]	C[a]	D[a]	E[a]	F[a]	G[a]	H[a]	I[a]	J[a]		
No. NSAIDs, mean (SD)	0.6 (1.4)	0.6 (1.4)	0.5 (1.3)	0.1 (0.5)	0.7 (1.5)	0.9 (1.7)	0.8 (1.7)	0.6 (1.3)	0.3 (0.9)	0.3 (0.9)	0.1 (0.4)	0.31	0.18
No. of antidepressants, mean (SD)	1.1 (2.5)	1.1 (3.4)	0.9 (2.3)	0.3 (0.9)	1.4 (2.7)	1.9 (3.3)	2.0 (3.3)	1.0 (2.2)	0.7 (1.9)	0.6 (1.6)	0.4 (0.8)	0.32	0.13
No. muscle relaxants, mean (SD)	0.3 (1.0)	0.2 (0.7)	0.2 (0.7)	0.2 (0.5)	0.5 (1.4)	0.8 (1.9)	0.8 (1.9)	0.2 (0.6)	0.2 (0.6)	0.2 (0.6)	0.2 (0.4)	0.19	0.06
No. other prescription fills, mean (SD)	16.0 (16.7)	16.0 (15.1)	11.4 (15.4)	3.9 (6.5)	21.1 (17.2)	24.4 (20.5)	21.6 (21.2)	14.5 (15.4)	7.6 (12.2)	6.7 (9.3)	3.7 (5.9)	0.72	0.40
County-level factors													
No. hospitals[c], mean (SD)	2.6 (3.4)	2.6 (3.4)	2.7 (3.3)	2.5 (3.3)	2.6 (3.2)	2.6 (3.7)	2.7 (3.2)	2.5 (3.3)	2.6 (3.0)	2.7 (3.0)	2.6 (3.4)	0.03	0.03
No. of physicians[c], mean (SD)	70.3 (30.9)	70.8 (31.0)	69.1 (30.2)	72.4 (28.9)	70.8 (31.5)	70.2 (31.5)	69.8 (30.6)	71.0 (30.9)	69.3 (30.2)	69.1 (29.8)	70.9 (30.6)	0.04	0.01
No. of hospitals with pain program[c], mean (SD)	0.8 (1.4)	0.8 (1.5)	0.9 (1.4)	0.8 (1.4)	0.8 (1.4)	0.8 (1.4)	0.9 (1.4)	0.8 (1.3)	0.9 (1.5)	0.9 (1.3)	0.8 (1.1)	0.04	0.04
No. of physical medicine/rehabilitation centers[c], mean (SD)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4 (0.7)	0.4 (0.6)	0.4 (0.6)	0.4 (0.7)	0.4 (0.6)	0.4 (0.7)	0.4 (0.6)	0.4 (0.6)	0.03	0.03
Resided in metropolitan counties, %	72.4	72.8	71.4	75.9	73.2	72.0	67.0	74.6	72.2	70.0	78.0	0.08	0.01
Median household income[d], mean (SD)	51 (14)	51 (14)	50 (13)	53 (14)	52 (14)	51 (14)	50 (14)	52 (14)	50 (13)	50 (13)	52 (13)	0.10	0.01
% unemployment, mean (SD)	5.7 (1.7)	5.7 (1.7)	5.7 (1.7)	5.6 (1.6)	5.7 (1.8)	5.7 (1.8)	5.7 (1.7)	5.7 (1.9)	5.7 (1.7)	5.7 (1.6)	5.6 (1.5)	0.04	0.03

Abbreviations: **ED**, emergency department; **GABA**, gabapentinoid; **IPTW**, inverse probability of treatment weighting; **LIS**, low-income subsidy; **MME**, morphine milligram equivalent; **No**, number; **NSAID**, nonsteroidal anti-inflammatory drug; **OPI**, opioid; **SD**, standard deviation; **SDD**, standardized daily dose **SMD**; standardized mean difference;

[a.] Trajectory groups: **A:** OPI-only early discontinuers (40.6% of the cohort); **B**: Consistent low-dose OPI-only users (MME ≤30; 16.6%); **C**: Consistent high-dose OPI-only users (MME>120; 1.8%); **D**: GABA-only early discontinuers (12.5%); **E**: Consistent low-dose GABA-only users (SDD <2; 11.0%); **F**: Consistent high-dose GABA-only users (SDD ≥3.5; 3.1%); **G**: Early discontinuation of OPIs and consistent low-dose GABA users (SDD ≤1; 6.9%); **H**: Consistent low-dose OPI-GABA users (MME <40 and SDD <1.5; 3.4%); **I**: Consistent low-dose OPI and high-dose GABA users (MME <30 and SDD ≥3; 3.2%); **J**: Consistent high-dose OPI and moderate-dose GABA users (MME >120 and 1.5< SDD ≤3; 0.9%)

[b.] Average SMD of 45 SMDs from group comparisons (e.g., group A vs B, group A vs C, and group A vs D). The maximum and minimum SMD were presented in eTable 3.3

[c] Per 10,000 population

[d] Annual median household income was represented in units of thousands ($)

3.10. SUPPLEMENTAL DATA

eTable 3.1. ICD-9-CM and ICD-10-CM Codes of Diseases and Conditions Used in the Study

Diseases (ordered alphabetically)	ICD-9-CM	ICD-10-CM
Anxiety	293.84, 300.0X, 300.10, 300.2X, 300.3X, 300.89, 300.9X, 308.X, 309.81, 313.0, 313.1, 313.21, 313.22, 313.3X, 313.82, 313.83	F06.4, F40.x, F41.x, F42.x, F43.0, F43.1x, F44.9, F45.8, F48.8, F48.9, F93.8, F99, R45.7
Any cancer except for non-melanoma skin cancer	140.x, 141.x, 142.x, 143.x, 144.x, 145.x, 146.x, 147.x, 148.x, 149.x, 150.x, 151.x, 152.x, 153.x, 154.x, 155.x, 156.x, 157.x, 158.x, 159.x, 160.x, 161.x, 162.x, 163.x, 164.x, 165.x, 170.x, 171.x, 172.x, 174.x, 175.x, 176.x, 179.x, 180.x, 181.x, 182.x, 183.x, 184.x, 185.x, 186.x, 187.x, 188.x, 189.x, 190.x, 191.x, 192.x, 193.x, 194.x, 195.x, 196.x, 197.x, 198.x, 199.x, 200.x, 201.x, 202.x, 203.x, 204.x, 205.x, 206.x, 207.x, 208.x, 209.x, 210.x, 211.x, 212.x, 213.x, 214.x, 215.x, 216.x, 217.x, 218.x, 219.x, 220.x, 221.x, 222.x, 223.x, 224.x, 225.x, 226.x, 227.x, 228.x, 229.x, 230.x, 231.x, 232.x, 233.x, 234.x, 235.x, 236.x, 237.x, 238.x, 239.x	C00.x, C01.x, C02.x, C03.x, C04.x, C05.x, C06.x, C07.x, C08.x, C09.x, C10.x, C11.x, C12.x, C13.x, C14.x, C15.x, C16.x, C17.x, C18.x, C19.x, C20.x, C21.x, C22.x, C23.x, C24.x, C25.x, C26.x, C30.x, C31.x, C32.x, C33.x, C34.x, C37.x, C38.x, C39.x, C40.x, C41.x, C43.x, C4A.x, C45.x, C46.x, C47.x, C48.x, C49.x, C50.x, C51.x, C52.x, C53.x, C54.x, C55.x, C56.x, C57.x, C58.x, C60.x, C61.x, C62.x, C63.x, C64.x, C65.x, C66.x, C67.x, C68.x, C69.x, C70.x, C71.x, C72.x, C73.x, C74.x, C75.x, C76.x, C77.x, C78.x, C79.x, C80.x, C7A.x, C7B.x, C81.x, C82.x, C83.x, C84.x, C85.x, C86.x, C88.x, C90.x, C91.x, C92.x, C93.x, C94.x, C95.x, C96.x, D00.x, D01.x, D02.x, D03.x, D04.x, D05.x, D06.x, D07.x, D09.x, D10.x, D11.x, D12.x, D13.x, D14.x, D15.x, D16.x, D17.x, D18.x, D19.x, D20.x, D21.x, D22.x, D23.x, D24.x, D25.x, D26.x, D27.x, D28.x, D29.x, D30.x, D31.x, D32.x, D33.x, D34.x, D35.x, D36.x, D37.x, D38.x, D39.x, D40.x, D41.x, D42.x, D43.x, D44.x, D45.x, D46.x, D47.x, D48.x, D3A.x, D49.x
Diabetic neuropathy	250.60, 250.61, 250.62, 250.63, 357.2	E11.40, E40.40, E08.42, E09.42, E10.42, E11.42, E13.42
Drug overdose	E850.x, E851.x, E852.x, E853.x, E854.x, E855.x, E858.6, E858.8, E858.9, 965.x, 966.x, 967.x, 968.x, 969.x, 970.x, 971.x, 972.x, 973.x, 975.x, 977.x	T39.x, T40.x, T41.x, T42.x, T43.x, T44.x, T46.x, T47.x, T48.x, T50.x
Epilepsy	345.x	G40.x
Fibromyalgia	729.1	M60.9, M79.1, M79.7

eTable 3.1. (Continued)

Diseases (ordered alphabetically)	ICD-9-CM	ICD-10-CM
Low back pain	721.42, 721.5-721.91, 722.10, 722.2, 722.30, 722.32, 722.52, 722.6, 722.73, 722.80, 722.83, 722.90, 722.93, 724.00, 724.02, 724.09, 724.2, 724.3, 724.4, 724.5, 724.6, 724.8, 724.9, 737.1x, 737.20, 737.3x, 738.4, 739.3, 739.4, 756.10, 756.12-756.19, 805.4, 805.6, 805.8, 846.0-846.9, 307.89, 996.4x	F45.42, M40.00, M40.209, M40.299, M40.40, M41.00, M41.20, M41.30, M41.80, M41.9, M43.00, M43.10, M43.27, M43.28, M43.8X9, M46.40, M46.47, M47.10, M47.16, M47.819, M48.00, M48.061, M48.08, M48.10, M48.20, M48.30, M48.9, M51.06, M51.26, M51.27, M51.34, M51.35, M51.36, M51.37, M51.46, M51.47, M51.86, M51.87, M51.9, M53.2X7, M53.3, M53.9, M54.08, M54.14, M54.15, M54.16, M54.17, M54.30, M54.5, M54.89, M54.9, M96.1, M96.2, M96.3, M96.5, M97.9XXA, M99.03, M99.04, S12.9XXA, S22.009A, S32.009A, S32.10XA, S32.2XXA, S33.6XXA, S33.8XXA, S33.9XXA, T84.019A, T84.029A, T84.039A, T84.059A, T84.069A, T84.099A, T84.119A, T84.129A, T84.199A, T84.498A, Q76.0, Q76.1, Q76.2, Q76.419, Q76.49
Non-opioid substance use disorders	304.1x, 304.2x, 304.3x, 304.4x, 304.6x, 304.8x, 304.9x, 305.2x, 305.3x, 305.4x, 305.6x, 305.7x, 305.8x, 305.9x, V11.3, V79.1, 303.X, 305.0x,	F10.1x, F10.220, F12.x, F13.1x, F13.2x, F13.90, F14.1x, F14.2x, F14.90, F15.1x, F15.2x, F15.90, F16.x, F18.10, F18.120, F18.20, F18.21, F18.90, F19.1x, F19.90, F55.x, Z65.8, Z13.89
Opioid use disorder	304.0x, 304.7x, 305.5x	F11.2x, F19.2x, F11.1x
Osteoarthritis	715.x	M15.x, M16.x, M17.x, M18.x, M19.x
Postherpetic neuralgia	053.10, 053.11, 053.12, 053.13, 053.14, 053.19	B02.21, B02.22, B02.23, B02.24, B02.29
Seizure	780.31, 780.32, 780.33, 780.39	R56.00, R56.01, R56.1, R56.9
Serious mental illness	296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7, 296.8x, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298.0, 298.1, 298.2, 298.3, 298.4, 298.8, 298.9	F22, F23, F24, F28, F29, F30.10, F30.11, F30.12, F30.13, F30.2, F30.3, F30.4, F30.8, F31.10, F31.11, F31.12, F31.13, F31.2, F31.30, F31.31, F31.32, F31.4, F31.5, F31.60, F31.61, F31.62, F31.63, F31.64, F31.73, F31.74, F31.75, F31.76, F31.77, F31.78, F31.81, F31.9, F32.3, F32.89, F44.89
Trigeminal neuralgia	350.1	G50.0

eTable 3.2. Nagin's Diagnostic Criteria for Group-Based Multi-Trajectory Models of Opioid and Gabapentinoid Use among Medicare Beneficiaries[a]

Trajectory Groups	Number of Samples	Model Estimate of Group Probability (95% CI)[b]	Proportion Classified in Group[c]	Average Posterior Probability[d]	Odds Correct Classification[e]
OPI only					
A. OPI-only early discontinuers	28,842	40.6 (40.3, 40.9)	40.6	0.99	17.3
B. Consistent low-dose OPI-only users	11,793	16.6 (16.4, 16.8)	16.6	0.99	10.2
C. Consistent high-dose OPI-only users	1,284	1.8 (1.7, 1.9)	1.8	0.99	35.5
GABA only					
D. GABA-only early discontinuers	8,854	12.5 (12.3, 12.7)	12.5	0.99	209.6
E. Consistent low-dose GABA-only users	7,802	11.0 (10.8, 11.2)	11.0	0.99	123.2
F. Consistent high-dose GABA-only users	2,179	3.1 (3.0, 3.2)	3.1	0.99	85.1
OPI-GABA					
G. Early discontinuation of OPIs and consistent low-dose GABA users	4,876	6.9 (6.8, 7.0)	6.9	0.99	102.1
H. Consistent low-dose OPI-GABA users	2,408	3.4 (3.3, 3.5)	3.4	0.98	42.2
I. Consistent low-dose OPI and high-dose GABA users	2,303	3.2 (3.1, 3.3)	3.2	0.99	82.6
J. Consistent high-dose OPI and moderate-dose GABA users	664	0.9 (0.8, 1.0)	0.9	0.99	322.0

[a] Largest Bayesian information criterion (BIC) value was -1,176,954

[b] 95% CIs, based on parametric bootstrap method, should be reasonably narrow

[c] Proportion classified in group is based on the maximum posterior probability rule. The values of the proportion classified in the group should be similar to the model estimates of group probabilities in the third column

[d] Average posterior probability is calculated by averaging the posterior probabilities for a given group for all individuals included in this group by the maximum posterior probability rule. Acceptable values for this criterion are ≥0.7

[e] Acceptable values of the odds correct classification are ≥5

Abbreviations: **CI**, confidence interval; **GABA,** gabapentinoid; **OPI,** opioid

eTable 3.3. Minimum and Maximum Standardized Mean Difference across Trajectory Group Comparisons

