CURRICULUM VITAE

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EDUCATION

Dec 2021	**PhD, Pharmaceutical Health Services Research** University of Maryland, Baltimore, MD **Thesis:** Patterns, factors and outcomes associated with gabapentin use in combination with opioids and benzodiazepines among Social Security Disability Insurance (SSI) eligible Medicare Beneficiaries **Degree conferral-December 2021**
May 2016	**Master of Public Health, Epidemiology** George Washington University, Washington, DC
May 2011	**Bachelors of Science, Nursing** Howard University, Washington, DC

RESEARCH EXPERIENCE

2017 - 2021 **Graduate Research Assistant, University of Maryland**

Principal Investigator: Linda Simoni-Wastila, PhD, MSPH

- Responsible for designing observational studies on multiple projects including NIH-funded study on antipsychotic utilization in nursing homes and Maryland Statewide Epidemiologic Outcomes Workgroup ―opioid, cannabis and other substance use profiles; Analyzed large datasets including administrative claims and IQVIA data; Co-authored multiple manuscripts and reports; Assisted with the writing of proposals and grants

2017 - 2018 **Graduate Research Assistant, University of Maryland**

Principal Investigator: Wendy Camelo-Castillo, PhD, MD

- Responsible for epidemiologic activities and analysis of complex survey data focused on multimorbidity

2015 - 2016 **Research Assistant, Elizabeth Glaser Pediatric AIDS Foundation**

Principal Investigator: Leila Katirayi, PhD

- Analyzing qualitative data from HIV positive pregnant and postpartum women receiving counseling services; Contributed to reports distributed to the Swaziland Ministry of Health

TEACHING EXPERIENCE

2016 - 2017	**Teaching Assistant** University of Maryland, School of Pharmacy, Baltimore • Pharmacoeconomics • Medical evidence

TEACHING EXPERIENCE (continued)

2019	**Guest Lecturer** University of Maryland, School of Pharmacy, Baltimore • The Medical Use of Cannabinoids

CLINICAL EXPERIENCE

2013 - Present	**Registered Nurse, Home health** Immaculate health care services, Washington, DC • Collaborating with an interdisciplinary health care team to provide specialized care to underserved patients within the community
2011 - 2012	**Registered Nurse, General Surgery** Howard University Hospital, Washington, DC

ACADEMIC SERVICE

2019 - Present	Committee member, Academy Health Behavioral Interest
2019	Abstract Reviewer, American Public Health Association
2019	Abstract Reviewer, Society of Epidemiology Research

LICENSURES

2011 - Present	District of Colombia Licensed Registered Nurse

PUBLICATIONS

Peer Reviewed Journal Articles

Olopoenia A, Onukwugha E, Simoni-Wastila L, Camelo-Castillo W, Villalonga-Olives E, Gandhi AB, Slejko J. Patterns of prescription opioid utilization among adolescents

and adults with comorbid chronic pain and mental health diagnosis. *Pain. 2020 Oct;161(10):2299-2307.*

Gandhi AB, Slejko JF, Villalonga-Olives E, Wickwire EM, **Olopoenia A**, Onukwugha E. Chronic non-cancer pain and its association with healthcare use and costs among individuals with obstructive sleep apnea. *Pain Manag. 2020 Nov;10(6):377-386*

Olopoenia A, Qato D, Fleming S, Simoni-Wastila L. (under review). Trends in gabapentin utilization among Medicare Beneficiaries, 2006-2015. *International Journal of Drug Policy*

Gressler L., Camelo-Castillo W, McRae J., Bajracharya R., **Olopoenia A.,** Qato D. (under review). Assessing multimorbidity in young and middle-aged adults in the United States: prevalence estimates from a nationally representative survey. *American journal of the Board of Family Medicine.*

Olopoenia A, Qato D, Camelo-Castillo W, Adekoya P, Palumbo F, Sera L, Wastila L. (under review). Patterns associated with gabapentin use in combination with opioids and benzodiazepines among disabled Medicare beneficiaries. *Drug and Alcohol Dependence.*

Holmes S, Kuzucan A, **Olopoenia A**, Wastila L. (in-progress). Association of antipsychotic medication use on health care transitions among Medicare nursing home residents.

Olopoenia A, Qato D, Camelo-Castillo W, Adekoya P, Palumbo F, Sera L. (in-progress). Prevalence of and factors associated with concurrent gabapentin, opioids and benzodiazepine utilization among disabled Medicare beneficiaries.

Non-Peer Reviewed Publications

Simoni-Wastila L, Fleming S, **Olopoenia A**, et al. 2020. Maryland State Epidemiologic profile on cannabis use and outcomes. University of Maryland School of Pharmacy

Simoni-Wastila L, Fleming S, Kuzucan A, **Olopoenia A**, et al. 2019. Maryland Epidemiological Profiles on Substance Use And Mental Health Among Alcohol Users in High School. University of Maryland School of Pharmacy

Simoni-Wastila L, Fleming S, Kuzucan, **Olopoenia A**, et al. 2018. Maryland State Epidemiologic profile on substance use and outcomes. University of Maryland School of Pharmacy

PRESENTATIONS

Olopoenia A, Fleming S, Simoni-Wastila L. Trends in gabapentin utilization in the United States, 2004-2016. ICPE Virtual Meeting 2020. Oral Presentation

Olopoenia A, Simoni-Wastila L. Prevalence Of And Factors Associated With Chronic Opioid Utilization Among Commercially Insured Us Adults With Co-morbid Chronic Pain And Mental Health Disorders. ICPE Virtual Meeting 2020. Poster Presentation

Olopoenia A, Simoni-Wastila L. Trends in gabapentin utilization among Medicare Beneficiaries, 2006-2015. AHSR Virtual Meeting 2020. Poster Presentation

Gressler L., Camelo-Castillo W, McRae J., Bajracharya R, **Olopoenia A.,** Qato D. Does the Methodology to Measure Multimorbidity Matter? Assessing Measurement Techniques of Multimorbidity in Nationally Representative Medical Expenditure Panel Survey Data. APHA (November 2019). Poster Presentation, Philadelphia, PA

Olopoenia A, Onukwugha E, Simoni-Wastila L, Camelo-Castillo W, Villalonga-Olives E, Gandhi AB, Slejko J. Patterns of prescription opioid utilization among adolescents and adults with co-morbid chronic pain and mental health diagnosis. Academy Health Meeting (June 2019). Oral Presentation, Behavioral Health services research interest group. Washington, DC

Olopoenia A, Onukwugha E, Simoni-Wastila L, Camelo-Castillo W, Villalonga-Olives E, Gandhi AB, Slejko J. Patterns of prescription opioid utilization among adolescents and adults with co-morbid chronic pain and mental health diagnosis. Academy Health Meeting (June 2019). Poster Presentation, Behavioral Health services research. Washington, DC

Olopoenia A, Camelo-Castillo W, Simoni-Wastila L**.** Concurrent Use Of Gabapentin, Benzodiazepines And Opioids: Prevalence And Risk Factors Among Commercially Insured United States Adults**.** ICPE (August 2019). Poster Presentation, Drug Utilization session. Philadelphia, PA

Olopoenia A, Camelo-Castillo W, Simoni-Wastila L**.** Patterns Of Prescription Opioid Use Among Commercially Insured United States Youth And Young Adults With Co-morbid Chronic Pain And Mental Health Conditions. ICPE (August 2019). Spotlight poster Presentation, Pediatrics session. Philadelphia, PA

Gandhi A., Slejo J., Villalonga-Olives E., **Olopoenia A**., et al. Chronic non-cancer pain and its association with healthcare use and costs among individuals with obstructive sleep apnea. ICPE (August 2019). Poster Presentation, Drug Utilization session. Philadelphia, PA

Olopoenia A, McRae J, Camelo-Castillo W, Qato D. Prescription opioid use among US youth and adults with co-morbid chronic pain and mental health multimorbidity. APHA (November 2018). Poster Presentation, San Francisco, CA

Olopoenia A, DosReis S, Park N, Fleming S, Simoni-Wastila L. Concurrent opioid, gabapentin and benzodiazepine use among adults. AHSR (October 2018). Poster Presentation, Savannah, GA

SKILLS

Statistical software (SAS, R and MAXQDA) and MS Office (Word, Excel, and Power point)

AWARDS

2020	ICPE Student Scholarship 2020
2017 - 2019	University of Maryland School of Pharmacy Dean's list
2018 - 2019	University of Maryland School of Pharmacy Student Travel Award
2011	Howard University Nursing Valedictorian
2011	Howard University Academic Excellence Award
2011	Howard University Compassionate Student Award

PROFESSIONAL MEMBERSHIP

2019 - Present	Academy Health
2018 - Present	American Public Health Association
2017 - Present	International Society for Pharmacoepidemiologists
2017 - Present	Rho Chi Honor society
2011 - Present	District of Colombia Nurses' Association
2010 - Present	Sigma Theta Tau International Honor society- Gamma beta chapter
2010 - Present	Golden Key International Honor society
2007 - Present	National Society of Collegiate scholars

ABSTRACT

Background: Little is known about the patterns, factors, and public health outcomes associated with concurrent utilization of gabapentin, opioids, and benzodiazepines (GABA+OP+BZD)

Objective: To examine the patterns, factors, and public health outcomes associated with concurrent utilization of GABA+OP+BZD among Social Security Disability Insurance (SSDI) eligible beneficiaries.