	Min		Max	
	Unwt.	Wt.	Unwt.	Wt.
Disease status, %				
Any low back pain	0.001	0.005	0.586	0.286
Any osteoarthritis	0.008	0.003	0.384	0.269
Any fibromyalgia	0.002	0.001	0.557	0.115
Any neuropathy	0.015	0.001	0.606	0.179
Socio-demographics				
Age, mean (SD)	0.002	0.001	1.219	0.562
Female, %	0.001	0.001	0.398	0.195
Race/ethnicity, %	0.02	0.008	0.416	0.241
White				
African American				
Hispanic				
Others				
Disability status, %	0.007	0.003	1.260	0.275
LIS/dual eligibility, %	0.028	0.005	0.286	0.222
LIS and dual eligibility				
LIS or dual eligibility				
No LIS/dual eligibility				
Health status factors				
Elixhauser index, mean (SD)	0.004	0.001	0.866	0.452
Mental disorders, %	0.003	0.001	0.236	0.112
Anxiety, %	0.011	0.002	0.241	0.108
No. outpatient visits, mean (SD)	0.003	0.002	0.476	0.262
No. inpatient/ED visits, mean (SD)	0.001	0.001	0.284	0.176
No. benzodiazepines or Z-hypnotics, mean (SD)	0.001	0.001	0.231	0.198
No. NSAIDs, mean (SD)	0.002	0.005	0.604	0.463
No. of antidepressants, mean (SD)	0.012	0.005	0.692	0.363
No. muscle relaxants, mean (SD)	0.001	0.005	0.471	0.169
No. other prescription fills, mean (SD)	0.027	0.001	1.378	1.041
County-level factors				
No. hospitals[a], mean (SD)	0.003	0.001	0.081	0.079
No. physicians[a], mean (SD)	0.001	0.001	0.113	0.103
No. hospitals with pain program[a], mean (SD)	0.001	0.001	0.402	0.085
No. physical medicine/rehabilitation centers[a], mean (SD)	0.002	0.001	0.077	0.208
Resided in metropolitan counties, %	0.005	0.003	0.248	0.067
Median household income[b], mean (SD)	0.004	0.001	0.218	0.087
% unemployment, mean (SD)	0.001	0.001	0.106	0.111

Abbreviations: **ED**, emergency department; **GABA**, gabapentinoid; **IPTW**, inverse probability of treatment weighting; **LIS**, low-income subsidy; **MME**, morphine milligram equivalent; **No**, number; **NSAID**, nonsteroidal anti-inflammatory drug; **OPI**, opioid; **SD**, standard deviation; **SDD**, standardized daily dose **SMD**; standardized mean difference; **Unwt**, unweighted; **Wt**, weighted

[a] Per 10,000 population;

[b] Annual median household income was represented in units of thousands ($)

eTable 3.4. Dual Trajectories of Opioid and Gabapentinoid Use and Risk of Subsequent Drug Overdose, Opioid Use Disorder, and Non-Opioid Substance Use Disorders among Medicare Beneficiaries

	Drug Overdose			OUD			Non-Opioid SUDs		
	Crude	HR (95%CI)		Crude	HR (95%CI)		Crude	HR (95%CI)	
Trajectory groups	rate[a]	Unadjusted	Adjusted[b]	rate[a]	Unadjusted	Adjusted[b]	rate[a]	Unadjusted	Adjusted[b]
OPI only									
A. OPI-only early discontinuers	0.8	Ref	Ref	0.6	Ref	Ref	2.8	Ref	Ref
B. Consistent low-dose OPI-only users	1.4	1.45 (1.18, 1.80)	1.47 (1.19, 1.82)	2.6	2.64 (2.18, 3.19)	2.74 (2.27, 3.32)	5.1	1.34 (1.20, 1.50)	1.39 (1.24, 1.56)
C. Consistent high-dose OUOPI-only users	2.7	4.60 (3.02, 7.00)	4.57 (2.99, 6.98)	11.5	9.83 (7.11, 13.60)	8.11 (5.85, 11.24)	8.1	2.56 (1.92, 3.42)	2.14 (1.61, 2.86)
GABA only									
D. GABA-only early discontinuers	1.3	1.38 (1.08, 1.76)	1.39 (1.09, 1.77)	2.3	2.42 (1.95, 3.00)	2.51 (2.03, 3.11)	4.3	1.17 (1.02, 1.34)	1.20 (1.05, 1.38)
E. Consistent low-dose GABA-only users	1.4	1.41 (1.10, 1.76)	1.44 (1.12, 1.85)	2.0	1.89 (1.49, 2.41)	2.07 (1.62, 2.63)	4.0	1.13 (0.98, 1.30)	1.22 (1.06, 1.41)
F. Consistent high-dose GABA-only users	1.6	1.44 (0.95, 2.18)	1.43 (0.94, 2.17)	3.0	2.17 (1.50, 3.14)	2.30 (1.59, 3.33)	6.2	1.35 (1.08, 1.69)	1.41 (1.12, 1.76)
OPI-GABA									
G. Early discontinuation of OPIs and consistent low-dose GABA users	1.1	1.22 (0.89, 1.67)	1.24 (0.90, 1.69)	1.0	1.32 (0.95, 1.82)	1.35 (0.98, 1.87)	3.1	1.01 (0.84, 1.20)	1.02 (0.85, 1.22)
H. Consistent low-dose OPI-GABA users	1.9	2.40 (1.70, 3.39)	2.49 (1.76, 3.52)	5.6	4.17 (3.11, 5.59)	4.21 (3.14, 5.64)	7.6	1.46 (1.17, 1.83)	1.48 (1.18, 1.85)
I. Consistent low-dose OPI and high-dose GABA users	2.8	2.44 (1.70, 3.50)	2.46 (1.71, 3.53)	3.9	3.92 (2.87, 5.37)	3.82 (2.79, 5.23)	6.1	1.36 (1.07, 1.73)	1.31 (1.03, 1.67)
J. Consistent high-dose OPI and moderate-dose GABA users	4.7	7.17 (4.44, 11.57)	7.22 (4.46, 11.69)	12.4	14.01 (9.57, 20.50)	10.89 (7.43, 15.96)	11.1	3.02 (2.08, 4.40)	2.42 (1.66, 3.53)

Abbreviations: **CI**, confidence interval; **GABA**, gabapentinoid; **HR**, hazard ratio; **OPI**, opioid; **OUD**, opioid use disorder; **SUD**, substance use disorder

[a] Per 100 person-years

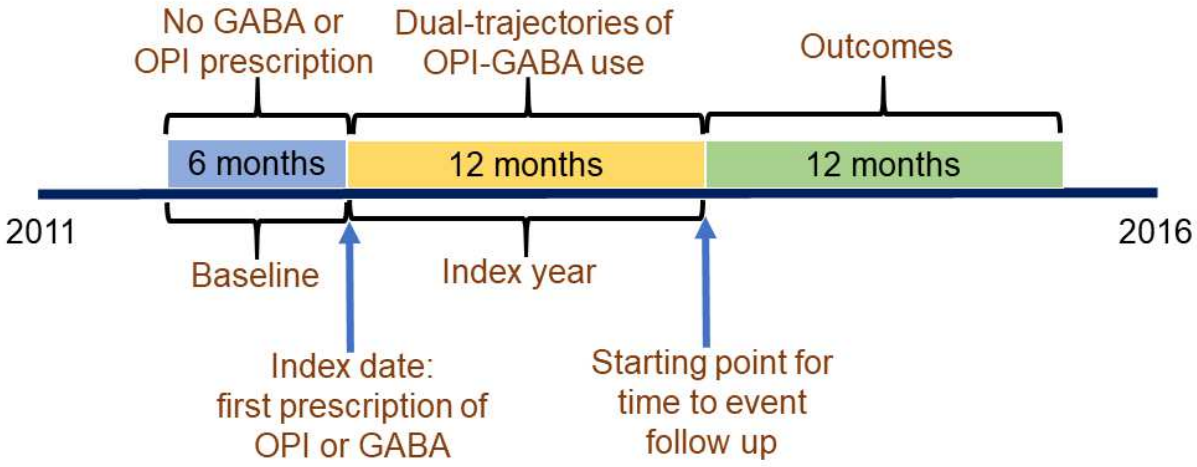
[b] Adjusted for age, disability, Elixhauser comorbidity index, number of prescriptions for nonsteroidal anti-inflammatory drugs, antidepressants, and other prescriptions

eTable 3.5. E-values of Hazard Ratio Estimates for Drug Overdose, Opioid Use Disorder, and Non-Opioid Substance Use Disorders among Medicare Beneficiaries

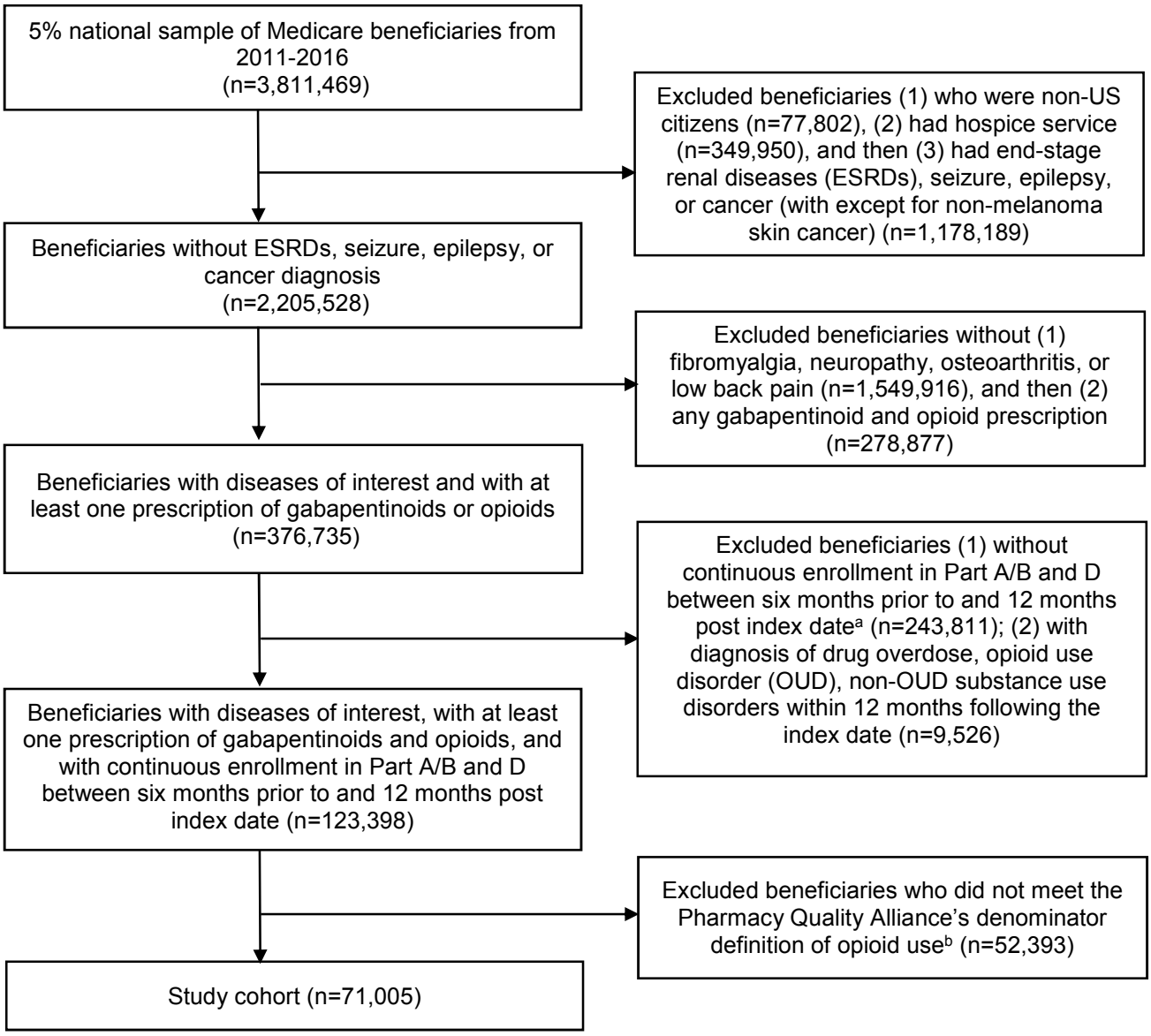
	Drug Overdose			OUD			Non-Opioid SUDs		
Trajectory Groups	**HRs (95% CI)**	**E-value for HR[a]**	**E-value for lower 95% CI**	**HRs (95% CI)**	**E-value for HR[a]**	**E-value for lower 95% CI**	**HRs (95% CI)**	**E-value for HR[a]**	**E-value for lower 95% CI**
OPI only									
A. OPI-only early discontinuers	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
B. Consistent low-dose OPI-only users	1.47 (1.19, 1.82)	2.30	1.67	2.74 (2.27, 3.32)	4.92	3.97	1.39 (1.24, 1.56)	2.13	1.79
C. Consistent high-dose OPI-only users	4.57 (2.99, 6.98)	8.61	5.43	8.11 (5.85, 11.24)	15.70	11.18	2.14 (1.61, 2.86)	3.70	2.60
GABA only									
D. GABA-only early discontinuers	1.39 (1.09, 1.77)	2.13	1.40	2.51 (2.03, 3.11)	4.46	3.48	1.20 (1.05, 1.38)	1.69	1.28
E. Consistent low-dose GABA-only users	1.44 (1.12, 1.85)	2.24	1.49	2.07 (1.62, 2.63)	3.56	2.62	1.22 (1.06, 1.41)	1.74	1.31
F. Consistent high-dose GABA-only users	1.43 (0.94, 2.17)	2.21	1.00	2.30 (1.59, 3.33)	4.03	2.56	1.41 (1.12, 1.76)	2.17	1.49
OPI-GABA									
G. Early discontinuation of OPIs and consistent low-dose GABA users	1.24 (0.90, 1.69)	1.79	1.00	1.35 (0.98, 1.87)	2.04	1.00	1.02 (0.85, 1.22)	1.16	1.00
H. Consistent low-dose OPI-GABA users	2.49 (1.76, 3.52)	4.42	2.92	4.21 (3.14, 5.64)	7.89	5.73	1.48 (1.18, 1.85)	2.32	1.64
I. Consistent low-dose OPI and high-dose GABA users	2.46 (1.71, 3.53)	4.36	2.81	3.82 (2.79, 5.23)	7.10	5.02	1.31 (1.03, 1.67)	1.95	1.21
J. Consistent high-dose OPI and moderate-dose GABA users	7.22 (4.46, 11.69)	13.92	8.40	10.89 (7.43, 15.96)	21.27	14.34	2.42 (1.66, 3.53)	4.27	2.71

Abbreviations: **CI**, confidence interval; **GABA**, gabapentinoid; **HR**, hazard ratio; **OPI**, opioid; **OUD**, opioid use disorder; **SUD**, substance use disorder

[a] E-value defined as the minimum strength of association that an unmeasured confounder would need to have with both the treatment and outcome to fully explain away a specific treatment-outcome association, conditioned on the measured covariates



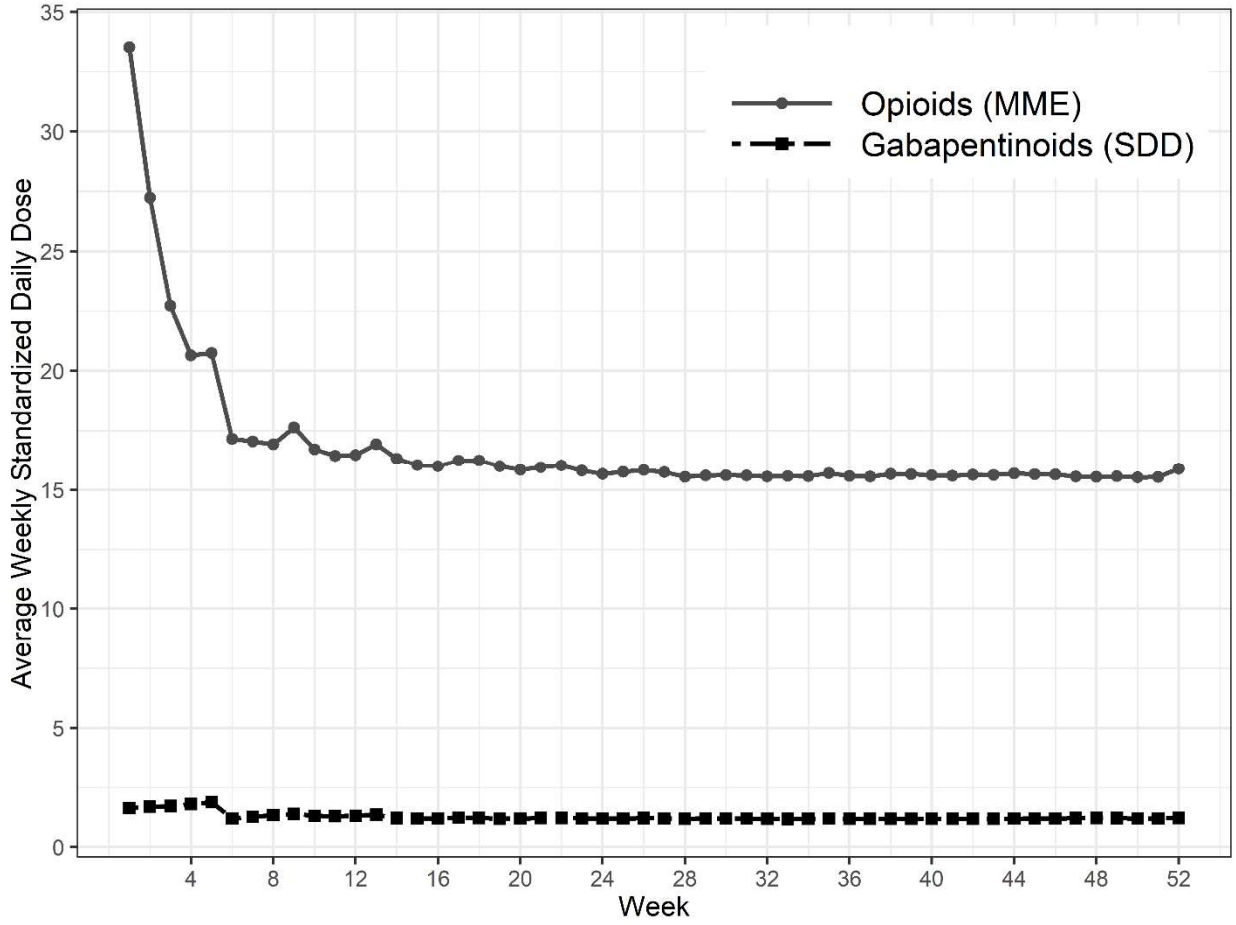
eFigure 3.1. Study Design Diagram



eFigure 3.2. Sample Size Flowchart

[a] Defined as the earliest prescription date of gabapentinoids or opioids, depending on which occurred first

[b] Two or more prescription claims for opioids filled on at least two separate days, for which the sum of the days' supply is ≥15 during the 12-month measurement year



eFigure 3.3. Average Weekly Standardized Daily Dose for Opioid and Gabapentinoid Prescriptions among Medicare Beneficiaries

Abbreviations: **MME**, morphine milligram equivalent; **SDD**, standardized daily dose

CHAPTER 4. ASSOCIATION BETWEEN DUAL-TRAJECTORIES OF OPIOID AND GABAPENTINOID USE AND HEALTHCARE EXPENDITURES AMONG UNITED STATES MEDICARE BENEFICIARIES

4.1. ABSTRACT

Objectives: The use of gabapentinoids (GABAs) may reduce the need for opioid (OPI) use while improving pain management that may decrease healthcare expenditures. On the contrary, concurrent opioid and gabapentinoid (hereafter OPI-GABA) use may indicate poor pain control, which increases medical utilization and overall health expenditures. The objective of this study was to examine the association between OPI-GABA trajectories and healthcare expenditures among Medicare beneficiaries.

Methods: This cross-sectional study included fee-for-service Medicare beneficiaries with fibromyalgia, low back pain, neuropathy, and/or osteoarthritis who newly initiated OPIs and/or GABAs from 2011-2016. We used group-based multi-trajectory models to identify distinct OPI-GABA dose and duration patterns, based on standardized daily dose (i.e., morphine milligram equivalent for OPIs and minimum effective daily dose for GABAs), within the year of initiating OPIs and/or GABAs. Concurrent annual healthcare expenditures within the same year were estimated using inverse probability of treatment weighted multivariable generalized linear regression, adjusting for socio-demographic and health status factors.

Results: Among 67,827 eligible beneficiaries (mean age ± SD= 63.6 ± 14.8 years, female=65.8%, White=77.1%), 11 distinct trajectories were identified (three OPI-only trajectories, four GABA-only trajectories, and four OPI-GABA trajectories). Among the identified trajectories, consistent high-dose OPI-only users ($22,908, 95% CI=$21,421-$24,497), consistent low-dose OPI-GABA users ($22,869, 95% CI=$21,841-$23,946), consistent low-dose OPI and high-dose GABA users ($20,281, 95% CI=$19,211-$21,411), and consistent high-dose OPI and moderate-dose GABA users ($28,464, 95% CI=$25,910-$31,271) were associated with higher healthcare expenditures compared with other trajectories (costs ranged from $10,607 to $18,309). The cost differences across trajectory groups were mainly driven by different inpatient and pharmacy expenditures.

Conclusions: There exists distinct OPI-GABA dose and duration patterns among fee-for-service Medicare beneficiaries. High-dose OPI-only users and all consistent OPI-GABA users (regardless of dose) were associated with higher healthcare expenditures.

Keywords: Gabapentinoids; opioids; trajectories; health expenditures; Medicare

4.2. INTRODUCTION

The United States (US) Food and Drug Administration (FDA) has approved gabapentinoids (GABAs), including gabapentin and pregabalin for partial seizures, postherpetic neuralgia, diabetic peripheral neuropathy (pregabalin only), fibromyalgia (pregabalin only), and restless legs syndrome in adults (gabapentin only).[1,2] According to the Medical Expenditure Panel Survey (MEPS) data, GABA use tripled from 1.2% in 2002 to 3.9% in 2015 among the US adults.[3] In 2016, the sales of pregabalin have reached to $4.4 billion, and the total number of gabapentin prescriptions increased to 64 million.[4]

Despite there is limited evidence for off-label use, GABAs have been extensively and increasingly used for various off-label pain conditions.[5-7] In many of these chronic conditions such as fibromyalgia, neuropathy, osteoarthritis, and low back pain,[8-10] no curative therapy currently exists and the economic burdens of management of these conditions are usually high. The annual direct medical costs are estimated to be $27,948 for fibromyalgia, $30,755 for diabetic peripheral neuropathy, $18,435 for osteoarthritis, and $8,386 for low back pain (in usual care settings) per capita.[11-14] The use of analgesics is a mainstay of disease management, and a better pain management (e.g., use of GABAs or integrated therapy) may improve patients' quality of life and decrease health services use, and thus reduce medical and other related costs (e.g., loss of work day).

On the contrary, a substantial increase in GABA use also raises safety concerns in the risk of misuse, abuse, dependence, and overdose of GABAs, especially among

individuals with a history of substance use disorders or co-administration with opioids (OPIs).[15-17] Over half (52%) of GABA users concurrently used OPIs in 2015.[18] Several recent studies showed that OPI-GABA use was associated with an increased risk of OPI-related deaths and other adverse outcomes (e.g., hospitalizations).[19-22] Therefore, concurrent OPI-GABA use may increase the occurrence of adverse health outcomes, resulting in an increase in healthcare expenditures.

Understanding the association between utilization patterns of OPIs-GABAs and healthcare expenditures may shed a light on the disease management of chronic pain conditions (e.g., osteoarthritis, and low back pain). Given that the dynamic changes in dose and duration of OPI-GABA use over time may reflect pain complexity and severity, the objectives of this study were first to apply group-based multi-trajectory models to identify the distinct dose and duration patterns of OPI and GABA use, and then to examine their associations with concurrent healthcare expenditures among Medicare beneficiaries. We chose Medicare because of the high prevalence of prescription OPI and GABA use and availability of national claims data, and Medicare is one of the largest health insurance payers in the US, accounting for ~20% of the overall healthcare spending ($672.1 billion) in 2016.[29]

4.3. METHODS

4.3.1. Data Source

This study used a 5% nationally representative sample of Medicare administrative claims data from 2011 to 2016 (~3.8 million unique beneficiaries). Medicare is the US governmental health insurance program provided for individuals aged ≥65 years and those aged <65 years but with certain disabilities or end-stage renal disease (ESRD).[23] We also linked the Medicare data to the public-available Area Health Resource Files (AHRF).[24] The AHRF data include the county-level information on healthcare providers (e.g., number of physicians), hospital and health facilities (e.g., number of hospitals and skilled nursing homes), and census-based demographic information (e.g., median household income).[24]

4.3.2. Study Design and Cohort

This cross-sectional study included fee-for-service beneficiaries with fibromyalgia, low back pain, neuropathy, or osteoarthritis, identified from ≥1 inpatient or ≥2 other medical claims using the International Classification of Diseases codes (see **eTable 4.1** for ICD-9-CM/ICD-10-CM codes). We restricted the analytical sample to the beneficiaries newly initiating OPIs or GABAs, with no OPI or GABA prescriptions within 6 months prior to the index date (i.e., first prescription date of either OPIs or GABAs, whichever occurred first, (**eFigure 4.1**). We excluded beneficiaries who: (1) were non-US residents, had hospice service, ESRD, seizures or epilepsies, and any type of cancer during the study period (excepting non-melanoma skin cancer; **eTable 4.1**); (2)

did not have continuous enrollment in Parts A, B, and D between 6 months prior to and 12 months post the index date; and (3) filled opioids for acute pain indications, which we defined as 1) filling only one OPI prescription, 2) filling two OPI prescriptions, but on the same day, or 3) filling <15 day opioid supply during the index year (**eFigure 4.2**).[25] The University of Arizona Institutional Review Board approved this study.

4.3.3. Exposures: Dual-Trajectories of Opioid and Gabapentinoid (OPI-GABA) Use

The exposure of interest was membership in a distinct dual-trajectory of OPI-GABA use within the year after initiating OPI or GABA prescriptions, constructed by (1) calculating standardized daily dose (SDD) for OPIs and GABAs, respectively, and (2) identifying the distinct dose and duration patterns of OPI-GABA use over time using the group-based multi-trajectory models with SDD as the outcomes.

First, we calculated the average daily SDD for OPIs using morphine milligram equivalent (MME) and for GABAs using minimum effective daily dose (i.e., 300mg for gabapentin and 150mg for pregabalin), based on dispensing date, quantity, unit strength, and days of supply. MME for each OPI prescription was calculated by the quantity dispensed multiplied by strength in milligrams, divided by days of supply, and further multiplied by a conversion factor provided by the Centers for Disease Control and Prevention (CDC).[26] Low-, moderate-, and high-dose opioid use was defined as an average daily dosage of MME <50, 50-90, and >90, respectively.[27] For GABA use, SDD <2, 2-3, and >3 were considered as low-, moderate-, and high-dose use. We created daily diary of OPI and GABA use for each patient by summing up the total SDD for OPIs and GABAs in one day, respectively. For example, the total SDD for GABAs is two if a

person had a 300 mg gabapentin prescription overlapped with a 150 mg pregabalin prescription on the same day.

Second, group-based multi-trajectory models were used to identify distinct utilization patterns of OPIs-GABAs by summarizing individuals with similar trajectories into subgroups.[28-33] We modeled the average daily MME for OPIs and SDD for GABAs as a longitudinal, continuous outcome for each week of the year after initiating OPIs or GABAs, and the time variable as weeks since the index date (week 1-52). We used the most flexible functional form of time, up to fifth order polynomial function, in the model to allow dynamic trajectories to emerge from the data. Outputs of group-based multi-trajectory models included estimated probabilities of group membership for each individual, estimated trajectory curve over time, and proportion of each group trajectory. The final model was selected based on a combination of (1) the Bayesian information criterion (BIC), where the largest value indicates the best-fitting model, and (2) application of Nagin's criteria to assess final model adequacy.[30,31,34] A well-performed trajectory model in accordance to the Nagin's criteria include an average posterior probabilities ≥0.7, odds of correct classification ≥5.0, and narrow confidence intervals for estimated group membership probabilities.[34]

4.3.4. Outcomes: Concurrent Healthcare Expenditures

The primary outcome was the total annual direct medical costs within the year following index date (i.e., concurrent healthcare expenditures of the year when the trajectories of OPIs-GABAs were measured). The direct medical costs were comprised of the payment amounts for inpatient, outpatient, emergency department (ED), and skill

nursing facility utilizations, and prescriptions and pharmacy services covered by Medicare, other health plans, and beneficiary's co-payment in the claims. The inpatient, ED, and skilled nursing facility expenditures included the costs of facility and professional health services received associated with an inpatient, ED, and skilled nursing admission, respectively. The outpatient services included services provided in clinician offices, free-standing clinics, and hospital outpatient departments. The pharmacy costs included the costs of prescriptions and health services received in the pharmacy (excluding the costs from inpatient stays). In order to make the costs identified in different years comparable to each other, all the expenditures were adjusted to the dollars in October, 2018, based on the consumer price index.[34] The secondary outcomes were separate total annual direct medical costs from inpatient, outpatient, ED, and skilled nursing facility, and pharmacy utilization, respectively.

4.3.5. Covariates

The covariate information were ascertained in the six months prior to the index date, including individual socio-demographic and health status factors and county-level factors.[20,36-39] Covariates were measured before the initiation of OPIs and GABAs to assess the prediction accuracy of the variables and to avoid including predictor changes that may themselves be consequences of use (or non-use) of OPIs and GABAs. Socio-demographics included age, sex, race/ethnicity (White, African American, Hispanic, and others), disability status, and receipt of low-income subsidy (LIS) or dual Medicaid eligibility (with both LIS and dual Medicaid eligibility, with either LIS or dual Medicaid eligibility, and no LIS or dual Medicaid eligibility). Health status factors included

Elixhauser comorbidity index (excluding metastatic cancers and solid tumors; range 0 to 27), serious mental health disorders, and anxiety disorders identified by ICD-9-CM/ICD-10-CM codes (**eTable 4.1**),[39] inpatient, outpatient, skilled nursing facility, and pharmacy costs.[40] The county-level factors included the standardized numbers of hospitals, non-federally employed physicians, hospitals with pain management program, and patient centers for physical medicine/rehabilitation per 10,000 population as a proxy for access to health care or certain specialties, population profile (metropolitan and non-metropolitan), annual median household income, and annual unemployment rate.

4.3.6. Statistical Analyses

First, we described the characteristics of beneficiaries in each OPI-GABA trajectory group, with mean and standard deviation (SD) for continuous variables, and frequency and percentage or median and interquartile range (IQR) as appropriate for categorical variables. Second, given that the identified trajectory groups were likely to be different in patient characteristics and disease complexity, we estimated the inverse probability of treatment weighting (IPTW) for each beneficiary using a multi-nominal logistic regression. Weighting subjects with IPTW would create a synthetic sample in which treatment assignment is independent of measured covariates.[42] We weighted subjects with IPTW in the analyses to minimize confounding across trajectories. We compared the characteristics across trajectories before and after weighting subjects with IPTW using the standardized mean difference (SMD), wherein SMD>0.1 was considered as having non-negligible differences.[42] Third, we used the IPTW-weighted multivariable generalized linear model, with gamma distribution and log link, to estimate

the total annual healthcare expenditures, adjusting for the covariates with non-negligible difference after IPTW weighting. The cost ratios (CRs) (also called “expenditure ratios”, interpreted as the mean expenditures in a given group divided by those in reference group) with 95% conference intervals (CIs) were also reported.[43] Finally, we conducted an additional secondary analysis to examine the associations between distinct dual-trajectories of OPI-GABA use and subsequent healthcare expenditures (i.e., the total annual medical costs within the year after the year of initiating OPIs or GABAs).