Methods: Using a 5% sample of 2013-2016 Medicare data, we utilized a retrospective cohort design to examine the following patterns of concurrent utilization: monotherapy, dual therapy, tri-therapy, switching, augmentation, discontinuation, and continuation. Similarly, a retrospective cohort design was utilized to examine the sociodemographic and clinical factors associated with the longest concurrent medication utilization episode, defined based on the overlap of prescriptions for GABA+OP+BZD. We used a nested case control design to examine the association between concurrent utilization of GABA+OP+BZD and adverse outcomes (respiratory depression, substance and opioid related overdose, and adverse drug-related events) among disabled beneficiaries with acute pain [AP], chronic pain [CP], and mental health conditions [MH].

Results: Among disabled beneficiaries, gabapentin initiators were significantly more likely to become dual and tri-therapy users ($p<0.01$) and to augment therapy (50.1%) when compared to opioid (28.7%) and benzodiazepine (38.7%) users; the majority augmented within 2-months after initiating therapy. Back pain [AOR(95%CI): 1.23(1.07-1.41)], chronic pain [1.27 (1.07-1.51)], mental health [1.16 (1.02-1.33)], opioid dose [1.05 (1.03-1.06)] and duration [1.07 (1.06-1.07)], and benzodiazepine duration [1.06 (1.05-1.06)] were positive predictors of having longest concurrent use involving

GABA+OP+BZD. Concurrent GABA+OP+BZD use was associated with increased odds of respiratory depression [AP: 1.35 (1.19-1.52), CP:1.24 (1.11-1.38) and MH: 1.16 (1.02-1.32)], opioid related overdose [AP: 1.43 (1.04-1.98), CP: 1.47 (1.07-2.00) and MH: 1.44 (1.04-2.00)], substance related overdose[AP: 1.77 (1.26-2.50), CP: 1.70 (1.24-2.34) and MH: 1.92 (1.31-2.82)] and adverse drug related events[AP: 1.36 (1.22-1.50), CP: 1.23 (1.10-1.36) and MH: 1.15 (1.02-1.30)].

Conclusion: Our study provides the first evidence of patterns, factors, and outcomes associated with concurrent utilization of GABA+OP+BZD. Given noted adverse outcomes associated with GABA+OP+BZD, it is imperative that the benefits and risks of co-prescribing these medications be examined comprehensively, especially for those at the greatest risk of being prescribed these medications.

Patterns, Factors and Outcomes associated with Gabapentin use in Combination with Opioids and Benzodiazepines among Social Security Disability Insurance (SSDI)-eligible Medicare Beneficiaries

by
Abisola Olopoenia

Dissertation submitted to the faculty of the Graduate School of the
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It truly has taken an entire village to get me through this five-year journey and I would like to thank everyone who has supported and encouraged me along the way. I would like to thank my dissertation committee; firstly, Dr Sera for all her feedback especially related to the clinical implications of my study. I am grateful to Dr Palumbo for the time and effort he put towards providing me feedback regarding policy implications and the larger impact of my study. I am thankful for Dr Qato, not only for her insight on my dissertation as well as multiple collaborative projects but also for being readily available and responsive throughout my entire time in the PHSR department. A big thank you to Dr Camelo-Castillo, for always pushing me to think deeply regarding the methodological details of my study. It has really helped make me a better researcher. Finally, my chair, Dr Wastila, it has been a privilege learning from her. She always believed in me and created a safe space where I always felt comfortable expressing myself. She has been both a mentor and a friend and I am confident that I can always count on her, even beyond PHSR.

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encouragement throughout my academic journey. A special shout out to my sister, Tomi, for letting me gabapentin her out. I would also like to thank my incredible partner, Somidotun Ajibola, who knew absolutely nothing about drug utilization at the start of my program but is now almost a gabapentin expert himself. I would like to thank him for always listening, even when he barely understood what I was saying.

Finally, I would like to dedicate my dissertation to one of my patients. In 2014, prior to joining the PHSR department, I had a patient who died from an opioid-related overdose. Even though, one never gets used to losing patients, this one was different in some ways. The memory of the last time I saw her never left me; the feeling that I was somehow failing her stayed with me even after her death. She had been on opioids and benzodiazepines intermittently for pain and sleep issues and had recently been started on gabapentin for better pain management. When I would visit her, I started to notice how lethargic she began to look following the addition of gabapentin to her regimen. Despite some back and forth with her physicians, I could never convince them that gabapentin was potentially an issue. After she died, I started asking my other patients about gabapentin. When I joined the department, Drs dosReis and Camelo-Castillo gave me the opportunity to expand my interest in gabapentin, through my coursework. My advisor, Dr Wastila believed in the story I wanted to tell and helped me tell it. I am incredibly grateful to share what I believe is a small part of her story through my work.

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LIST OF ABBREVIATIONS

SSDI	Social Security Disability Insurance
GABA only	Gabapentin only
OP only	Opioid only
BZD only	Benzodiazepines only
GABA+OP	Gabapentin and opioids only
GABA+BZD	Gabapentin and benzodiazepines only
GABA+OP+BZD	Gabapentin, opioid and benzodiazepines
AP	Acute Pain
CP	Chronic Pain
MH	Mental Health disorders
AOR	Adjusted Odds Ratio

CHAPTER I: INTRODUCTION

Section A: Specific Aims

Gabapentin is increasingly prescribed as monotherapy or as an adjunct to conventional therapies to treat pain and anxiety.[1-11] Recommendations for gabapentin prescribing vary across distinct populations of individuals with acute pain, chronic pain, and those with mental health conditions.[1-11] Given the high likelihood of gabapentin use among individuals with pain and anxiety, a subpopulation among which opioid and benzodiazepine use also is prevalent, it is important to examine outcomes associated with gabapentin's utilization. While clinical trials have previously indicated that gabapentin has low abuse potential and relatively few side effects, several case series[11-20] and observational studies[21-24] have linked use to somnolence and dizziness. Other recent studies have associated gabapentin use with several adverse drug related events including sedation, euphoria, and psychedelic amphetamine-like effects.[22-23] These side effects can result in impaired cognition and physical impairment. Another serious side effect is gabapentin's potential for respiratory depression when used alone or in combination with opioids, sedatives, and other medications.[21-23] Findings from a recent Canadian study suggest that concurrent use of gabapentin and opioids is associated with increased risk of respiratory depression induced opioid-related death.[21]

Despite the increased likelihood of gabapentin use among opioid and benzodiazepine users, little is known about the adverse consequences of concurrent tri-therapy with all three medication classes. The ***primary goal*** of our study is to examine patterns of use, factors and adverse outcomes associated with gabapentin alone and in combination with opioids and benzodiazepines among Social Security Disability

Insurance (SSDI) eligible Medicare beneficiaries. This specific population provides access to a cohort of individuals who, due to disability, are more likely to be prescribed gabapentin, benzodiazepines, and/or opioids. Further, since patterns, factors and responses associated with use of these medications potentially differ across indications our analyses were completed in three sub-cohorts. We accomplished the following ***specific aims*** using a nationally representative 5% random sample of SSDI beneficiaries in the 2013-2016 Chronic Condition Data Warehouse (CCW) Medicare data files.

Aim 1) Describe and compare the patterns of gabapentin, opioids, and benzodiazepine use among SSDI eligible Medicare beneficiaries overall, and those with: 1) acute pain; 2) chronic pain; and 3) mental health conditions;

Aim 2) Describe and compare factors associated with concurrent tri-therapy (gabapentin, opioids, and benzodiazepines), dual therapy (gabapentin and opioids; gabapentin and benzodiazepines), and single therapy (gabapentin; opioids; benzodiazepines) among SSDI eligible Medicare beneficiaries overall

Aim 3) Quantify the associations between concurrent therapy (involving gabapentin, opioids, and benzodiazepines) and public health outcomes (respiratory depression events, opioid-related overdose events, substance-related overdose events, and adverse drug related events) among SSDI eligible Medicare beneficiaries with: 1) acute pain; 2) chronic pain; and 3) mental health conditions. We hypothesize that Medicare disabled beneficiaries with acute pain, chronic pain or mental health conditions with concurrent therapy will have higher odds of adverse public health outcomes when compared to their peers with single therapy.