The group-based multi-trajectory models were estimated using STATA 15.0 (Stata-Corp LP, College Station, TX) and Traj package (http://www.andrew.cmu.edu/user/bjones/traj/), and all other analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA).

4.4. RESULTS

4.4.1 Dual-Trajectories of Opioid and Gabapentinoid (OPI-GABA) Use

Among 67,827 eligible beneficiaries initiating OPI or GABA prescriptions, the overall mean MME and SDD were 19.1 (SD=38.7) for OPIs and 1.4 (SD=2.1) for GABAs, respectively, within the year of initiating OPIs or GABAs (**eFigure 4.3**). According to a combination of BIC values (largest BIC=-1,148,321) and Nagin's criteria, 11 distinct dual-trajectories were identified (**eTable 4.2**).

Among the 11 distinct OPI-GABA trajectories (**Figure 4.1**), three trajectories comprised OPIs only, four trajectories comprised GABAs only, and the remaining four trajectories comprised OPIs-GABAs. Specifically, the 11 trajectory groups included: (1) OPI-only early discontinuers (Group A; 39.3% of the cohort), (2) consistent low-dose OPI-only users (Group B; 16.4%; MME ≤30), (3) consistent high-dose OPI-only users (Group C; 2.0%; MME ≥150), (4) GABA-only early discontinuers (Group D; 11.9%), (5) consistent low-dose GABA-only users (Group E; 9.5%; SDD <2), (6) consistent moderate-dose GABA-only users (Group F; 4.8%; 2< SDD ≤3), (7) consistent high-dose GABA-only users (Group G; 1.1%; SDD >5), (8) early discontinuation of OPIs and consistent low-dose GABA users (Group H; 7.4%; SDD ≤1), (9) consistent low-dose OPI-GABA users (Group I; 3.8%; MME <40 and SDD <1.5), (10) consistent low-dose OPI and high-dose GABA users (Group J; 2.8%; MME <30 and SDD ≥3), and (11) consistent high-dose OPI and moderate-dose GABA users (Group K; 1.0%; MME >120 and 1.5< SDD ≤3).

4.4.2. Characteristics Overall and by Trajectory Group

Of the 67,827 beneficiaries, the majority had low back pain (80.6%) or osteoarthritis (70.3%) (**Table 4.1**). The mean age was 63.6 (SD=14.8) years, 65.8% were female, and 77.1% were White. Over 40% had a disability (43.5%) and both LIS and dual Medicaid eligibility (45.4%). The average Elixhauser comorbidity index was 2.6 (SD=2.2). The median outpatient and pharmacy costs within the 6 months prior to initiation of OPIs or GABAs were $306 (IQR=$1,242) and $565 (IQR=$1,569), respectively. Over 70% of beneficiaries resided in metropolitan counties.

The identified 11 trajectory groups had significantly different characteristics before IPTW weighting (**Table 4.1**). For example, consistent high-dose OPI and moderate-dose GABA users were more likely to have low back pain (95.1% vs 80.6%) and fibromyalgia (40.4% vs 22.1%), to be younger (51.4 ± 12.0 years vs 63.6 ± 14.8 years), male (46.2% vs 34.2%), and White (86.9% vs 77.1%), and to have disability (83.3% vs 43.5%), compared to the overall study cohort. Consistent high-dose OPI and moderate-dose GABA users also had lower outpatient (median [IQR]: $0 [$522] vs $306 [$1,242]) and pharmacy (median [IQR]: $203 [$507] vs $565 [$1,569]) costs within the 6 months prior to initiation of OPIs or GABAs. After weighting subjects with IPTW, most of the characteristics were comparable across trajectory groups, except for the proportion of low back pain, age, and pharmacy costs. The minimum and maximum SMD across the 55 group comparisons were presented at **eTable 4.3**.

4.4.3. Inverse Probability Treatment Weighting Multivariable Generalized Linear Models for Total Annual Health Expenditures

The concurrent annual healthcare expenditures varied by trajectory groups (**Table 4.2**). Using OPI-only early discontinuers as a reference group ($13,830, 95% CI=$13,643-$14,019), significantly higher expenditures were observed among consistent high-dose OPI-only users ($22,908, 95% CI=$21,421-$24,497; adjusted CR [aCR]=1.66, 95% CI=1.55-1.77), consistent low-dose OPI-GABA users ($22,869, 95% CI=$21,841-$23,946; aCR=1.65, 95% CI=1.58-1.73), consistent low-dose OPI and high-dose GABA users ($20,281, 95% CI=$19,221-$21,411; aCR=1.47, 95% CI=1.39-1.55), and consistent high-dose OPI and moderate-dose GABA users ($28,464, 95% CI=$25,910-$31,271; aCR=2.06, 95% CI=1.87-2.26). Specifically, high-dose OPI-only users and all consistent OPI-GABA users had higher inpatient ($23,444-$29,057 vs $22,070), ED ($9,142-$12,053 vs $8,386), and pharmacy costs ($3,419-$12,192 vs $2,618) (**Tables 4.3-4.4**).

Additional secondary analyses of examining the association between OPI-GABA trajectories and annual healthcare expenditures in the subsequent year yielded similar findings as primary analyses (**eTable 4.4**). Consistent high-dose OPI-only users and all consistent OPI-GABA users had significantly higher subsequent healthcare expenditures compared to OPI-only early discontinuers. The cost differences across trajectory groups were mainly driven by the difference in inpatient, ED, and pharmacy costs (**eTables 4.5-4.6**).

4.5. DISCUSSION

This study identified 11 distinct trajectories of OPI-GABA use in the year after initiating OPIs or GABAs among fee-for-service Medicare beneficiaries with fibromyalgia, low back pain, neuropathy, or osteoarthritis. This high variability in the dose and duration patterns may attribute to a combination of patient factors (e.g., pain diagnosis/-es; pain chronicity and severity; medication preferences), prescriber factors (e.g., prescribing preferences; actual or perceived level of patient risk), and payer factors (e.g., formulary tiers; co-pays). We found that 57.7% of the beneficiaries used OPIs only, 27.3% used GABAs only, and 15.0% had OPI-GABA use concurrently. Trajectories characterized by consistent high-dose OPI-only users (MME ≥150) and all consistent OPI-GABA users (regardless of dose) were associated with significantly higher healthcare expenditures during the year of initiating OPIs and/or GABAs across trajectory groups. Similar associations were observed when examining healthcare expenditures in subsequent year.

According to our findings, inpatient, ED, and pharmacy costs were the major drivers of increased healthcare expenditures for all consistent OPI-GABA users (regardless of dose) as they had relatively higher proportion of ED visits and inpatient, ED, and pharmacy expenditures. Over half of consistent OPI-GABA users had at least one ED visit within the year of initiating OPIs and GABAs. They also had the highest inpatient ($29,057, 95% CI=$26,265-$32,146) and pharmacy ($12,192, 95% CI=$11,263-$13,197) expenditures across trajectory groups. Similarly, compared to non-consistent OPI-GABA users, high-dose OPI-only users had higher pharmacy

expenditures ($10,311) and highest ED expenditures ($12,053), but with the lowest proportion of outpatient visits across trajectory group (59.3%). The cost components that comprise the healthcare expenditures for consistent high-dose OPI-only users and all consistent OPI-GABA users were slightly different, but they all had higher ED and pharmacy costs than other trajectory groups. A possible explanation is that they had intensified (e.g., long-term high-dose OPI use) or integrated pain treatment (e.g., consistent OPI-GABA use) than other trajectory groups due to their potential more severe pain and thus, they had a higher risk of visiting ED due to drug-related adverse events and also had higher pharmacy costs.

To our knowledge, this is the first study examining healthcare expenditures associated with trajectories of OPI-GABA use. Previous observational studies have only examined the association between OPI-GABA use and adverse outcomes (e.g., OPI-related deaths) using arbitrary single value measures (e.g., any overlapping OPI and GABA use in the 120 days before OPI-related deaths).[19-22] Using an arbitrary single value may mask distinct heterogeneities in the dose and duration medication use patterns over time. Alternatively, group-based multi-trajectory models have strengths to (1) account for dynamic medication use over time and identify subgroups with similar changes over time, (2) simultaneously examine dose and duration thresholds and other patterns most relevant to outcomes, and (3) develop intuitive graphical results of trajectories.[30,34]

According to 2019 Updated American Geriatrics Society Beers Criteria® for potentially inappropriate medication use in older adults, it recommends avoiding OPI-GABA use, exception for (1) transitioning from OPI therapy to GABA, or (2) using

GABAs to reduce OPI dose.[44] Recently, given more restrictions on OPI prescribing, health providers have been increasingly co-prescribe OPIs-GABAs in clinical practice, to reduce the OPI dose and duration of use.[45,46] Based on the results of Aim 2 analyses, compared to consistent high-dose OPI-only users, lower risk of drug overdose were observed among consistent low-dose OPI-GABA users and consistent low-dose OPI and high-dose GABA users (consistent high-dose OPI-only users, consistent low-dose OPI-GABA, and consistent low-dose OPI and high-dose GABA users were likely to be switchable in analgesic use). These findings agreed with the Beers Criteria® recommendation in terms of co-administration of OPI-GABA to reduce OPI dose. However, the current study indicated that, from the cost perspective, OPI-GABA use was not associated with lower healthcare expenditures ($20,281-$22,869, 95% CI=$19,211-$23,946), compared to high-dose OPI-only users ($22,908, 95% CI=$21,421-$24,497). A possible explanation is that high-dose OPI-only users may achieve better pain management effects and thus, decrease the likelihood of inpatient (21.4% vs 28.6%-30.4%), outpatient (75.8% vs 88.0%-89.3%), and skilled nursing visit (3.9% vs 6.1%-6.5%), while they may have a higher risk of adverse health outcomes and pharmacy expenditures, compared to OPI-GABA users.

Understanding healthcare expenditures associated with different OPI-GABA trajectories may better guide management of patients with fibromyalgia, neuropathy, osteoarthritis, and low back pain. For Medicare beneficiaries who are still working (more susceptible to indirect medical cost loss due to loss of work day from physician visit) or have less access to healthcare service (e.g., residing in rural area), high-dose OPI-only treatment may be a better option as it is associated with less likelihood of inpatient and

outpatient visit. However, for those beneficiaries who have multiple chronic conditions with polypharmacy use (more susceptible to drug-related adverse events), co-administration of OPI-GABA may be a better treatment option as it is associated with less risk of adverse health outcomes (e.g., drug overdose). Therefore, the benefit (less likelihood of inpatient and outpatient visits associated with high-dose OPI-only use) and risk (higher risk of drug overdose and pharmacy costs associated with high-dose OPI-only use) profiles should be both taken in consideration when deciding the treatment strategy of OPI and GABA use.

Several limitations of the current study should be noted. First, our claims-based analyses have limited clinical and socio-behavioral information such as pain severity. It is unknown whether beneficiaries obtain the drugs from streets, friends, or other sources, or divert the prescriptions to others in our claims data analysis. Second, the unmeasured confounding, an inherent limitation of observational study, could not be completed ruled out. Third, the results have limited generalizability to other payers (e.g., Medicaid) and Medicare beneficiaries using OPIs or GABAs for conditions other than the included four chronic diseases in current study.

4.6. CONCLUSION

There exists distinct OPI-GABA dose and duration patterns among fee-for-service Medicare beneficiaries, and each trajectory of OPI-GABA use was associated with different healthcare expenditures. High-dose OPI-only users and all consistent OPI-GABA users (regardless of dose) were associated with the highest healthcare

expenditures. The benefit-risk profiles should be both taken into consideration when deciding the treatment strategy for chronic pain conditions in clinical practice.

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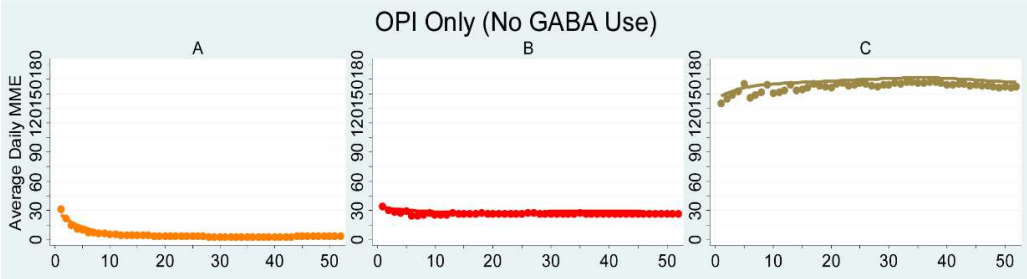
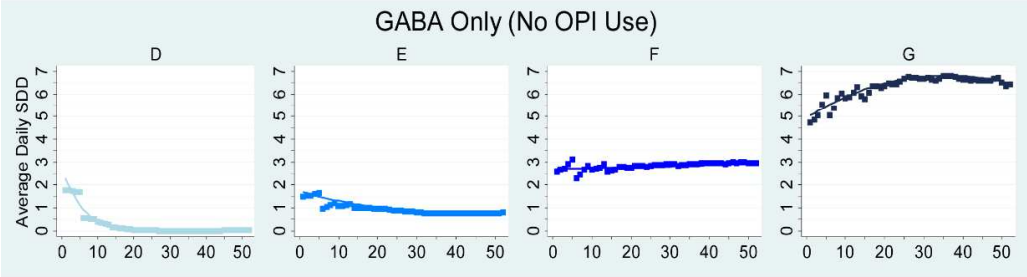
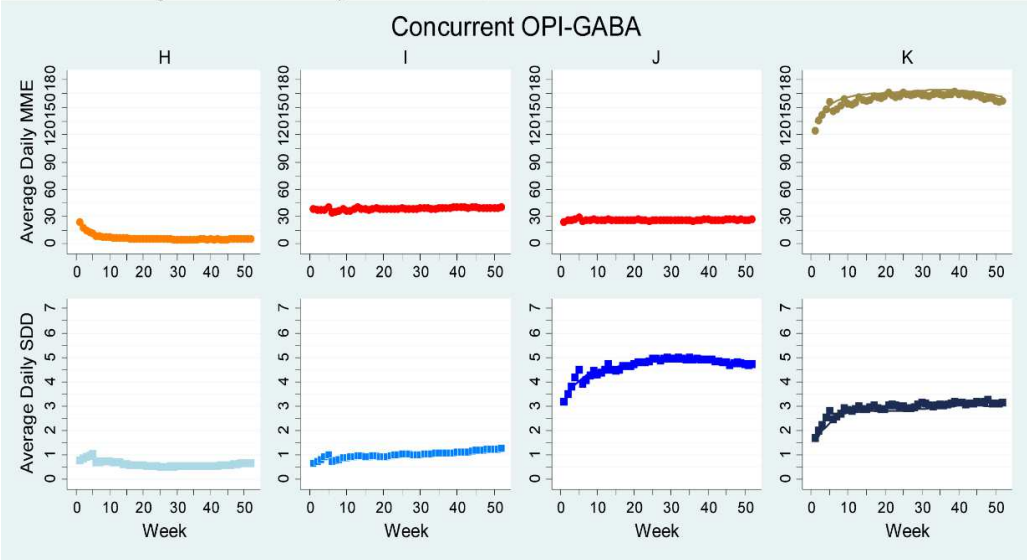
4.8. FIGURE