Using rigorous methodological approaches applied to a nationally representative data, the study will provide evidence essential to understanding the impact of concurrent gabapentin therapy with opioids and benzodiazepines. Furthermore, given the widespread and growing use of gabapentin in the United States, a comprehensive examination of potential outcomes associated with its use will inform prescribing patterns across the nation. If supported, our hypothesis suggests that policies which attempt to address the opioid epidemic must target individuals with pain and mental health conditions. These individuals represent a vulnerable population among whom concurrent therapy with gabapentin, opioids, and benzodiazepines is not only potentially higher but may also be associated with increased adverse outcomes.

Section B: Rationale and Significance

The opioid epidemic is one of the most significant public health concerns within the United States. Efforts to curb this growing crisis have led to increased prescribing of medications which due to cost, perceived safe profile, and uncontrolled status at the Federal level, are often viewed as safer alternatives to opioids.[1,2] Gabapentin is one of such medications. In 2016, gabapentin was the tenth most commonly prescribed medication in the United States.[1,2] At the national level, although gabapentin is only FDA approved for treatment of partial seizures and post herpetic neuralgia, it is increasingly prescribed for a variety of off-label conditions including: neuropathic pain, osteoarthritis, fibromyalgia, periodic limb movement disorders of sleep, anxiety disorders, other forms of chronic pain, and psychiatric conditions.[1-11] Although gabapentin has been previously perceived to have a benign profile, emerging evidence from several case reports[11-20] and

some observational studies[21-24] suggest that gabapentin's use is associated with somnolence, lethargy and respiratory depression.

This evidence is particularly worrisome because, given the widespread prescribing of gabapentin, the likelihood of gabapentin prescriptions among individuals prescribed other CNS depressants, such as opioids and benzodiazepines, is high. *Despite increased potential of co-prescription of gabapentin, opioids, and benzodiazepines, little is known about the patterns of co-prescribing including how treatment trajectories lead to co-prescriptions for these medications and whether 1) gabapentin is added to reduce opioid or benzodiazepine use among concurrent users, or 2) it is prescribed after poor therapeutic response to opioids and/or benzodiazepines. Finally, if gabapentin is typically prescribed after opioids and benzodiazepines, does the addition of gabapentin then result in changes in the patterns of opioid and benzodiazepine use?* In addition to lack of research on patterns of co-use, there have been no in-depth explorations of factors associated with concurrent therapy of all three medications. The few studies that have examined factors associated with concurrent therapy have focused on those associated with potential abuse or misuse. *Little is known about the overall prevalence of concurrent gabapentin, opioids, and/or benzodiazepines. In addition, no studies have examined specific sociodemographic and clinical factors associated with receipt of one or more of these medications and how these factors may differ depending on the specific medications and/or combinations of medications: gabapentin/opioids, gabapentin/benzodiazepines, and gabapentin/opioids/benzodiazepines.* While several studies have focused on the adverse consequences of opioids alone and in combination with benzodiazepines[25-31], only few studies have examined outcomes associated with gabapentin and opioid

utilization.[21-22,24] *Further, there are currently no studies that have explored the potential outcomes associated with concurrent use of gabapentin, opioids, and benzodiazepines.*

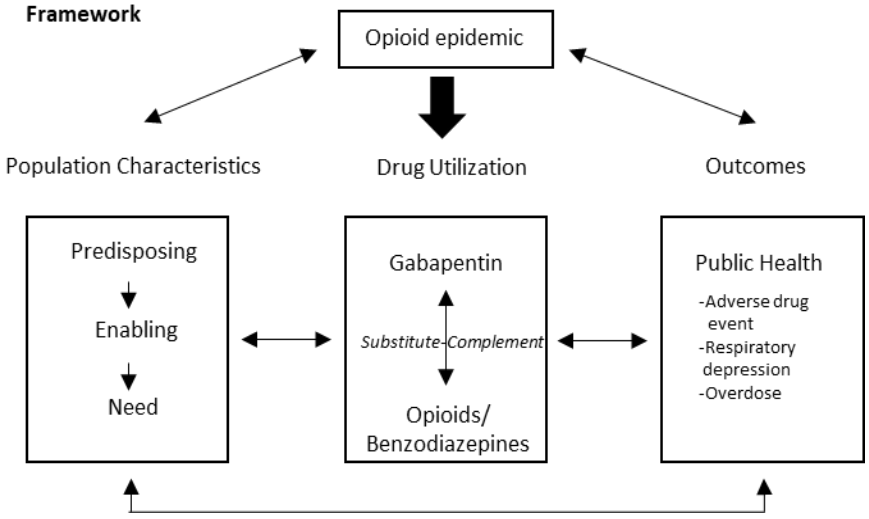
Through addressing the three study aims, our study will address knowledge gaps in the use of and outcomes associated with gabapentin, alone and concomitantly with opioids and/or benzodiazepines. By utilizing a SSDI eligible population, we capture a population of individuals who, due to disability, have high rates of pain and psychiatric diagnosis and are potentially, more likely to be prescribed any or all of these medication classes. [30,32]Thus, this population is a high-risk group among whom prescription analgesic and psychotropic use with their related outcomes are observable. A comprehensive examination of patterns and factors associated with concurrent use is necessary to identify individuals at most risk for adverse drug and respiratory-related outcomes. Further, the in-depth exploration of potential adverse outcomes —adverse drug related events, respiratory depression, substance and opioid related overdose —will provide better understanding of the individual and public health impacts of commonly co-prescribed medications.

Section C: Conceptual Framework

The conceptual framework which guides our study is based on Anderson's Behavioral Model of Health Services Use **(Figure 1.)** Developed in 1968 by a US medical sociologist and health services researcher, Anderson's Behavioral Health model has been widely utilized in various studies involving substance utilization.[52] This model suggests that behavior and associated outcomes are a function of three collective domains of population characteristics.[52] Predisposing factors are demographic factors, such as age

and gender, which predispose individuals to seek care. Enabling factors include income, insurance, and other determinants of access to care. Need factors are co-morbidities and overall health factors which influence an individual's health care utilization. We modified Anderson's Behavioral model by incorporating drug utilization measures; our study is based on the conceptualization that a bidirectional relationship exists between the population characteristics and the different patterns of drug utilization. The model further posits there is a substitute-complement relationship between gabapentin, opioids, and benzodiazepines. We hypothesize that, depending on the substitute-complement nature of drug utilization, patterns observed outcomes may vary. Specifically, individuals with complement use of all medications will potentially have higher odds of adverse outcomes.

Figure 1. Conceptual Framework



CHAPTER II. LITERATURE REVIEW

Section A: Patterns of gabapentin, opioid, and benzodiazepine utilization

Previous studies that have examined gabapentin utilization have suggested that co-prescription of gabapentin, opioids, and benzodiazepines is common. One study conducted by Michael Johansen using Medical Expenditure Panel survey (MEPS) data examined the use of gabapentin in the United States between 2002 and 2015.[33] This study noted that use of gabapentinoids tripled during this time period, and was concentrated among individuals with opioid and benzodiazepine prescriptions.[33] This finding is consistent with results from a toxicology study where Peterson et al. noted that 7% of driving impairment cases tested positive for solely gabapentin; the rest of the gabapentin positive samples involved benzodiazepines (44%), opioids (43%), antidepressants (43%), other CNS depressants (25%), cannabinoids (15%), stimulants (11%) and, ethanol (6%).[34]

Several case reports and some controlled trials have examined the utilization of gabapentin as monotherapy or adjunctive therapy in the management of chronic pain and psychiatric conditions. The studies that have explored the efficacy of gabapentin in the treatment of psychiatric conditions have provided mixed results. While some studies suggest there is evidence of benefit when gabapentin is prescribed for social phobia, insomnia, posttraumatic stress disorder and generalized anxiety disorder, other studies have indicated no benefit when prescribed in bipolar disorder, cocaine dependence, and obsessive-compulsive disorder.[3-10] The most promising and consistent evidence of benefit has been as a mono-therapeutic or adjunctive agent for management of generalized anxiety disorder, a sub-population among whom concomitant psychiatric medications,

especially benzodiazepines was common.[3,6-7] Despite this suggested evidence of high co-occurrence of gabapentin and benzodiazepine utilization, only one study has examined patterns of benzodiazepine utilization in combination with gabapentin. In this Norwegian study, Sandvik et al. examined the impact of initiation of gabapentin on benzodiazepine utilization.[35] They noted that in the 182 days following gabapentin initiation, greater than 70% of prior benzodiazepine users continued benzodiazepine use and 14-21% of prior non benzodiazepine users newly initiated benzodiazepine use.[35] Furthermore, the percentage of benzodiazepine users before (68.1%) and after (78.4%) gabapentin initiation was highest among those with a psychiatric indication for gabapentin.[35]

Studies that have examined the efficacy of gabapentin for pain and pain related conditions have also yielded mixed results.[1-2,36-40] While the majority of trials and case reports have shown little to no evidence of benefit when gabapentin is prescribed for migraine prophylaxis, low back pain and post-operative pain, the most consistent evidence of benefit has been noted for gabapentin in the management of neuropathic pain and restless leg syndrome.[36,38-39] Evidence regarding other pain-related conditions such as fibromyalgia and osteoarthritis is inconsistent.[36-37] No studies have examined the role gabapentin plays in the management of these pain-related conditions—much remains unclear about whether gabapentin is prescribed as monotherapy after opioid failure or whether it is prescribed in combination with opioids as an adjunct agent, perhaps in some cases to reduce opioid dosing.

The likelihood of co-prescription of opioids and benzodiazepines with gabapentin is high, particularly among the Medicare-SSDI eligible population. In fact, in an observational retrospective study conducted to examine the rate of concurrent opioid and

benzodiazepine use among the Medicare population, the CDC noted that the rate of concurrent opioid and benzodiazepine use among the disabled was almost twice that of the non-disabled (36.6% vs. 19.5%).[30] Despite this high concurrency of opioids with benzodiazepines in this population and the further potential for gabapentin use associated with pain and psychiatric disorders common within the disabled population, little is known about the overall patterns of gabapentin, opioid, and benzodiazepine utilization.[41] Interpretation of findings from the few studies that have examined the utilization of gabapentin with opioids and benzodiazepines independently have been limited by: insufficient follow up, heterogeneous populations across studies, inconsistent dosing of medications across studies, a lack of appropriate controls and inconsistent reporting of outcomes across studies. *Our study addresses many of these gaps by focusing on an at-risk disabled population and utilize a methodologically rigorous approach to tease out patterns in the utilization of gabapentin, opioids and benzodiazepines. Furthermore, we examine patterns of utilization among clinically distinct subgroups of individuals (with acute pain, chronic pain, and mental health conditions) for whom these patterns may vary based on recommended guidelines for treatment.*

Section B: Factors associated with concurrent tri, dual and single therapy

Much of the available evidence regarding combination use of opioids and other sedating drugs have explored potential factors related to concurrent opioid and benzodiazepine utilization.[30,31] Results from these studies suggest that concomitant opioid and benzodiazepine use is more common among individuals diagnosed with pain, chronic obstructive pulmonary disease, substance use disorders, depression, anxiety, and other

psychiatric conditions.[30,31] Findings from studies conducted within the Medicare population have yielded similar results. Hernandez et al. noted that white dually-eligible disabled and low-income subsidy eligible beneficiaries were significantly more likely to be prescribed opioids and benzodiazepines concurrently.[42] They also noted that depression, anxiety and the number of prescribers of opioids and benzodiazepines were associated with increasing overlap in the days of opioid and benzodiazepine prescriptions.[42] Similarly, a 2016 report by CMS using Medicare data found that among 12, 753,301 opioid users in 2015, 24% were also concurrent benzodiazepine users. Of these concurrent opioid and benzodiazepine users, 68% had multiple concurrent use episodes and among those with multiple episodes, over 50% had greater than 120 days of concurrent opioid and benzodiazepine use.[30]

Much less is known about the factors associated with concurrent use of gabapentin/opioids, gabapentin/benzodiazepines, and gabapentin/opioids/ benzodiazepines. Most studies that have examined gabapentin and opioids have typically focused on factors associated with potential abuse or misuse.[3-11.43] Alyssa Peckham and colleagues examined the predictors of gabapentin overuse with and without concomitant opioids.[44] They noted that the strongest predictors of sustained overuse (defined as three or more rolling quarters exceeding dosage thresholds [gabapentin > 3600mg/day, opioids >50 Morphine Milligram equivalent[MMEs]]) were similar among gabapentin and opioid concomitant users and gabapentin only users and included: history of detoxification, depression, anxiety, bipolar disorder, addiction, and benzodiazepine use.[44] However, although pain predicted sustained overuse among concomitant gabapentin and opioid users, it was not a predictor among gabapentin only users.[44] Findings from this study

support previously documented high use of gabapentin among opioid and benzodiazepine users as well as those with mental health conditions. In addition, it supports the hypothesis that sociodemographic and clinical factors may differ depending on the specific medication utilization category (tri-therapy, dual therapy and single therapy.)

While there is strong evidence that gabapentin use is high among both opioid and benzodiazepine users and further some evidence suggesting factors associated with the receipt of any or all of these medications may vary, little is known about the specific sociodemographic and clinical factors associated with receipt of one or more of these medications —and how these factors may change based on specific combination patterns. An in-depth examination of these factors is not only important to understand prescribing patterns within the nation but is also essential to identify a cohort of individuals at high risk of receiving a combination of depressant drugs. Proper identification of this cohort will be pertinent to cohort selection in focused research studies which will examine outcomes associated with utilization of gabapentin, opioids, and benzodiazepines. *Our study addressed these gaps by focusing on factors associated with any concurrent use, rather than those specifically related to abuse, misuse, or dependence. Furthermore, our study is the first study to tease out specific factors that may differ between the patterns of utilization previously described. Baseline utilization of higher combinations of medications may vary within sub-cohorts of the population; hence, we examined factors associated with concurrent tri-therapy, dual therapy, and single therapy overall, and within subgroups of individuals diagnosed with acute pain, chronic pain, and mental health conditions.*

Section C: Adverse outcomes associated with concurrent therapy

Drug related overdose deaths nearly tripled between 1999 and 2015; in 2015 alone, drug overdoses involving opioids accounted for 33,091 deaths, half of which involved prescription opioids.[45] Focused attention has been devoted to the increased risk of opioid related overdose associated with concurrent benzodiazepine use among opioid users.[30-31,42,46] In the Medicare population specifically, the risk of overdose associated with concurrent opioid and benzodiazepine use is more than five times higher in the first ninety days of concomitant use.[42] This documented increased risk of overdose led to the FDA issuing a black box warning on prescription opioids and benzodiazepines in 2016.

While much attention has been focused on outcomes associated with opioid and benzodiazepine use, until recently very little was known about outcomes associated with concomitant gabapentin and opioid use. Much of the initial evidence regarding these outcomes were documented in case reports where symptoms of CNS depression and sedation were reported among gabapentin users alone and those who potentially also used opioids.[11-16,20] These case reports involved individual cases and were significantly limited by the lack of controls. Evidence regarding outcomes associated with gabapentin utilization have also been documented in toxicology data.[17-19, 34] Slavova et al. documented the prevalence of gabapentin among drug overdose decedents in five geographically diverse jurisdictions within the United States—Kentucky, Maricopa county in Arizona, North Carolina, West Virginia and Northeast Tennessee.[18] They noted that although fatal drug overdose due to gabapentin alone was fairly low in all regions, 26% of all opioid related overdose deaths involved gabapentin.[18] The prevalence of gabapentin in these opioid involved deaths varied across jurisdiction: 4% in Northeast

Tennessee, 9% in Maricopa county, 26% in West Virginia, 26% in North Carolina, and 42% in Kentucky.[18]Another study completed using toxicology data in Finland noted similar findings.[19] Poisoning cases involving only gabapentin accounted for 4.7% of all gabapentin cases whereas opioids were noted in 87.5% of all gabapentin poisoning cases.[19] Evidence from toxicology data is certainly important; however, interpretations from these studies are vastly limited by significant underreporting (gabapentin is absent from routine postmortem testing) in the majority of states across the United States.

More recently, several well-designed epidemiologic studies have examined outcomes associated with concurrent gabapentin and opioid utilization.[21-24] These studies have suggested adverse outcomes including: respiratory depression, adverse drug events, opioid related overdoses, increased health care utilization are more common among individuals with concomitant use of gabapentin and opioids.[21-24] In one of such studies, a Canadian population-based case control study, Gomes et al. investigated the risk of opioid related death among the publicly insured. They found the rate of unintentional fatal opioid overdose was 49% higher among individuals with concomitant opioid and gabapentin use.[21] Furthermore, individuals with fatal opioid overdose were more likely to have been exposed to benzodiazepines in the 120 days preceding the overdose.[21] Within the United States, Alyssa Peckham et al. examined the odds of all cause and adverse drug-related medical events associated with overuse of gabapentin and/or opioid medications among a commercially insured population.[22] Adverse drug events included: diagnosed adverse drug reactions, addiction or facility approved detoxification, altered mental states (diagnosis of altered mental state, anxiety, catatonia, euphoria, insomnia and sedation), ataxia, blurred vision, convulsions, extrapyramidal symptoms (dystonia,

abnormal movement disorders and drug induced tremors), nystagmus, palpitations, slurred speech, tachycardia, respiratory depression and weakness/syncope.[22] Results from the study suggest that even without the inclusion of overuse, concomitant gabapentin and opioid use was associated with increased odds of both all cause (OR: 1.98 95%CI:1.84-2.15) and adverse drug-related (OR: 1.65 95%CI:1.46-1.85) inpatient utilization.[22] In addition, the odds of hospitalization and emergency room visits for respiratory depression were doubled and quadrupled among concomitant gabapentin/opioid users and concomitant gabapentin/opioid users with overuse respectively.[22] One plausible mechanism of action underlying the increased risk of adverse outcomes noted in previous studies is the increased risk of gabapentin potentiation of opioid analgesia through a shared physiologic pathway.[47-50] Increased potentiation of opioids may also occur due to a decrease in renal clearance of gabapentin when it is used concurrently with opioids.[50]