A: OPI-only early discontinuers (39.3%)
B: Consistent low-dose OPI-only users (MME≤30; 16.4%)
C: Consistent high-dose OPI-only users (MME≥150; 2.0%)



D: GABA-only early discontinuers (11.9%)
E: Consistent low-dose GABA-only users (SDD<2; 9.5%)
F: Consistent moderate-dose GABA-only users (2<SDD≤3; 4.8%)
G: Consistent high-dose GABA-only users (SDD>5; 1.1%)



H: Early discontinuation of OPIs and consistent low-dose GABA users (SDD≤1; 7.4%)
I: Consistent low-dose OPI-GABA users (MME<40 and SDD<1.5; 3.8%)
J: Consistent low-dose OPI and high-dose GABA users (MME<30 and SDD≥3; 2.8%)
K: Consistent high-dose OPI and moderate-dose GABA users (MME>120 and 1.5<SDD≤3; 1.0%)

4.1. Dual-Trajectories of Opioid and Gabapentinoid Use among Medicare Beneficiaries 2011-2016

4.9. TABLES

4.1. Characteristics of Medicare Beneficiaries Initiating Opioids or Gabapentinoids and by Trajectory Group

Characteristics	Overall	OPI Only			GABA Only				OPI-GABA				SMD[b] before IPTW	SMD[b] after IPTW
		A[a]	B[a]	C[a]	D[a]	E[a]	F[a]	G[a]	H[a]	I[a]	J[a]	K[a]		
No. of beneficiaries	67,827	26,673	11,125	1,393	8,052	6,410	3,223	763	4,999	2,600	1,905	738		
% of the overall cohort	100	39.3	16.4	2.0	11.9	9.5	4.8	1.1	7.4	3.8	2.8	1.0		
Disease status, %														
Any low back pain	80.6	75.2	81.9	92.9	83.0	81.9	83.1	84.3	84.3	91.7	87.7	95.1	0.20	0.10
Any osteoarthritis	70.3	73.1	71.9	54.1	68.1	70.3	66.8	59.4	69.9	66.4	63.8	63.4	0.14	0.06
Any fibromyalgia	22.1	15.3	20.8	32.9	27.0	27.3	28.3	32.2	24.4	34.1	34.1	40.4	0.19	0.03
Any neuropathy	19.4	13.9	13.2	10.2	23.0	31.9	33.6	27.1	26.5	22.4	30.2	20.3	0.24	0.05
Socio-demographics														
Age, mean (SD)	63.6 (14.8)	66.9 (14.1)	62.0 (14.6)	52.8 (12.9)	63.5 (15.3)	64.1 (14.5)	60.2 (13.7)	55.1 (13.6)	64.2 (14.3)	56.6 (14.2)	56.7 (13.5)	51.4 (12.0)	0.46	0.13
Female, %	65.8	67.9	61.9	51.6	67.0	69.1	63.4	57.1	67.8	62.2	63.1	53.8	0.14	0.05
Race/Ethnicity, %													0.19	0.08
White	77.1	76.7	79.9	87.2	72.7	72.9	81.5	84.5	73.6	78.6	83.9	86.9		
African American	13.5	13.4	13.9	8.7	14.5	14.7	11.4	8.4	14.6	14.8	9.7	8.1		
Hispanic	3.6	3.9	2.4	1.6	5.0	5.2	2.5	2.1	4.5	2.5	1.7	1.9		
Others	5.8	6.0	3.8	2.5	7.8	7.2	4.6	5.0	7.3	4.1	4.7	3.1		
Disabled, %	43.5	31.4	48.4	77.5	47.4	48.0	58.2	68.5	37.9	64.1	63.3	83.3	0.43	0.04
LIS or dual Medicaid eligibility, %													0.15	0.06
LIS and dual eligibility	45.4	39.1	46.0	44.2	51.9	55.7	53.4	55.2	43.2	51.3	49.4	46.7		
LIS or dual eligibility	6.8	6.0	6.8	8.3	7.7	8.1	8.0	9.0	5.9	7.7	7.5	7.9		
No LIS/dual eligibility	47.8	54.9	47.2	47.5	40.4	36.2	38.6	35.8	50.9	41.0	43.1	45.4		
Health status														
Elixhauser index, mean (SD)	2.6 (2.2)	2.6 (2.1)	2.3 (2.3)	1.4 (1.9)	2.8 (2.2)	3.2 (2.4)	3.1 (2.4)	2.5 (2.3)	2.6 (2.2)	2.1 (2.2)	2.2 (2.4)	1.6 (2.0)	0.31	0.06
Mental illness, %	5.3	4.4	4.9	3.6	7.1	7.0	9.0	10.6	4.6	4.8	4.9	3.4	0.11	0.06
Anxiety, %	13.9	10.8	13.6	14.1	18.2	18.0	20.5	23.1	12.1	15.9	13.5	15.5	0.12	0.04

4.1. (Continued)

Characteristics	Overall	OPI Only			GABA Only				OPI-GABA				SMD[b] before IPTW	SMD[b] after IPTW
		A[a]	B[a]	C[a]	D[a]	E[a]	F[a]	G[a]	H[a]	I[a]	J[a]	K[a]		
Inpatient costs[c], median (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.07	0.03
Outpatient costs[c], median (IQR)	306 (1,242)	375 (1,317)	144 (890)	0 (433)	425 (1,490)	411 (1,549)	422 (1,608)	284 (1,387)	329 (1,206)	143 (992)	129 (920)	0 (522)	0.13	0.04
Skilled nursing facility costs[c], median (IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.07	0.02
Pharmacy costs[c], median (IQR)	565 (1,569)	607 (1,529)	226 (915)	189 (515)	1,041 (1,916)	1,251 (2,363)	1,193 (2,486)	860 (2,288)	509 (1,432)	149 (515)	155 (495)	203 (507)	0.34	0.16
County-level factors														
No. hospitals[d], mean (SD)	2.6 (3.3)	2.6 (2.1)	2.7 (3.3)	2.4 (3.0)	2.6 (3.2)	2.6 (3.8)	2.8 (3.6)	2.7 (3.0)	2.5 (3.3)	2.6 (3.0)	2.8 (3.5)	2.6 (3.5)	0.04	0.03
No. physicians[d], mean (SD)	70.4 (31.0)	70.7 (31.2)	69.3 (30.3)	72.9 (29.0)	71.3 (31.8)	70.4 (31.7)	69.8 (31.7)	69.8 (30.5)	70.9 (30.6)	68.7 (30.6)	69.4 (30.3)	70.5 (30.4)	0.04	0.03
No. hospitals with pain program[d], mean (SD)	0.8 (1.4)	0.8 (1.5)	0.9 (1.4)	0.8 (1.4)	0.8 (1.4)	0.8 (1.5)	0.9 (1.3)	0.9 (1.5)	0.8 (1.4)	0.9 (1.6)	0.8 (1.4)	0.8 (1.2)	0.04	0.03
No. physical medicine/rehabilitation centers[d], mean (SD)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4 (0.7)	0.4 (0.8)	0.4 (0.7)	0.4 (0.7)	0.4 (0.7)	0.4 (0.6)	0.04	0.03
Metropolitan area, %	72.1	72.5	71.2	76.8	72.9	72.2	68.2	65.2	74.3	70.6	68.1	75.6	0.09	0.02
Median household income[e], mean (SD)	51 (14)	52 (14)	50 (13)	53 (14)	52 (14)	51 (14)	50 (14)	49 (14)	52 (14)	50 (13)	50 (13)	52 (14)	0.11	0.02
Unemployment rate, mean (SD)	5.7 (1.7)	5.7 (1.8)	5.7 (1.7)	5.5 (1.5)	5.7 (1.8)	5.7 (1.8)	5.7 (1.7)	5.8 (1.8)	5.7 (1.9)	5.7 (1.7)	5.7 (1.7)	5.5 (1.5)	0.05	0.03

Abbreviations: **ED**, emergency department; **FM**, fibromyalgia; **IPTW**, inverse probability of treatment weighting; **IQR**, interquartile range; **LIS**, low-income subsidy; **NSAID**, nonsteroidal anti-inflammatory drugs; **OA**, osteoarthritis; **SD**, standard deviation

[a] Trajectory groups: **A:** OPI-only early discontinuers (39.3% of the cohort); **B**: Consistent low-dose OPI-only users (MME ≤30; 16.4%); **C**: Consistent high-dose OPI-only users (MME≥150; 2.0%;); **D**: GABA-only early discontinuers (11.9%); **E**: Consistent low-dose GABA-only users (SDD<2; 9.5%); **F**: Consistent moderate-dose GABA-only users (2<SDD≤3; 4.8%); **G**: Consistent high-dose GABA-only users (SDD>5; 1.1%); **H**: Early discontinuation of OPIs and consistent low-dose GABA users (SDD≤1; 7.4%); **I**: Consistent low-dose OPI-GABA users (MME<40 and SDD<1.5; 3.8%); **J**: Consistent low-dose OPI and high-dose GABA users (MME<30 and SDD≥3; 2.8%); **K**: Consistent high-dose OPI and moderate-dose GABA users (MME>120 and 1.5<SDD≤3; 1.0%)

[b] Average SMD of 55 SMDs from group comparisons (e.g., group A vs B, group A vs C, and group A vs D). The maximum and minimum SMD were presented in eTable 4.3

[c] Included the payment amount paid by the Medicare, other primary health plan other than Medicare, and co-pay of beneficiary

[d] Per 10,000 population

[e] Annual median household income was represented in units of thousands ($)

4.2. Total Annual Healthcare Expenditures across the Identified Trajectory Groups among Medicare Beneficiaries Initiating Opioids or Gabapentinoids

	Total annual healthcare expenditures					
	Unadjusted		Adjusted[a]			
Trajectories	**Mean**	**(95% CI)**	**Mean**	**(95% CI)**	**CRs**	**(95% CI)**
OPI only						
A. OPI-only early discontinuers	14,782	(14,577, 14,991)	13,830	(13,643, 14,019)		Reference
B. Consistent low-dose OPI-only users	16,713	(16,356, 17,078)	15,721	(15,395, 16,055)	1.14	(1.11, 1.17)
C. Consistent high-dose OPI-only users	22,372	(20,879, 23,972)	22,908	(21,421, 24,497)	1.66	(1.55, 1.77)
GABA only						
D. GABA-only early discontinuers	11,530	(11,237, 11,830)	10,607	(10,345, 10,876)	0.77	(0.75, 0.79)
E. Consistent low-dose GABA-only users	13,470	(13,085, 13,866)	12,397	(12,053, 12,751)	0.89	(0.87, 0.92)
F. Consistent moderate-dose GABA-only users	12,814	(12,297, 13,353)	11,713	(11,254, 12,191)	0.85	(0.81, 0.88)
G. Consistent high-dose GABA-only users	14,303	(13,134, 15,576)	13,659	(12,574, 14,838)	0.99	(0.91, 1.07)
OPI-GABA						
H. Early discontinuation of OPIs and consistent low-dose GABA users	19,298	(18,683, 19,932)	18,309	(17,743, 18,893)	1.32	(1.28, 1.37)
I. Consistent low-dose OPI-GABA users	22,059	(21,039, 23,128)	22,869	(21,841, 23,946)	1.65	(1.58, 1.73)
J. Consistent low-dose OPI and high-dose GABA users	19,751	(18,679, 20,885)	20,281	(19,211, 21,411)	1.47	(1.39, 1.55)
K. Consistent high-dose OPI and moderate-dose GABA users	25,408	(23,066, 27,988)	28,464	(25,910, 31,271)	2.06	(1.87, 2.26)

[a] Adjusted for age, disability, low back pain, pharmacy cost at baseline
Abbreviations: **CI**, confidence interval; **CR**, cost ratio; **GABA**, gabapentinoid; **OPI**, opioid

4.3. Total Annual Inpatient, Outpatient, and Emergency Department Expenditures across Identified Trajectory Groups among Medicare Beneficiaries Initiating Opioids or Gabapentinoids

Trajectories	No. beneficiaries	Inpatient			Emergency Department			Outpatient		
		%	Mean[a]	(95% CI)	%	Mean[a]	(95% CI)	%	Mean[a]	(95% CI)
OPI only										
A. OPI-only early discontinuers	26,673	16.2	22,070	(21,504, 22,650)	46.1	8,386	(8,206, 8,571)	72.8	3,498	(3,439, 3,559)
B. Consistent low-dose OPI-only users	11,125	13.4	25,371	(24,314, 26,475)	42.4	9,931	(9,582, 10,293)	69.1	3,602	(3,506, 3,700)
C. Consistent high-dose OPI-only users	1,339	11.8	23,444	(20,514, 26,794)	43.0	12,053	(10,797, 13,456)	59.3	3,353	(3,067, 3,666)
GABA only										
D. GABA-only early discontinuers	8,052	10.2	22,895	(21,557, 24,317)	42.6	8,192	(7,839, 8,562)	67.9	2,813	(2,724, 2,906)
E. Consistent low-dose GABA-only users	6,410	10.7	25,637	(23,969, 27,422)	43.5	9,222	(8,769, 9,699)	71.1	3,030	(2,924, 3,140)
F. Consistent moderate-dose GABA-only users	3,223	10.9	24,078	(21,751, 26,654)	43.7	7,877	(7,321, 8,475)	73.2	32,998	2,851, 3,153)
G. Consistent high-dose GABA-only users	763	12.2	22,969	(18,928, 27,873)	45.4	7,859	(6,771, 9,122)	70.3	3,612	(3,247, 4,018)
OPI-GABA										
H. Early discontinuation of OPIs and consistent low-dose GABA users	4,999	19.6	25,510	(24,176, 26,918)	52.2	10,191	(9,708, 10,698)	74.8	3,926	(3,776, 4,082)
I. Consistent low-dose OPI-GABA users	2,600	19.5	28,286	26,172, 30,571)	54.0	10,696	(9,955, 11,493)	71.5	4,408	(4,161, 4,668)

4.3. (Continued)

Trajectories	No. beneficiaries	Inpatient			Emergency Department			Outpatient		
		%	Mean[a]	(95% CI)	%	Mean[a]	(95% CI)	%	Mean[a]	(95% CI)
J. Consistent low-dose OPI and high-dose GABA users	1,905	16.3	29,057	(26,265, 32,146)	50.2	9,142	(8,358, 10,000)	76.2	3,730	(3,491, 3,985)
K. Consistent high-dose OPI and moderate-dose GABA users	738	15.5	26,907	(22,968, 31,523)	50.8	11,987	(10,401, 13,816)	66.4	4,961	(4,407, 5,584)

[a] Adjusted for age, disability, low back pain, and pharmacy cost at baseline
Abbreviations: **CI**, confidence interval; **GABA**, gabapentinoid; **No**, number; **OPI**, opioid

4.4. Total Annual Pharmacy and Skilled Nursing Expenditures across Identified Trajectory Groups among Medicare Beneficiaries Initiating Opioids or Gabapentinoids