In response to emerging evidence, several states have adopted regulation, legislation and monitoring requirements for gabapentin. As of December 2020, Kentucky, Michigan and Tennessee remain the only states where gabapentin is classified as a schedule V medication; however, seven other states require mandated gabapentin reporting to prescription drug monitoring programs.[51] Despite the increasing awareness being created regarding gabapentin, little is known about adverse consequences associated with gabapentin when used with other CNS depressants such as benzodiazepines. In addition, despite the increased likelihood for prescribing all three medications, little is known about the additional impact of benzodiazepines on gabapentin and opioid utilization. The previous study that examined overdoses associated with gabapentin and opioid focused only on fatal overdoses. Since prior non-fatal

overdose increases the risk of future overdose, a comprehensive examination of all overdose events—both fatal and non-fatal— is essential to quantifying the risk associated with these medications. *Our study addresses these identified gaps in the literature by incorporating measures of overall substance related overdoses as well as opioid specific overdose events. Furthermore, we will incorporate non-fatal overdoses, a measure not previously captured. We will utilize a methodologically rigorous design which allows for proper control of potential confounders; thus, limiting any potential residual factors which may influence our findings. Finally, our study will also incorporate several approaches to address any potential biases including expanding definitions of our exposure and outcome variables.*

CHAPTER III. METHODOLOGY

Section A: Overall objective

The overall objective of this study is to examine the patterns, factors and outcomes associated with gabapentin, opioid and benzodiazepine utilization in the Medicare disabled population.

Section B: Specific study aims

To achieve this overall objective, we conducted a series of analyses to address these three specific aims:

- **Aim 1)** Describe and compare the patterns of gabapentin, opioids, and benzodiazepine use among SSDI eligible Medicare beneficiaries overall, and those with: 1) acute pain 2) chronic pain; and 3) mental health conditions
- **Aim 2)** Describe and compare factors associated with concurrent tri-therapy (gabapentin, opioids, and benzodiazepines), dual therapy (gabapentin and opioids; gabapentin and benzodiazepines), and single therapy (gabapentin; opioids; benzodiazepines) among SSDI eligible Medicare beneficiaries
- **Aim 3)** Quantify the associations between concurrent therapy (involving gabapentin, opioids, and benzodiazepines) and public health outcomes (respiratory depression events, opioid and substance-related overdose events, and adverse drug related events) among SSDI eligible Medicare beneficiaries with: 1) acute pain; 2) chronic pain; and 3) mental health conditions.

Results from **Aim 1** describe the specific patterns associated with co-prescriptions of gabapentin, opioids, and benzodiazepines among Medicare SSDI eligible beneficiaries.

Identification of these patterns is crucial to understanding treatment trajectories that lead to co-prescriptions for all three medications. Results from **Aim 2** describe and compare sociodemographic and clinical characteristics associated with receipt of one or more combinations of these medications—gabapentin, opioids, benzodiazepines and how these factors may change based on specific medication combination patterns. Results from **Aim 3** estimate and compare the association between concurrent use of these medications and adverse outcomes including respiratory depression, opioid related overdose, substance related overdose and adverse drug related events.

Section C: Methods

Section C.1. Data Source

We utilized a 5% random sample of 2013-2015 CCW Medicare data files including Medicare administrative data obtained from the Center for Medicare & Medicaid Services (CMS) for Aim 1 and Aim 2. For Aim 3, we included an additional year of data and conducted analyses using 2013-2016 CCW data files. CCW data includes the Part D prescription drug files, Part A (inpatient) and Part B(outpatient) files, and the Master Beneficiary Summary File (MBSF). We obtained basic demographic information such as age, sex, race, original reason for entitlement, and indicators for enrollment from the MBSF. Diagnostic codes for inpatient and outpatient health care utilization were obtained from Medicare Parts A and B files, and comprehensive prescription drug information will be derived from Medicare Part D files. For all analyses we focused on fee for service (FFS) claims since we require diagnostic data for the majority of the aims.

Section C.2. Cohorts

Medicare FFS beneficiaries who met the following criteria were included in the sample: 1) SSDI eligibility, defined using the original reason for entitlement in Medicare flag. SSDI-eligible beneficiaries will include those younger than 65 years old and those 65 years old and older but who originally entered Medicare based on disability;
2) continuously enrolled in Medicare Parts A, B and D during the study period. The specific month requirement for continuous enrollment will depend on each specific aim. For Aim 1, we will require continuous Medicare Part A & B eligibility in the 6-months prior to index medication receipt and Medicare part D eligibility in the 6-months after index medication receipt. For Aim 2, we will require continuous Medicare Parts A, B, and D eligibility in the 6-months prior to observed index concurrency episode. For Aim 3, we will require continuous Medicare Part A, B, and D eligibility in the 6-months prior to and 12-months following cohort entry. Other exclusion criteria will be discussed further under the study design and analytic approach specific to each aim.

Sub-cohort

In sub-cohort analysis, we examined **Aim 1 and Aim 3** among sub-cohorts of beneficiaries with a claim for i) acute pain, ii) chronic pain, or iii) a mental health condition. Due to the wide availability of gabapentin and potential for confounding by indication, analyses for Aim 1 and Aim 3 were completed separately for the three sub-cohorts of interest (acute pain, chronic pain, and mental health populations.) These sub-cohorts of individuals diagnosed with acute pain, chronic pain, and mental health disorders were identified using International Classification of Disease, Ninth and Tenth

Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes. Based on previous definitions, chronic pain included diagnostic claims for back pain, neck pain, arthritis/joint pain, chronic pain, and headache/migraine,[53-56] conditions which are considered the most persistent chronic pain conditions worldwide.[57] We modified this definition of chronic pain to include neuropathic pain because a large proportion of gabapentin use is related to neuropathic pain.

We used a modified definition of acute pain to capture temporomandibular joint pain, extremity pain, abdominal pain, chest pain, kidney pain, pelvic pain, fractures, fibromyalgia, sprain, and restless leg syndrome.[53-54] We incorporated mental health categories previously defined by the Agency for Healthcare Research and Quality (AHRQ), including mood disorders, personality disorders, adjustment disorders, depression, schizophrenia, anxiety disorders, attention deficit hyperactive disorder (ADHD), substance use disorders, and miscellaneous disorders such as sleep and eating disorders.[54-55,58-59] **(See Appendix A for specific definitions of these conditions.)**

Section C.3. Aim 1 methods

Additional cohort criteria

We included disabled beneficiaries who utilized at least one medication of interest during the study period. The index date was defined as the date of the earliest prescription fill for a gabapentin, opioid, or benzodiazepine. We excluded beneficiaries who received more than one medication class on the index date because their baseline treatment regimen and disease severity potentially differ from those who initiated on a single medication class. Further, we were specifically interested in how individuals initiated specific therapies

rather than how they were maintained on those therapies. Prescriptions for buprenorphine were excluded from opioid calculations because buprenorphine is not FDA approved for the treatment of pain in the United States. To ensure that we had access to beneficiaries' health care utilization and prescription drug information, we excluded individuals without continuous Parts A and B coverage in the 6 months before the index date and those without Part D coverage in the 6-month post-index period. We also excluded beneficiaries with Medicare Advantage in the 6-month pre-index period. Because patterns of prescription drug utilization among beneficiaries with cancer or hospice may differ from those of the general population, especially for pain medications, we also excluded individuals with evidence of cancer or hospice benefits.[53,55-56]

Study Design

We utilized a retrospective cohort design to examine the patterns of gabapentin, opioid and benzodiazepine utilization following the index date, date of receipt of initial therapy (**Figure 2**.) For the sub-cohort analysis, the index date is the date of initial therapy following a diagnosis of acute pain, chronic pain or mental health condition. (**Figure 2.1)**.

Figure 2. SSDI beneficiaries overall

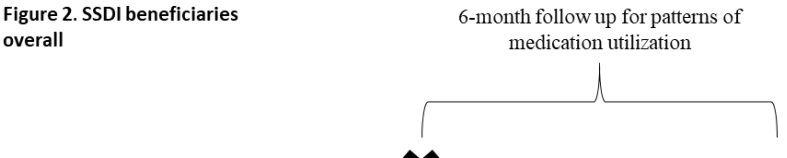
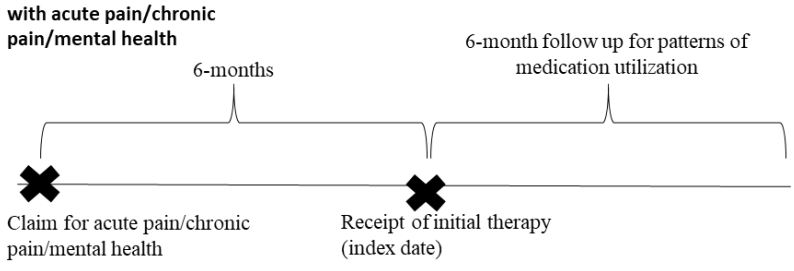


Figure 2.1 SSDI beneficiaries with acute pain/chronic pain/mental health



Measures

Main outcome

The following patterns were examined in the 6-month period after the index date: monotherapy, dual therapy, tri-therapy, augmentation, switching, discontinuation, time to switch, and time to augmentation. Monotherapy was defined as the utilization of only one medication class from initiation of index therapy through follow-up. Dual therapy was defined as the utilization of two medication classes from initial therapy through follow-up, and tri-therapy was defined as utilization of all three medication classes during follow-up. We defined discontinuation as a gap of 60 days or more between the end of the previous prescription and the start of the next prescription (for the same medication) or no subsequent medication fills in the follow-up period.[60-61] Discontinuation was assessed only among monotherapy users.

Augmentation was defined as a prescription for a different medication class in addition to prescription for initial medication during the follow-up period.[60-61] Switching referred to a prescription for a different medication class and no subsequent fills for the initial medication in the follow-up period.[60-61] Time to switch referred to the number of months between the start of initial therapy and date of first switch among dual therapy and tri-therapy users.[60-61] Time to augmentation was defined as the number of months between initial therapy and the start of the first and second augmented therapy among dual and tri-therapy users, respectively.[60-61]

Analytic Plan

Patterns of gabapentin, opioid, and benzodiazepine utilization among disabled Medicare beneficiaries.

We calculated the proportions of gabapentin, opioid, or benzodiazepine initiators with monotherapy, dual therapy, and tri-therapy, as well as the proportions of initiators who switched, discontinued, or augmented therapy. We conducted bivariate analyses with chi-square tests to examine the association between initial therapy and the patterns examined. Among those who switched or augmented, subsequent therapy was also described. We generated cumulative distribution function curves to describe time to augmentation and switching.

Gabapentin initiators

Proportion of monotherapy users= (# of unique beneficiaries who used only gabapentin)÷(# of gabapentin initiators)

Proportion of dual therapy users= (# of unique beneficiaries who used gabapentin and either opioids or benzodiazepines)÷(# of gabapentin initiators)

Proportion of tri-therapy users= (# of unique beneficiaries who used gabapentin, benzodiazepines, and opioids)÷(# of gabapentin initiators)

Proportion of augmenters= (# of unique beneficiaries who continued gabapentin after adding on opioids or benzodiazepines)÷(# of gabapentin initiators)

Proportion of switchers= (# of unique beneficiaries who switched from gabapentin to opioids or benzodiazepines)÷(# of gabapentin initiators)

Proportion of discontinuers= (# of unique monotherapy users who discontinued gabapentin)÷(# of gabapentin initiators)

Opioid initiators

Proportion of monotherapy users= (# of unique beneficiaries who used only opioids)÷(# of opioid initiators)

Proportion of dual therapy users= (# of unique beneficiaries who used opioids and either gabapentin or benzodiazepines)÷(# of opioid initiators)

Proportion of tri-therapy users= (# of unique beneficiaries who used opioids, benzodiazepines, and gabapentin)÷(# of opioid initiators)

Proportion of augmenters= (# of unique beneficiaries who continued opioids after adding on gabapentin or benzodiazepines)÷(# of opioid initiators)

Proportion of switchers= (# of unique beneficiaries who switched from opioids to gabapentin or benzodiazepines)÷(# of opioid initiators)

Proportion of discontinuers= (# of unique monotherapy users who discontinued opioid)÷(# of opioid initiators)

Benzodiazepine initiators

Proportion of monotherapy users= (# of unique beneficiaries who used only benzodiazepines)÷(# of benzodiazepine initiators)

Proportion of dual therapy users= (# of unique beneficiaries who used benzodiazepines and either opioids or gabapentin)÷(# of benzodiazepine initiators)

Proportion of tri-therapy users= (# of unique beneficiaries who used gabapentin, benzodiazepines, and opioids)÷(# of benzodiazepine initiators)

Proportion of augmenters= (# of unique beneficiaries who continued benzodiazepines after adding on opioids or gabapentin)÷(# of benzodiazepine initiators)

Proportion of switchers= (# of unique beneficiaries who switched from benzodiazepines to gabapentin or opioids)÷(# of benzodiazepines initiators)

Proportion of discontinuers= (# of unique monotherapy users who discontinued benzodiazepines)÷(# of benzodiazepine initiators)

Patterns were described overall and across our three sub-cohorts of interest. In secondary analyses, we calculated the proportions of new gabapentin initiators who continued use of opioids and/or benzodiazepines after gabapentin initiation and the proportion of these initiators who newly initiated opioids and/or benzodiazepines in the follow-up period. A two-sided $p<0.05$ was considered statistically significant. All analyses were conducted with SAS v. 9.4 (SAS, Cary, NC).

Section C.4. Aim 2 methods

Additional cohort criteria

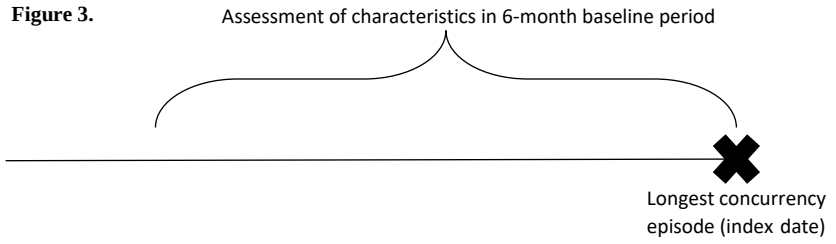
To estimate the prevalence of gabapentin, opioid, and benzodiazepine use, we included all disabled beneficiaries who received at least one medication of interest and had continuous Part D eligibility in the 6-month period after their earliest prescription. Because patterns of prescription medication utilization, especially for pain-related conditions, may differ among those with terminal conditions, we excluded beneficiaries

with evidence of cancer and/or hospice benefits.[53,55-56] To identify factors associated with concurrent therapy, we identified the date of the longest concurrent medication utilization (index date) and excluded beneficiaries with Medicare Advantage and those without continuous Parts A, B, and D eligibility in the 6-month pre-index period.

Study design

Similar to Aim 1, we utilized a retrospective cohort design to examine factors associated with the longest concurrent use category (**Figure 3)**. For individuals with multiple concurrency episodes of the same length, we utilized the first of these multiple episodes as the index date. In sensitivity analyses, we compared factors associated with any concurrency episode to those identified for the longest concurrency episode.

Figure 3.



Measures

Outcome

The primary outcome is the longest concurrency episode for our medications of interest. We examined daily gabapentin, opioid and benzodiazepine exposure in the 6-month period following beneficiaries' earliest prescription for either medication. For each prescription in the period following initial therapy, we defined intervals starting the day of prescription fill through the last day based on number of days supplied provided in that

prescription. The total number of prescription days of overlap across all prescription medications was quantified and used to define the longest concurrency episode for each beneficiary. Beneficiaries whose longest concurrency episode involved prescriptions for all three medications were categorized as GABA+OP+BZD users. Those beneficiaries whose longest concurrency episode involved prescriptions for gabapentin and opioids only or gabapentin and benzodiazepines only were grouped in the GABA+OP and GABA+BZD category, respectively. The remainder of beneficiaries whose longest episodes involved a single medication were categorized as GABA only, OP only, and BZD only, depending on the specific medication involved. Since our analysis was primarily focused on concomitant gabapentin use and because much of the literature has focused on factors associated with concurrent opioid and benzodiazepine utilization, concurrent opioid and benzodiazepine users were not included in our analyses.

Independent variables

Primary independent variables included socio-demographics, health insurance, clinical, and pharmacologic factors. These factors were examined in the 6-month period prior to the longest concurrency episode. Sociodemographic factors included age at baseline (<65 and 65+), sex (male and female), and race/ethnicity (white, black, hispanic, and other). Health insurance factors included Medicaid-Medicare dual eligibility status categorized

Socio-demographic, health insurance, clinical and pharmacologic variables	
Predisposing	**Age** (<65, 65+) **Gender** (males and females) **Race/ethnicity** (white, black, hispanic and other)
Enabling	**Medicaid-Medicare dual eligibility status** (yes/no)
Need	**Co-morbidities**: co-morbidity count including: Chronic lung disease, diabetes, hypertension, liver disease, connective tissue disease, cerebrovascular disease, peripheral vascular disease, peptic ulcer disease, renal disease, seizures, dementia, myocardial infarction, congestive heart failure and hypothyroidism. Prior history of substance use disorder (alcohol, opioid and non-opioid), acute pain, chronic pain, and mental health conditions **Disease severity**: Past year health care utilization **Pharmacologic factors**: opioids, benzodiazepines, gabapentin, pregabalin, non-benzodiazepine sedatives/hypnotics, muscle relaxants, opioid dose calculated in morphine milligram equivalents (MME) and gabapentin dose

Table III.A

as a binary (yes/no) measure. In Aim 2 analyses, chronic pain, acute pain and mental health conditions were included as independent variables rather than as sub-cohort measures. The definition of these variables have been previously described in **Appendix A.** A count of up to 14 other co-morbidities (chronic lung disease, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, connective tissue disease, cerebrovascular disease, peptic ulcer disease, liver disease, renal disease, hypertension, hypothyroidism, seizure disorder and dementia), which potentially influence medication utilization were also included as clinical factors in our analyses. Clinical conditions were ascertained using International Classification of Disease, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes for at least one inpatient or two outpatient visits **(See Appendix B for relevant ICD-9-CM and ICD-10-CM codes**.)