Trajectories	No. beneficiaries	Pharmacy			Skilled nursing		
		%	Mean[a]	(95% CI)	%	Mean[a]	(95% CI)
OPI only							
A. OPI-only early discontinuers	26,673	100	2,618	(2,588, 2,648)	6.8	21,155	(20,229, 22,123)
B. Consistent low-dose OPI-only users	11,125	100	4,341	(4,265, 4,419)	6.4	19,819	(18,586, 21,135)
C. Consistent high-dose OPI-only users	1,339	100	10,311	(9,744, 10,911)	3.9	24,168	(19,523, 29,919)
GABA only							
D. GABA-only early discontinuers	8,052	100	2,526	(2,473, 2,580)	4.1	20,270	(18,351, 22,391)
E. Consistent low-dose GABA-only users	6,410	100	3,291	(3,214, 3,370)	6.0	20,954	(18,911, 23,218)
F. Consistent moderate-dose GABA-only users	3,223	100	3,978	(3,846, 4,114)	4.3	20,278	(17,112, 24,029)
G. Consistent high-dose GABA-only users	763	100	5,139	(4,793, 5,510)	2.6	27,029	(18,677, 39,116)
OPI-GABA							
H. Early discontinuation of OPIs and consistent low-dose GABA users	4,999	100	3,419	(3,330, 3,511)	7.8	24,023	(21,882, 26,373)
I. Consistent low-dose OPI-GABA users	2,600	100	6,021	(5,792, 6,259)	6.5	24,113	(21,341, 27,245)

4.4. (Continued)

Trajectories	No. beneficiaries	Pharmacy			Skilled nursing		
		%	Mean[a]	(95% CI)	%	Mean[a]	(95% CI)
J. Consistent low-dose OPI and high-dose GABA users	1,905	100	7,104	(6,787, 7,436)	6.0	16,970	(14,448, 19,933)
K. Consistent high-dose OPI and moderate-dose GABA users	738	100	12,192	(11,263, 13,197)	3.3	15,213	(11,065, 20,914)

[a] Adjusted for age, disability, low back pain, and pharmacy cost at baseline
Abbreviations: **CI**, confidence interval; **GABA**, gabapentinoid; **No**, number; **OPI**, opioid

4.10. SUPPLEMENTAL DATA

eTable 4.1. ICD-9-CM and ICD-10-CM Codes of Diseases Included and Excluded in the Study

Diseases(ordered alphabetically)	ICD-9-CM	ICD-10-CM
Anxiety	293.84, 300.0X, 300.10, 300.2X, 300.3X, 300.89, 300.9X, 308.X, 309.81, 313.0, 313.1, 313.21, 313.22, 313.3X, 313.82, 313.83	F06.4, F40.x, F41.x, F42.x, F43.0, F43.1x, F44.9, F45.8, F48.8, F48.9, F93.8, F99, R45.7
Any cancer except for non-melanoma skin cancer	140.x, 141.x, 142.x, 143.x, 144.x, 145.x, 146.x, 147.x, 148.x, 149.x, 150.x, 151.x, 152.x, 153.x, 154.x, 155.x, 156.x, 157.x, 158.x, 159.x, 160.x, 161.x, 162.x, 163.x, 164.x, 165.x, 170.x, 171.x, 172.x, 174.x, 175.x, 176.x, 179.x, 180.x, 181.x, 182.x, 183.x, 184.x, 185.x, 186.x, 187.x, 188.x, 189.x, 190.x, 191.x, 192.x, 193.x, 194.x, 195.x, 196.x, 197.x, 198.x, 199.x, 200.x, 201.x, 202.x, 203.x, 204.x, 205.x, 206.x, 207.x, 208.x, 209.x, 210.x, 211.x, 212.x, 213.x, 214.x, 215.x, 216.x, 217.x, 218.x, 219.x, 220.x, 221.x, 222.x, 223.x, 224.x, 225.x, 226.x, 227.x, 228.x, 229.x, 230.x, 231.x, 232.x, 233.x, 234.x, 235.x, 236.x, 237.x, 238.x, 239.x	C00.x, C01.x, C02.x, C03.x, C04.x, C05.x, C06.x, C07.x, C08.x, C09.x, C10.x, C11.x, C12.x, C13.x, C14.x, C15.x, C16.x, C17.x, C18.x, C19.x, C20.x, C21.x, C22.x, C23.x, C24.x, C25.x, C26.x, C30.x, C31.x, C32.x, C33.x, C34.x, C37.x, C38.x, C39.x, C40.x, C41.x, C43.x, C4A.x, C45.x, C46.x, C47.x, C48.x, C49.x, C50.x, C51.x, C52.x, C53.x, C54.x, C55.x, C56.x, C57.x, C58.x, C60.x, C61.x, C62.x, C63.x, C64.x, C65.x, C66.x, C67.x, C68.x, C69.x, C70.x, C71.x, C72.x, C73.x, C74.x, C75.x, C76.x, C77.x, C78.x, C79.x, C80.x, C7A.x, C7B.x, C81.x, C82.x, C83.x, C84.x, C85.x, C86.x, C88.x, C90.x, C91.x, C92.x, C93.x, C94.x, C95.x, C96.x, D00.x, D01.x, D02.x, D03.x, D04.x, D05.x, D06.x, D07.x, D09.x, D10.x, D11.x, D12.x, D13.x, D14.x, D15.x, D16.x, D17.x, D18.x, D19.x, D20.x, D21.x, D22.x, D23.x, D24.x, D25.x, D26.x, D27.x, D28.x, D29.x, D30.x, D31.x, D32.x, D33.x, D34.x, D35.x, D36.x, D37.x, D38.x, D39.x, D40.x, D41.x, D42.x, D43.x, D44.x, D45.x, D46.x, D47.x, D48.x, D3A.x, D49.x
Diabetic neuropathy	250.60, 250.61, 250.62, 250.63, 357.2	E11.40, E40.40, E08.42, E09.42, E10.42, E11.42, E13.42
Epilepsy	345.x	G40.x
Fibromyalgia	729.1	M60.9, M79.1, M79.7

eTable 4.1. (Continued)

Diseases(ordered alphabetically)	ICD-9-CM	ICD-10-CM
Low back pain	721.42, 721.5-721.91, 722.10, 722.2, 722.30, 722.32, 722.52, 722.6, 722.73, 722.80, 722.83, 722.90, 722.93, 724.00, 724.02, 724.09, 724.2, 724.3, 724.4, 724.5, 724.6, 724.8, 724.9, 737.1x, 737.20, 737.3x, 738.4, 739.3, 739.4, 756.10, 756.12-756.19, 805.4, 805.6, 805.8, 846.0-846.9, 307.89, 996.4x	F45.42, M40.00, M40.209, M40.299, M40.40, M41.00, M41.20, M41.30, M41.80, M41.9, M43.00, M43.10, M43.27, M43.28, M43.8X9, M46.40, M46.47, M47.10, M47.16, M47.819, M48.00, M48.061, M48.08, M48.10, M48.20, M48.30, M48.9, M51.06, M51.26, M51.27, M51.34, M51.35, M51.36, M51.37, M51.46, M51.47, M51.86, M51.87, M51.9, M53.2X7, M53.3, M53.9, M54.08, M54.14, M54.15, M54.16, M54.17, M54.30, M54.5, M54.89, M54.9, M96.1, M96.2, M96.3, M96.5, M97.9XXA, M99.03, M99.04, S12.9XXA, S22.009A, S32.009A, S32.10XA, S32.2XXA, S33.6XXA, S33.8XXA, S33.9XXA, T84.019A, T84.029A, T84.039A, T84.059A, T84.069A, T84.099A, T84.119A, T84.129A, T84.199A, T84.498A, Q76.0, Q76.1, Q76.2, Q76.419, Q76.49
Osteoarthritis	715.x	M15.x, M16.x, M17.x, M18.x, M19.x
Postherpetic neuralgia	053.10, 053.11, 053.12, 053.13, 053.14, 053.19	B02.21, B02.22, B02.23, B02.24, B02.29
Serious mental illness	296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7, 296.8x, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298.0, 298.1, 298.2, 298.3, 298.4, 298.8, 298.9	F22, F23, F24, F28, F29, F30.10, F30.11, F30.12, F30.13, F30.2, F30.3, F30.4, F30.8, F31.10, F31.11, F31.12, F31.13, F31.2, F31.30, F31.31, F31.32, F31.4, F31.5, F31.60, F31.61, F31.62, F31.63, F31.64, F31.73, F31.74, F31.75, F31.76, F31.77, F31.78, F31.81, F31.9, F32.3, F32.89, F44.89
Trigeminal neuralgia	350.1	G50.0

eTable 4.2. Nagin's Diagnostic Criteria for Group-Based Multi-Trajectory Models of Opioid and Gabapentinoid Use among Medicare Beneficiaries[a]

Trajectory Groups	Number of Samples	Model Estimate of Group Probability (95% CI)[b]	Proportion Classified in Group[c]	Average Posterior Probability[d]	Odds Correct Classification[e]
OPI only					
A. OPI-only early discontinuers	26,673	39.3 (39.0, 39.6)	39.3	0.99	46.4
B. Consistent low-dose OPI-only users	11,125	16.4 (16.1, 16.7)	16.4	0.99	249.6
C. Consistent high-dose OPI-only users	1,339	2.0 (1.9, 2.1)	2.0	0.99	2812.8
GABA only					
D. GABA-only early discontinuers	8,052	11.9 (11.7, 12.1)	11.9	0.99	128.1
E. Consistent low-dose GABA-only users	6,410	9.5 (9.3, 9.7)	9.5	0.99	185.5
F. Consistent moderate-dose GABA-only users	3,223	4.8 (4.6, 5.0)	4.8	0.99	466.7
G. Consistent high-dose GABA-only users	763	1.1 (1.0, 1.2)	1.1	0.99	2315.6
OPI-GABA					
H. Early discontinuation of OPIs and consistent low-dose GABA users	4,999	7.4 (7.2, 7.6)	7.4	0.99	103.9
I. Consistent low-dose OPI-GABA users	2,600	3.8 (3.7, 3.9)	3.8	0.99	290.8
J. Consistent low-dose OPI and high-dose GABA users	1,905	2.8 (2.7, 2.9)	2.8	0.99	433.3
K. Consistent high-dose OPI and moderate-dose GABA users	738	1.0 (0.9, 1.1)	1.0	0.99	1276.0

[a] Largest Bayesian information criterion (BIC) value was -1,148,321

[b] 95% CIs, based on parametric bootstrap method, should be reasonably narrow

[c] Proportion classified in group is based on the maximum posterior probability rule. The values of the proportion classified in the group should be similar to the model estimates of group probabilities in the third column

[d] Average posterior probability is calculated by averaging the posterior probabilities for a given group for all individuals included in this group by the maximum posterior probability rule. Acceptable values for this criterion are ≥0.7

[e] Acceptable values of the odds correct classification are ≥5

Abbreviations: **CI**, confidence interval; **GABA,** gabapentinoid; **OPI,** opioid

eTable 4.3. Minimum and Maximum Standardized Mean Difference across Trajectory Group Comparisons

	Min		Max	
	Unwt.	Wt.	Unwt.	Wt.
Disease status, %				
Any low back pain	0.001	0.002	0.671	0.320
Any osteoarthritis	0.009	0.002	0.414	0.229
Any fibromyalgia	0.001	0.001	0.593	0.101
Any neuropathy	0.015	0.001	0.600	0.137
Socio-demographics				
Age, mean (SD)	0.008	0.002	1.212	0.409
Female, %	0.001	0.001	0.371	0.151
Race/ethnicity, %	0.027	0.007	0.950	0.154
White				
African American				
Hispanic				
Others				
Disability status, %	0.009	0.001	1.277	0.112
LIS/dual eligibility, %	0.022	0.002	0.394	0.212
LIS and dual eligibility				
LIS or dual eligibility				
No LIS/dual eligibility				
Health status factors				
Elixhauser index, mean (SD)	0.001	0.001	0.897	0.206
Mental disorders, %	0.004	0.001	0.290	0.180
Anxiety, %	0.004	0.001	0.330	0.116
Inpatient costs, mean (SD)	0.007	0.001	0.238	0.080
Outpatient costs, mean (SD)	0.001	0.001	0.324	0.111
Skilled nursing facility costs, mean (SD)	0.005	0.001	0.195	0.096
Pharmacy costs, mean (SD)	0.004	0.001	0.661	0.477
County-level factors				
No. hospitals[a], mean (SD)	0.001	0.001	0.141	0.108
No. physicians[a], mean (SD)	0.001	0.001	0.141	0.091
No. hospitals with pain programs[a], mean (SD)	0.001	0.001	0.094	0.115
No. physical medicine/rehabilitation centers[a], mean (SD)	0.001	0.001	0.092	0.119
Resided in metropolitan counties, %	0.006	0.001	0.258	0.059
Median household income[b], mean (SD)	0.005	0.001	0.289	0.079
% unemployment, mean (SD)	0.001	0.001	0.162	0.085

Abbreviations: **ED**, emergency department; **GABA**, gabapentinoid; **IPTW**, inverse probability of treatment weighting; **LIS**, low-income subsidy; **MME**, morphine milligram equivalent; **No**, number; **NSAID**, nonsteroidal anti-inflammatory drug; **OPI**, opioid; **SD**, standard deviation; **SDD**, standardized daily dose **SMD**; standardized mean difference;

[a] Per 10,000 population

[b] Annual median household income was represented in units of thousands ($)

eTable 4.4. Subsequent Annual Healthcare Expenditures across Identified Trajectory Groups among Medicare beneficiaries

	Subsequent healthcare expenditures					
	Unadjusted		Adjusted[a]			
Trajectories	**Mean**	**(95% CI)**	**Mean**	**(95% CI)**	**CRs**	**(95% CI)**
OPI only						
A. OPI-only early discontinuers	12,831	(12,639, 13,026)	11,831	(11,659, 12,006)		Reference
B. Consistent low-dose OPI-only users	15,316	(14,966, 15,674)	14,597	(14,272, 14,929)	1.23	(1.20, 1.27)
C. Consistent high-dose OPI-only users	20,558	(19,096, 22,132)	21,032	(19,573, 22,600)	1.78	(1.65, 1.91)
GABA only						
D. GABA-only early discontinuers	12,592	(12,248, 12,947)	11,644	(11,334, 11,964)	0.98	(0.95, 1.01)
E. Consistent low-dose GABA-only users	13,861	(13,437, 14,297)	12,837	(12,455, 13,231)	1.09	(1.05, 1.12)
F. Consistent moderate-dose GABA-only users	15,011	(14,365, 15,686)	14,019	(13,431, 14,633)	1.18	(1.13, 1.24)
G. Consistent high-dose GABA-only users	15,317	(13,985, 16,775)	14,953	(13,685, 16,338)	1.26	(1.16, 1.38)
OPI-GABA						
H. Early discontinuation of OPIs and consistent low-dose GABA users	15,081	(14,566, 15,615)	14,055	(13,587, 14,539)	1.19	(1.14, 1.23)
I. Consistent low-dose OPI-GABA users	17,828	(16,948, 18,754)	18,137	(17,265, 19,054)	1.53	(1.46, 1.61)
J. Consistent low-dose OPI and high-dose GABA users	19,586	(18,452, 20,789)	20,152	(19,015, 21,357)	1.70	(1.60, 1.80)
K. Consistent high-dose OPI and moderate-dose GABA users	27,161	(24,495, 30,117)	29,439	(26,619, 32,558)	2.49	(2.25, 2.75)

[a] Adjusted for age, disability, low back pain, and pharmacy costs
Abbreviations: **CI**, confidence interval; **CR**, cost ratio; **GABA**, gabapentinoid; **OPI**, opioid

eTable 4.5. Total Subsequent Annual Inpatient, Outpatient, and Emergency Department Expenditures across Identified Trajectory Groups among Medicare Beneficiaries Initiating Opioids or Gabapentinoids