Prescription data on gabapentin, opioids, benzodiazepines, pregabalin, non-benzodiazepine sedatives, and muscle relaxants utilized in the 6-month pre-index period was collected. Muscle relaxants and pregabalin were examined because they are typically used as adjunct therapy in pain management. Because prior gabapentin, opioids and benzodiazepine use may be related to concurrent use of these medications, we also examined the dose and duration of gabapentin, opioids, and benzodiazepines received in

the pre-index period. The average daily dose of opioids was calculated by converting the daily dose of each opioid prescription in the pre-index period into morphine milligram equivalent (MME) using conversion factors available in the literature[62] and then dividing the MME of all opioids utilized in this period by the total days supplied.[53,55-56] Since oral formulations of buprenorphine are not approved by the FDA for pain management, these prescriptions were excluded from all opioid calculations. Similarly, the average daily dose of all gabapentin prescriptions was calculated by summing the dose of all gabapentin prescriptions and dividing by the days supplied. The duration of gabapentin, opioids, and benzodiazepines used in the pre-index period was categorized as chronic for medications used for 90 days and more and as acute for those used for less than 90 days. We used Anderson's Behavioral Model to categorize these factors (**Table III.A.)**

Analytic Plan

Factors associated with concurrent tri-therapy (GABA+OP+BZD), dual therapy (GABA+OP; GABA+BZD), and single therapy (GABA only; OP only; BZD only). Among disabled beneficiaries who used at least one medication during the 6-month period after their earliest prescription, we calculated the proportions of individuals who used gabapentin and opioids, gabapentin and benzodiazepines, and gabapentin, opioids, and benzodiazepines. Of the beneficiaries who used multiple therapies during follow-up, we also calculated the proportions of those who used these medications concurrently for at least one day.

Proportion of gabapentin and opioids= (# of unique beneficiaries who used gabapentin and opioids)÷(# of unique beneficiaries who used any opioids)

Proportion of gabapentin and opioids= (# of unique beneficiaries who used gabapentin and opioids)÷(# of unique beneficiaries who used any gabapentin)

Proportion of gabapentin and benzodiazepines= (# of unique beneficiaries who used gabapentin and opioids)÷(# of unique beneficiaries who used any gabapentin)

Proportion of gabapentin and benzodiazepines= (# of unique beneficiaries who used gabapentin and opioids)÷(# of unique beneficiaries who used any benzodiazepines)

Proportion of concurrent gabapentin and opioids use = (# of unique beneficiaries with an overlap in prescriptions for gabapentin and opioids for at least one day)÷(# of unique beneficiaries who used any gabapentin and opioids)

Proportion of concurrent gabapentin and benzodiazepine use = (# of unique beneficiaries with an overlap in prescriptions for gabapentin and benzodiazepine for at least one day)÷(# of unique beneficiaries who used any gabapentin and benzodiazepines)

Proportion of gabapentin, opioids, and benzodiazepines= (# of unique beneficiaries who used gabapentin, opioids, and benzodiazepines)÷(# of unique beneficiaries who used any gabapentin and opioids)

Proportion of gabapentin, opioids, and benzodiazepines= (# of unique beneficiaries who used gabapentin, opioids, and benzodiazepines)÷(# of unique beneficiaries who used any gabapentin and benzodiazepines)

Proportion of concurrent gabapentin, opioids, and benzodiazepines = (# of unique beneficiaries with an overlap in prescriptions for gabapentin, opioids, and

benzodiazepines for at least one day)÷(# of unique beneficiaries who used any gabapentin, opioids, and benzodiazepines)

Bivariate analyses using t-test and chi-square tests were completed to compare factors associated with each of the longest concurrent use categories. Multinomial logistic regression models estimated associations between independent variables (including socio-demographic, clinical, and pharmacologic factors) and longest concurrent use categories and reported as adjusted odds ratios (AOR) and 95% confidence intervals (95%CIs). A 2-sided $p<.05$ was considered statistically significant. All analyses were conducted using SAS, version 9.4 (SAS Institute Inc). The models for estimating the associations between individual factors and concurrent use categories are summarized in the equations below:

$$\text{Logit}[\Pr(_{GABA+OP+BZD})] = \beta_0 + \beta*(\text{sociodemographics}) + \beta*(\text{health insurance}) + \beta*(\text{clinical factors}) + \beta*(\text{pharmacologic factors})$$

$$\text{Logit}[\Pr(_{GABA+OP})] = \beta_0 + \beta*(\text{sociodemographics}) + \beta*(\text{health insurance}) + \beta*(\text{clinical factors} + \beta*(\text{pharmacologic factors})$$

$$\text{Logit}[\Pr(_{GABA+BZD})] = \beta_0 + \beta*(\text{sociodemographics}) + \beta*(\text{health insurance} + \beta*(\text{clinical factors}) + \beta* (\text{pharmacologic factors})$$

$$\text{Logit}[\Pr(_{OP\ only})] = \beta_0 + \beta*(\text{sociodemographics}) + \beta*(\text{health insurance}) + \beta*(\text{clinical factors}) + \beta*(\text{pharmacologic factors})$$

$$\text{Logit}[\Pr(_{BZD\ only})] = \beta_0 + \beta*(\text{sociodemographics}) + \beta*(\text{health insurance}) + \beta*(\text{clinical factors}) + \beta*(\text{pharmacologic factors})$$

In the above equations, the reference category is GABA only users. The interpretation of parameters in the equations are summarized below:

$\Pr(_{GABA+OP+BZD})$ refers to the probability of gabapentin, opioid and benzodiazepines

$\Pr(_{GABA+OP})$ refers to the probability of concurrent gabapentin and opioids

$\Pr(_{GABA+BZD})$ refers to the probability of concurrent gabapentin and benzodiazepines

$Pr(_{OP\ only})$ refers to the probability of opioid only

$Pr(_{BZD\ only})$ refers to the probability of benzodiazepines only

β*(sociodemographics) is a set of parameters for socio-demographic factors

β*(health insurance) is a set of parameters for health insurance factors

β*(clinical factors) is a set of parameters for clinical factors

β*(pharmacologic factors) is a set of parameters for pharmacologic factors

Sensitivity analyses

In sensitivity analyses we compared factors associated with any concurrent use of gabapentin, opioids, and/or benzodiazepines to results from our main analyses. We varied the definition of exposure to capture any concurrent use. Beneficiaries with an overlap of at least one day in prescriptions for gabapentin, opioids and benzodiazepines were grouped as GABA+OP+BZD users. Those with an overlap of at least one day in prescriptions for gabapentin and opioids but not benzodiazepines were categorized as GABA+OP users and those with an overlap of at least one day in prescriptions for gabapentin and benzodiazepines but not opioids were categorized as GABA+BZD users. The remainder were categorized as OP only, GABA only and BZD only users.

Section C.4. Aim 3 methods

Additional cohort selection criteria

We included disabled beneficiaries with at least one prescription for gabapentin, opioids or benzodiazepines. The cohort entry date was defined as the date of the earliest prescription fill for any of our medications of interest. To address confounding by indication related to these medications, we also required beneficiaries to have diagnoses

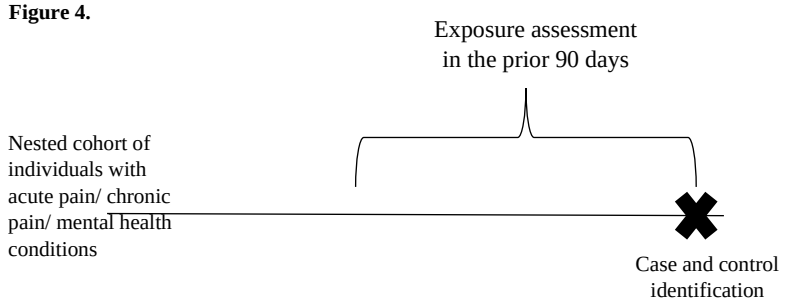
of acute pain, chronic pain, or mental health conditions in the 6-months prior to receipt of any of our medications of interest. To ensure availability of beneficiaries' health care utilization and prescription drug information, we excluded beneficiaries without continuous Medicare Parts A, B and D coverage and those with Medicare Advantage coverage in the 6-months prior to and 12-months following the cohort entry date. Because patterns of medication utilization among individuals with cancer/hospice benefits potentially differs from those of the general Medicare population, we also excluded beneficiaries with these conditions during the entire study period.[53,55-56] Prior evidence suggests that chronic kidney disease increases the risk of gabapentin related respiratory depression;[23] hence, we excluded beneficiaries diagnosed with this condition during our study period. Additionally, because prior events increase the risk for subsequent outcome/events, we completed analyses in four distinct cohorts for each outcome —in each cohort, we excluded beneficiaries diagnosed with the outcome of interest in the 6-month period prior to cohort entry. To examine the association between concurrent medication utilization and respiratory depression or opioid related overdose, we excluded beneficiaries who used gabapentin only/benzodiazepines only/opioid and benzodiazepines only in the 90-day pre-index period. Similarly, for our substance related overdose and adverse drug-related event analysis, we excluded beneficiaries who used opioids or benzodiazepines only as well as those who only used both concurrently.