Trajectories	No. beneficiaries	Inpatient			Emergency Department			Outpatient		
		%	Mean[a]	(95% CI)	%	Mean[a]	(95% CI)	%	Mean[a]	(95% CI)
OPI only										
L. OPI-only early discontinuers	26,673	10.2	22,489	(21,139, 23,925)	37.9	8,919	(8,708, 9,135)	67.0	2,823	(2,771, 2,877)
M. Consistent low-dose OPI-only users	11,125	11.1	22,535	(20,556, 24,704)	40.0	10,904	(9,526, 11,911)	65.8	3,078	(2,991, 3,168)
N. Consistent high-dose OPI-only users	1,339	10.9	24,758	(18,905, 32,423)	41.0	10,652	(9,526, 11,911)	58.9	3,505	(3,189, 3,852)
GABA only										
O. GABA-only early discontinuers	8,052	10.3	24,387	(21,678, 27,434)	43.3	9,513	(9,106, 9,938)	65.4	2,735	(2,642, 2,831)
P. Consistent low-dose GABA-only users	6,410	10.6	23,708	(20,772, 27,060)	44.7	10,194	(9,670, 10,714)	69.1	2,891	(2,783, 3,002)
Q. Consistent moderate-dose GABA-only users	3,223	12.9	25,106	(21,133, 29,825)	45.6	9,508	(8,856, 10,208)	71.7	2,904	(2,754, 3,061)
R. Consistent high-dose GABA-only users	763	13.1	16,816	(11,689, 24,192)	49.9	9,530	(8,308, 10,932)	67.4	3,829	(3,428, 4,277)
OPI-GABA										
S. Early discontinuation of OPIs and consistent low-dose GABA users	4,999	11.9	27,290	(23,871, 31,199)	41.5	8,998	(8,520, 9,503)	68.9	3,155	(3,024, 3,291)
T. Consistent low-dose OPI-GABA users	2,600	13.4	25,394	(21,026, 30,671)	46.7	11,441	(10,588, 12,362)	68.0	3,594	(3,380, 3,822)

eTable 4.5. (Continued)

Trajectories	No. beneficiaries	Inpatient			Emergency Department			Outpatient		
		%	%	Mean[a]	%	Mean[a]	(95% CI)	%	Mean	(95% CI)
U. Consistent low-dose OPI and high-dose GABA users	1,905	15.6	27,602	(22,237, 34,261)	50.0	10,359	(9,453, 11,352)	73.1	3,918	(3,650, 4,204)
V. Consistent high-dose OPI and moderate-dose GABA users	738	14.5	19,108	(13,548, 26,950)	49.3	17,066	(14,663, 19,862)	64.8	4,248	(3,749, 4,812)

[a] Adjusted for age, disability, low back pain, and pharmacy costs at baseline
Abbreviations: **CI**, confidence interval; **GABA**, gabapentinoid; **No**, number; **OPI**, opioid

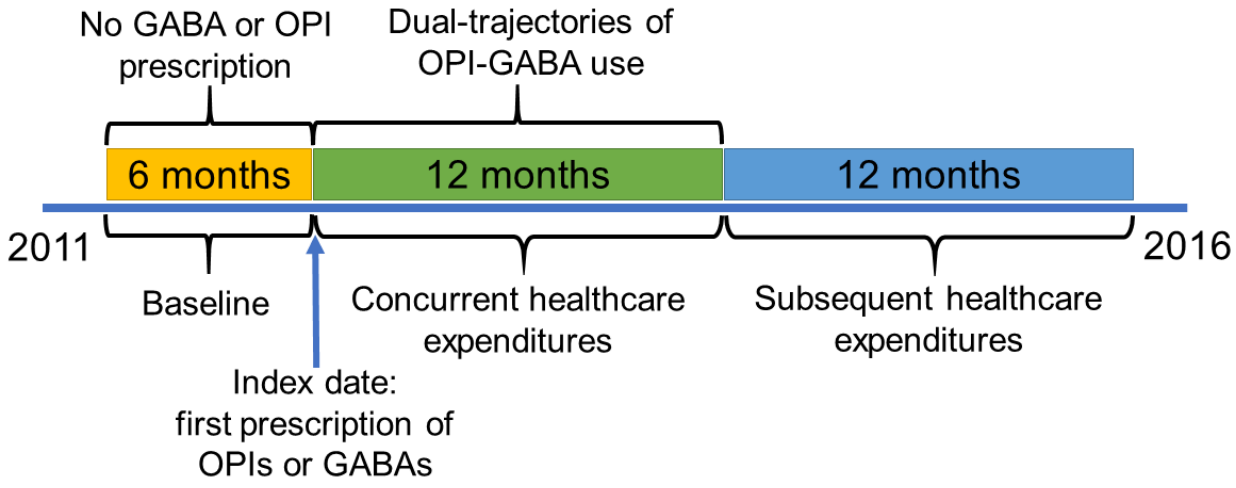
eTable 4.6. Total Subsequent Annual Pharmacy and Skilled Nursing Expenditures across Identified Trajectory Groups among Medicare Beneficiaries Initiating Opioids or Gabapentinoids

Trajectories	No. beneficiaries	Pharmacy			Skilled nursing		
		%	Mean[a]	(95% CI)	%	Mean[a]	(95% CI)
OPI only							
A. OPI-only early discontinuers	26,673	97.3	2,893	(2,855, 2,931)	5.7	22,595	(21,538, 23,704)
B. Consistent low-dose OPI-only users	11,125	98.4	4,550	(4,460, 4,641)	5.9	20,558	(19,229, 21,980)
C. Consistent high-dose OPI-only users	1,339	98.8	8,951	(8,402, 9,536)	3.6	24,919	(20,183, 30,766)
GABA only							
D. GABA-only early discontinuers	8,052	96.5	2,708	(2,643, 2,774)	4.7	22,418	(20,412, 24,621)
E. Consistent low-dose GABA-only users	6,410	98.9	3,460	(3,369, 3,554)	6.9	22,452	(20,468, 24,629)
F. Consistent moderate-dose GABA-only users	3,223	99.5	4,336	(4,175, 4,502)	6.1	22,710	(19,771, 26,085)
G. Consistent high-dose GABA-only users	763	99.3	5,702	(5,274, 6,165)	3.4	23,478	(16,233, 39,957)
OPI-GABA							
H. Early discontinuation of OPIs and consistent low-dose GABA users	4,999	97.6	3,860	(3,747, 3,978)	5.4	21,264	(19,068, 23,713)
I. Consistent low-dose OPI-GABA users	2,600	98.9	6,007	(5,752, 6,274)	5.0	17,554	(15,307, 20,131)

eTable 4.6. (Continued)

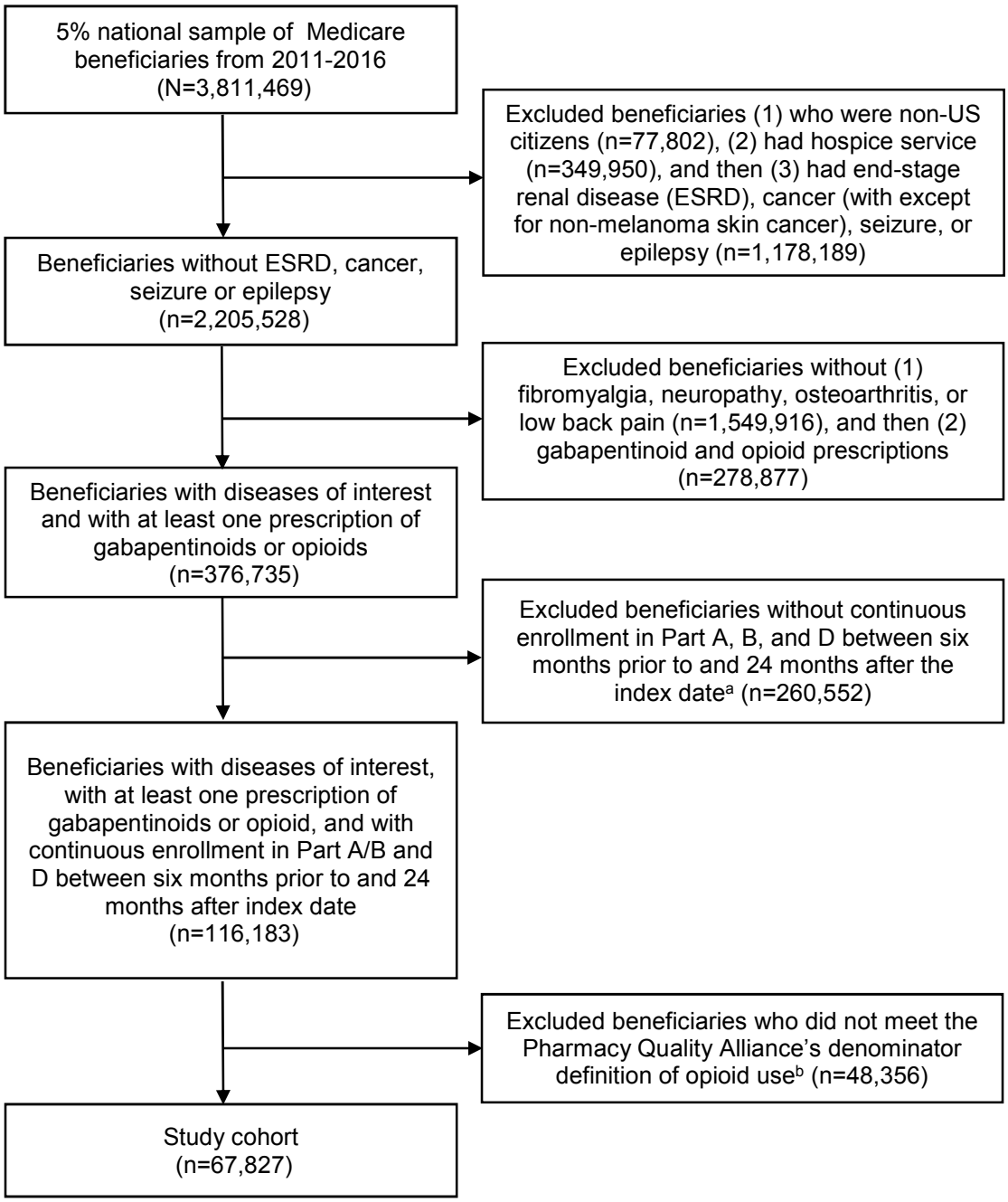
Trajectories	No. beneficiaries	Pharmacy			Skilled nursing		
		%	Mean[a]	(95% CI)	%	Mean[a]	(95% CI)
J. Consistent low-dose OPI and high-dose GABA users	1,905	99.3	7,228	(6,867, 7,607)	5.8	21,809	(18,239, 26,077)
K. Consistent high-dose OPI and moderate-dose GABA users	738	99.7	13,336	(12,205, 14,571)	4.6	31,737	(24,042, 41,895)

[a] Adjusted for age, disability, low back pain, and pharmacy costs at baseline
Abbreviations: **CI**, confidence interval; **GABA**, gabapentinoid; **No**, number; **OPI**, opioid



eFigure 4.1. Study Design Diagram

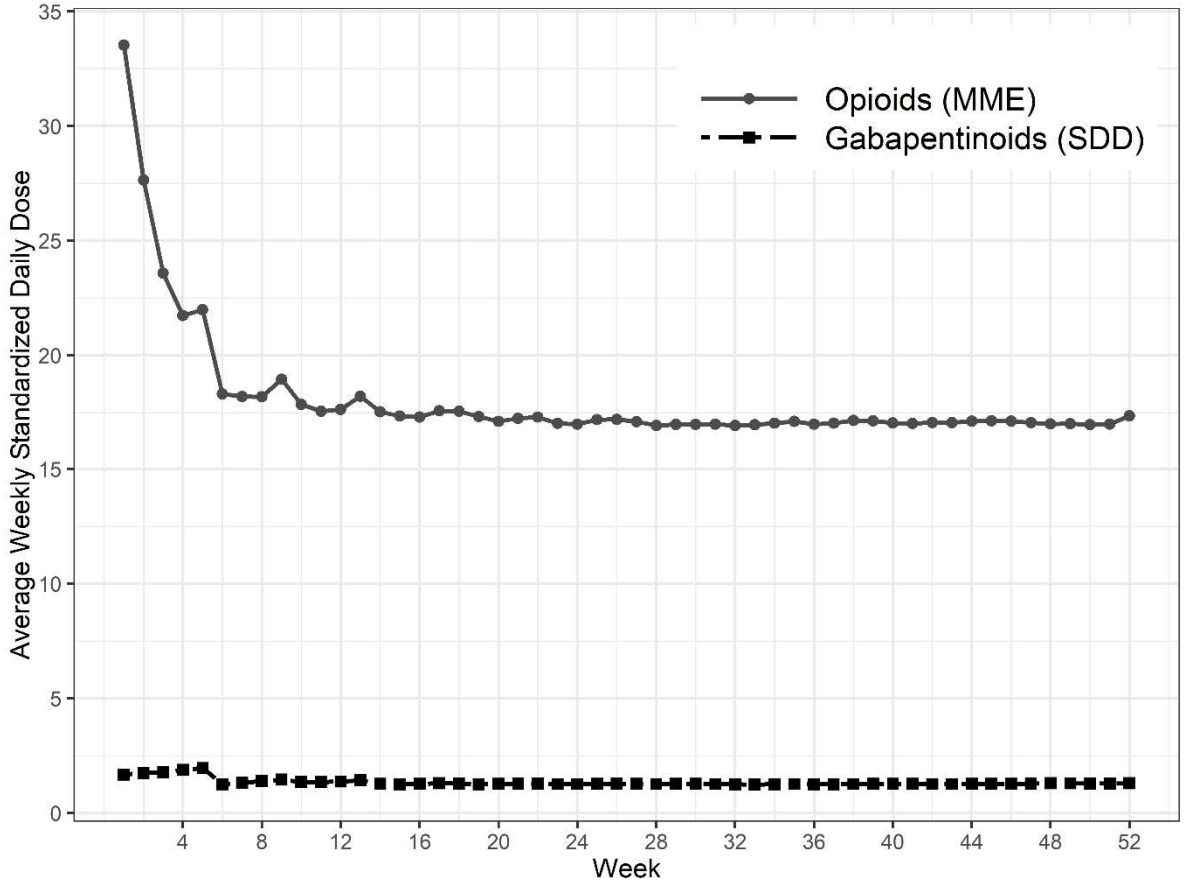
Abbreviations: **GABA**, gabapentinoid; **OPI**, opioid



eFigure 4.2. Sample Size Flowchart

[a] Defined as the earliest prescription date of gabapentinoids or opioids, depending on which occurred first

[b] Two or more prescription claims for opioids filled on at least two separate days, for which the sum of the days supply is ≥15 during the 12-month measurement year



eFigure 4.3. Average Weekly Standardized Daily Dose for Opioid and Gabapentinoid Prescriptions among Medicare Beneficiaries

Abbreviations: **MME**, morphine milligram equivalent; **SDD**, standardized daily dose

CHAPTER 5. DISCUSSION AND CONCLUSION

5.1. SUMMARY OF STUDY FINDINGS AND CONTRIBUTIONS TO THE LITERATURE

5.1.1. Trends, Patient and Prescriber Characteristics, and Off-Label Use of Gabapentinoids among United States Ambulatory Care Visits from 2003-2015

Using the National Ambulatory Medical Care Survey (NAMCS) data, our study found that the visits involving gabapentinoids (GABAs) quadrupled in the United States (US) ambulatory care settings from 2003 to 2015 (primarily driven by gabapentin). Potential off-label use of GABAs was overwhelmingly high (98% vs 83% for gabapentin in 2001 reported by Radley et al.[1]). Similar to the Johansen's Medical Expenditure Panel Survey study[2], GABA visits were more likely to be from older age, females and those with more chronic conditions. Half of the GABA visits had concurrent opioid (OPI) and/or benzodiazepine use. Notably, we additionally identified other characteristics associated with GABA use, including Caucasian, having a governmental insurance policy, primary care physicians, physician whose practices are located in metropolitan and southern regions, and continuous use of GABA.

Current initiatives implemented in part of the US health systems to reduce high-risk GABA use included prior authorization and step therapy for pregabalin, mandatory reporting of gabapentin use to the prescription drug monitoring programs (PDMPs) in some states (e.g., Ohio, Virginia, and Massachusetts), and classification of gabapentin as a Schedule V Substance with prescribing quantity limits (Kentucky).[3,4] However,

definitions for high-risk GABA use varies. While GABAs are promoted as a key constituent of multimodal analgesia to reduce the OPI dosage in perioperative and other acute pain settings, more evidence is needed to evaluate the safety of OPI and GABA interactions with respect to dose, duration, and interactions given increasing awareness of adverse outcomes.[5] Our study underscores the need for safety evaluation regarding GABA use in the US ambulatory care setting, especially with the substantially high prevalence of concurrent OPI and GABA (hereafter OPI-GABA) use and off-label use of GABAs.

5.1.2. Dual-Trajectories of Opioid and Gabapentinoid Use and Risk of Subsequent Adverse Health Outcomes in United States Medicare

Our study yielded three important insights into initiating OPIs or GABAs among fee-for-service Medicare beneficiaries with fibromyalgia, low back pain, neuropathy, or osteoarthritis. First, we identified ten distinct dual-trajectories of OPI-GABA use in the 12 months after initiating OPIs and GABAs. This high variability may arise from a combination of patient pain severity, disease complexity, provider decision-making, and payer restrictions. Second, nearly 60% of the beneficiaries only used OPIs, 26.6% only used GABAs, and 14.4% had OPI-GABA use, with distinct dose and duration patterns. Third, trajectories characterized by consistent high-dose OPI-only users (morphine milligram equivalent [MME] >120) and consistent OPI-GABA users (regardless of doses) were associated with more than doubled risk of drug overdose, compared to OPI-only early discontinuers. Similar risk magnitudes were observed for the outcomes of opioid use disorder and non-opioid substance use disorders.

To our knowledge, only four studies have previously examined OPI-GABA use and associated adverse outcomes.[6-9] However, the operational definitions of concurrent use vary substantially, and thus may lead to overly broad and ineffective interventions. OPI-GABA use has been defined as having any overlapping OPI-GABA use in the 120 days preceding the outcomes (e.g., opioid-related death),[6,9] having any pregabalin use during receiving opioid maintenance treatment,[8] or having concurrent use ≥120 days in 12 months.[7] In reality, treatment needs and sequelae including OPI-GABA duration and dose vary by patient characteristics and comorbid conditions and severity. Consequently, it may not be possible to avoid co-prescribing in certain patients, even with known risk, and OPI-GABA risk-benefit will vary. Using single values (e.g., any overlapping day of concurrent use) over a fixed time period provides a gross measure of use patterns that could mask distinct heterogeneity in concurrent use and risk. Applying arbitrary thresholds of OPI-GABA dose or duration to all patients without better understanding or validation imposes challenges in clinical care and policies around OPI-GABA use. Alternatively, group-based multi-trajectory models may be valuable to better characterize concurrent use. The strengths of the models include (1) the ability to account for dynamic medication use and identify subgroups with similar changes over time; (2) the ability to simultaneously examine dose and duration thresholds and other patterns most relevant to outcomes; and (3) the development of intuitive graphical results of trajectories.[10,11]

Our overall findings were consistent with the previous evidence on OPI-GABA use associated with an increased risk of adverse health outcomes.[6-9] Potential mechanisms could attribute to the additive respiratory depression effects on one's

central nervous system,[12] and an increase in GABA's bioavailability due to drug-drug interaction (e.g., an increase in gabapentin absorption by 44% when concurrent use of gabapentin and morphine).[13] Our study also advances the knowledge from previous studies (i.e., one retrospective cohort study of commercial insurers in US, two case-control studies of residents in Ontario, Canada, and one retrospective cohort study in Sweden[6-9]). In addition to the ability of simultaneously examining dynamic dose and duration utilization over time, our study also has three major advantages over prior studies, including (1) examining both gabapentin and pregabalin (whereas only focusing on gabapentin or pregabalin in previous studies), (2) allowing to examine the heterogeneity within normal dose (rather than only focusing on identifying dose over Food and Drug Administration's [FDA's] recommended maximum dose), and (3) characterizing both short- and long-term of OPI-GABA use over time.

Recently, several clinical trials suggested an efficacy of GABA use in relieving off-label pain conditions (e.g., chronic sciatica) and reducing acute and chronic postoperative pain and OPI use among different types of surgeries (e.g., breast cancer surgery).[14-19] However, given the safety concerns about GABAs, there has been calls for placing more stringent regulations for gabapentin at the Federal level and to include gabapentin monitoring in the state prescription drug monitoring programs (PDMPs) to promote drug use safety as the hazard ratio (HR) of consistent high-dose OPI and moderate-dose GABA user in this study was 7.22 (95% confidence interval [CI] =4.46-11.69). At state level, several states, including Minnesota, Ohio, Virginia, and Kentucky, have required mandatory reporting for gabapentin use in PDMPs.[20] Kentucky further classified gabapentin as a Schedule V Controlled Substance and restricted prescribing

amount of gabapentin.[20] Other targeted interventions suggested in clinical practice include promoting health provider education and awareness of potential risk for OPI-GABA use, auto-alert electronic health system, and close monitoring and additional assessment of individuals at OPI-GABA use. Our trajectory subgroups (e.g., consistent high-dose OPI and moderate-dose GABA use) may be valuable to better guide target interventions.

5.1.3. Association between Dual-Trajectories of Opioid and Gabapentinoid Use and Healthcare Expenditures among United States Medicare Beneficiaries

This study identified 11 distinct trajectories of OPI-GABA use in the year after initiating OPIs or GABAs among fee-for-service Medicare beneficiaries with fibromyalgia, low back pain, neuropathy, or osteoarthritis. This high variability in the dose and duration patterns may attribute to the different patient pain severity, disease complexity, provider decision-making, and payer restrictions. We found that 57.7% of the beneficiaries used OPIs only, 27.3% used GABAs only, and 15.0% had OPI-GABA use concurrently. Trajectories characterized by consistent high-dose OPI-only users (MME ≥150) and all consistent OPI-GABA users (regardless of dose) were associated with significantly higher healthcare expenditures during the year of initiating OPIs and/or GABAs across trajectory groups. Similar associations were observed when examining healthcare expenditures in subsequent year.

According to our findings, inpatient and pharmacy costs were the major drivers of increased healthcare expenditures for all consistent OPI-GABA users (regardless of dose) as they had relatively higher proportion of inpatient visits and inpatient and

pharmacy expenditures. Over a quarter of consistent high-dose OPI and moderate-dose GABA users had at least one inpatient visit within the year of initiating OPIs and GABAs. They also had the highest inpatient ($28,456, 95% CI=$25,313-$31,988) and pharmacy ($12,192, 95% CI=$11,263-$13,197) expenditures across trajectory groups. Similarly, compared to non-consistent OPI-GABA users, high-dose OPI-only users had higher pharmacy expenditures ($10,311 vs $2,618-5,139), but with the lowest proportion of outpatient visits across trajectory group (75.8% vs 82.3%-89.3%). The cost components that comprise the healthcare expenditures for consistent high-dose OPI-only users and all consistent OPI-GABA users were slightly different, but they all had higher pharmacy costs than other trajectory groups. A possible explanation is that they had intensified (e.g., long-term high-dose OPI use) or integrated pain treatment (e.g., consistent OPI-GABA use) than other trajectory groups due to their potential more severe pain and thus, they had higher pharmacy costs.

To our knowledge, this is the first study examining healthcare expenditures associated with trajectories of OPI-GABA use. Previous observational studies have only examined the association between OPI-GABA use and adverse outcomes (e.g., OPI-related deaths) using arbitrary single value measures (e.g., any overlapping OPI and GABA use in the 120 days before OPI-related deaths).[19-22] Using an arbitrary single value may mask distinct heterogeneities in the dose and duration medication use patterns over time. Alternatively, group-based multi-trajectory models have strengths to (1) account for dynamic medication use over time and identify subgroups with similar changes over time, (2) simultaneously examine dose and duration thresholds and other

patterns most relevant to outcomes, and (3) develop intuitive graphical results of trajectories.[29,33]

According to 2019 Updated American Geriatrics Society Beers Criteria® for potentially inappropriate medication use in older adults, it recommends avoiding OPI-GABA use, exception for (1) transitioning from OPI therapy to GABA, or (2) using GABAs to reduce OPI dose.[43] Recently, given more restrictions on OPI prescribing, health providers have been increasingly co-prescribe OPIs-GABAs in clinical practice, to reduce the OPI dose and duration of use.[44,45] Based on the results of Aim 2 analyses, compared to consistent high-dose OPI-only users, lower risk of drug overdose were observed among consistent low-dose OPI-GABA users and consistent low-dose OPI and high-dose GABA users (consistent high-dose OPI-only users, consistent low-dose OPI-GABA, and consistent low-dose OPI and high-dose GABA users were likely to be switchable in analgesic use). These findings agreed with the Beers Criteria® recommendation in terms of co-administration of OPI-GABA to reduce OPI dose. However, the current study indicated that, from the cost perspective, OPI-GABA use was not associated with lower healthcare expenditures ($20,281-$22,869, 95% CI=$19,211-$23,946), compared to high-dose OPI-only users ($22,908, 95% CI=$21,421-$24,497). A possible explanation is that high-dose OPI-only users may achieve better pain management effects and thus, decrease the likelihood of inpatient (21.4% vs 28.6%-30.4%), outpatient (75.8% vs 88.0%-89.3%), and skilled nursing visit (3.9% vs 6.1%-6.5%), while they may have a higher risk of adverse health outcomes and pharmacy expenditures, compared to OPI-GABA users.

Understanding healthcare expenditures associated with different OPI-GABA trajectories may better guide management of patients with fibromyalgia, neuropathy, osteoarthritis, and low back pain. For Medicare beneficiaries who are still working (more susceptible to indirect medical cost loss due to loss of work day from physician visit) or have less access to healthcare service (e.g., residing in rural area), high-dose OPI-only treatment may be a better option as it is associated with less likelihood of inpatient and outpatient visit. However, for beneficiaries who have multiple chronic conditions with polypharmacy use (more susceptible to drug-related adverse events), co-administration of OPI-GABA may be a better treatment option as it is associated with less risk of adverse health outcomes (e.g., drug overdose). Therefore, the benefit (less likelihood of inpatient and outpatient visits associated with high-dose OPI-only use) and risk (higher risk of drug overdose and pharmacy costs associated with high-dose OPI-only use) profiles should be both taken in consideration when deciding the treatment strategy of OPI and GABA use.

5.2. STUDY LIMITATIONS

Our study of examining “Aim 1: Trends, Patient and Prescriber Characteristics, and Off-Label Use of Gabapentinoids among United States Ambulatory Care Visits from 2003-2015” had several limitations. First, gabapentinoid use and FDA-approved indications may be underestimated because only eight medications and three International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were available in the NAMCS data. Second, NAMCS data lack of duration

and dose information of medication use. Third, our findings represent visit-level data rather than patient-level.

In addition, several limitations of the studies of "Aim 2: Dual-Trajectories of Opioid and Gabapentinoid Use and Risk of Subsequent Adverse Health Outcomes in United States Medicare" and "Aim 3: Association between Dual-Trajectories of Opioid and Gabapentinoid Use and Healthcare Expenditures among United States Medicare Beneficiaries" should be noted. First, these two studies did not include the prevalent opioid and/or gabapentinoid users. The rationale of using a "new drug user" design in this study is to eliminate the potential prevalent user bias (i.e., the risk of outcomes and covariate characteristics change as the duration of drug use). Second, our claims-based analyses have limited clinical and socio-behavioral information such as pain severity. We also cannot capture or measure whether beneficiaries obtain the drugs from streets, friends, or other sources in our claims data analysis. Although unmeasured confounding could not be completed ruled out, our sensitivity analyses of Aim 2 showed that the results are robust to potential unmeasured confounders based on the E-values of HR estimates. Third, our diagnosis-based outcomes are likely to be underestimated due to under-coding issues because of reasons such as stigma in clinical practice. Prior studies showed high specificity but low sensitivity in substance use disorder-related outcomes (e.g., OPI overdose).[21,22] Finally, the study results have limited generalizability to other payers (e.g., Medicaid) and Medicare beneficiaries using OPIs or GABAs for other conditions than the included four chronic diseases in current study.

5.3. FUTURE RESEARCH

Future studies should be conducted to answer the research questions that were not answered in this dissertation, as well as studies that are able to overcome the limitations of this dissertation. In Aim 1 of this dissertation, given the limited information available in NAMCS data (e.g., eight medications, three ICD-9-CM codes, and no dose or duration information), we may underestimate the gabapentinoid use and FDA-approved indications, and are not able to further look into the gabapentinoid dose and duration patterns in the US ambulatory care settings. Therefore, future studies should employ a data source with more comprehensive clinical information including diagnosis, medication use, and patient and prescriber characteristics, to complement the results of Aim 1 of this dissertation. In addition, the results of Aim 1 only reflect the gabapentinoid use characteristics in the US ambulatory care settings. Future studies are suggested to examine other clinical settings, such as inpatient, emergency department, and hospital outpatient, as they may have distinct gabapentinoid use characteristics.

In both Aim 2 and Aim 3 of this dissertation, we used a “new drug user” design by including the Medicare beneficiaries newly initiating opioids and gabapentinoids. However, most individuals are likely to be a prevalent opioid and/or gabapentinoid user in Medicare given the age characteristics (primarily elderly individuals ≥65 years) and high prevalence of chronic pain in this population.[23,24] Therefore, future studies should also examine the trajectories of OPI-GABA use among the prevalent opioid and gabapentinoid users in Medicare and explore their associations with risk of subsequent health outcomes and healthcare expenditures. Exploring the prevalent users of opioids

and gabapentinoids may be more likely to reflect the real-world clinical practice in Medicare. In addition, Aim 2 and Aim 3 of this dissertation only included fee-for-service Medicare beneficiaries and thus, have limited generalizability to other payers, such as Medicare Advantage plan, Medicaid, and commercial insurance programs that may have different reimbursement policies that further influence the medication use patterns. Future studies examining the utilization patterns of OPIs-GABAs and associations with risk of drug overdose and healthcare expenditures in other payers are warranted.

5.4. CONCLUSION

The increasing trend and extensive off-label use of GABAs, especially concurrent use with OPIs identified from the NAMCS data, highlight the greater need for an understanding of long-term safety of GABA use. The distinct OPI-GABA dose and duration patterns were associated with different risk of adverse health outcomes and healthcare expenditures among fee-for-service Medicare beneficiaries. High-dose OPI-only users and all consistent OPI and GABA users, especially high-dose OPI and moderate-dose GABA users, were associated with the highest risk of adverse health outcomes and healthcare expenditures. Clinicians should consider carefully when prescribing concurrent OPI and GABA use. When the co-administration is necessary, patients should be monitored closely and assessed the benefit-risk profiles on a regular basis.

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