Study design

We utilized a nested case control (NCC) design to examine the association between concurrent use categories and public health outcomes **(Figure 4).** Disabled beneficiaries

diagnosed with acute pain, chronic pain or mental health conditions within our nested cohort were followed for 12-months following cohort entry to ascertain outcome and exposure status**.** The NCC is a useful study design for assessment of infrequent outcomes. Previous evidence suggests that in settings where outcomes are rare and exposure also occurs infrequently, the NCC design provides a less biased estimate of the association between exposure and outcome when compared to the cohort design.[63-64] The NCC design also has the advantage of minimizing bias related to control selection, a bias common in other case control designs. [63-64]

Figure 4.



Measures

Outcome variables

The primary outcomes of interest are outpatient and inpatient hospital visits associated with respiratory depression, opioid-related overdose, substance-related overdose, and adverse drug-related events **(Appendix C.)** Based on a previously utilized algorithm, we defined a drug-related adverse event as a composite measure which includes adverse drug reactions, altered mental states (diagnosis of altered mental state, anxiety, catatonia, euphoria, insomnia and sedation), ataxia, blurred vision, extrapyramidal symptoms (dystonia, abnormal movement disorders and drug induced tremors), nystagmus, palpitations, slurred speech, tachycardia, respiratory depression and weakness/syncope.[22]

Substance related overdose events included opioid, sedative and/or epileptic poisoning and opioid related overdose events included opioid related poisonings. Overdose events included both intentional and unintentional poisonings. We excluded overdose events related to heroin to focus specifically on overdose events related to prescription opioids. ICD-9-CM codes were mapped to ICD-10-CM codes for all events. All outcomes were constructed as binary variables. Only the first event for all outcomes of interest were considered in this analysis. Although prior events such as prior overdoses increase the potential for subsequent events, our analysis was not designed to examine recurrent events.

Case definition: Cases were beneficiaries within the nested cohort with at least one inpatient claim or two outpatient claims for an outcome of interest in the 12-months post cohort entry. The index date for cases was assigned as the date of the first outcome event.

Control definition: Controls were beneficiaries within the nested cohort without any of the outcomes of interest within the 12-month follow up period. The index dates for potential controls were randomly assigned based on the distribution of the index dates for cases.

Independent variable

The primary independent variable was concurrent medication utilization. The exposure categories differed based on the outcome event examined. For respiratory depression and opioid related overdose events, we included GABA+OP+BZD users, GABA+OP users and OP only users. Beneficiaries with an overlap of at least one day in the days supplied of prescriptions for gabapentin, opioids, and benzodiazepines were considered GABA+

OP+BZD users. Those with overlap of at least 1 day in prescriptions for gabapentin and opioids but not benzodiazepines were considered GABA+OP users and the remaining beneficiaries were classified as OP only users. For adverse drug related events and substance overdose events, we included GABA + OP + BZD users, GABA+OP users, GABA+BZD users and GABA only users. Beneficiaries with an overlap of at least one day in the days supplied of prescriptions for gabapentin, opioids, and benzodiazepines were considered GABA + OP + BZD users. Those with an overlap of at least 1 day in prescriptions for gabapentin and opioids but not benzodiazepines or gabapentin and benzodiazepines but not opioids were considered GABA +OP users and GABA+BZD users, respectively. The remaining beneficiaries were classified as GABA only users. Concurrent medication utilization was assessed in the 90 days before the index date for cases and controls. Previous studies have utilized varying time windows ranging from 30 days to 2 years to assess combination drug use in the period before a specified event.[65-68] Furthermore, a previous study focused on gabapentin and opioid exposure used a time window of 120 days for assessment of concomitant medication use.[21] Since current guidelines suggest that pain therapies should be assessed after 90 days, we utilized a time window of 90 days for exposure ascertainment.[65-66]

Covariates

The factors summarized in **Table III.A.** will be included as covariates in the analysis for aim 3. **Predisposing characteristics** included age, race/ethnicity and sex. **Enabling characteristics** included Medicaid-Medicare dual eligibility. **Need factors** included clinical factors such as co-morbidities, service utilization and pharmacologic variables.

These factors were derived from the Medicare enrollment and claims files and their definitions are similar to those utilized in Aim 2. In this aim, we examined clinical conditions previously listed under a co-morbid count in aim 2 (chronic lung disease, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, connective tissue disease, cerebrovascular disease, peptic ulcer disease, liver disease, hypertension, hypothyroidism, seizure disorder and dementia), separately. Additionally, we included a measure for the number of inpatient and outpatient visits to properly adjust for health care utilization pattern in our analyses. Based on the distribution of these visits, we categorized number of inpatient visits into four categories (none, 1-5, 6-10, >10) and number of inpatient visits into three categories (none, 1, and >1.) An important covariate that has not been previously well studied in the context of concomitant gabapentin, opioid, and benzodiazepine use is substance use disorder. The prior study that examined gabapentin and opioid utilization focused solely on alcohol use disorder. Our study will expand this definition by examining alcohol, opioid and non-opioid related substance use disorders. Using recently available unredacted medical and provider claims as well as substance use disorder diagnostic and procedural codes, we will adjust for estimates of substance use disorder in subsequent analyses. These covariates were measured in the 6-month baseline period prior to cohort entry for cases and controls.

Analytical approach.

Quantify the associations between concurrent therapy and public health outcomes: respiratory depression events, opioid or substance-related overdose events, and adverse drug-related events.

We utilized a disease risk score to summarize the relationship between covariates and outcome. Disease risk scores reduce the number of covariates included in a model by summarizing the disease risk associated with potential confounders into a summary score which is then adjusted for in subsequent analysis.[69-72] A disease risk score is particularly useful in our analysis because highly evolving prescriber preferences related to our exposure categories makes a propensity score relatively unstable.[69-72] This score was constructed by fitting a logistic regression model linking confounders and outcome (with exposure set as zero). [69-72]The estimated probability of disease occurrence (under the assumption of no exposure) for each beneficiary within our cohort was used as the assigned disease risk score for that beneficiary.[69-72] Specific information on the covariates included in our disease risk score estimation is included in **Appendix D**. We constructed separate disease risk scores for each outcome within separate cohorts of beneficiaries diagnosed with acute pain, chronic pain, and mental health conditions. To increase comparability between cases and controls, incident density sampling was used to match each case with up to four controls on the following characteristics: disease risk score, age, race, dual eligibility status, sex, and cohort entry year. The caliper used for matching on disease risk scores differed based on the specific outcome modeled— for respiratory depression, the caliper was 0.03, for opioid and substance-related overdose, a caliper of 0.008 was used and for adverse drug events, a caliper of 0.08 was used. When a full number of matches could not be found, we matched as many available controls to cases. Descriptive statistics were used to compare baseline characteristics between cases and controls. We used multivariable conditional logistic regression (PROC LOGISTIC using STRATA option) to account for matching in estimating the association between

outcomes (adverse drug-related event, respiratory depression, and overdose) and our concurrent use categories. Selected reference categories for comparison in logistic regression analysis differed based on the specific outcome. For respiratory depression and opioid related overdose, conditional logistic regression was used to compare the odds of the outcome among GABA+OP+BZD and GABA+OP users to the odds among OP only users. For overall substance-related overdose and adverse drug-related events, however, we compared the odds of each outcome among GABA+OP+BZD, GABA+BZD, and GABA+OP users to the odds among GABA only users . We estimated odds ratios (OR) and 95% confidence intervals for all comparisons and adjusted for any covariates not previously matched on. All analyses was completed using SAS v.9.4. A 2-sided $p<.05$ was considered statistically significant.

The following hypothesis were tested:

- H_1: The odds of respiratory depression is higher among GABA+OP+BZD and GABA+OP users when compared to OP only users.
- H_2: The odds of opioid-related overdose is higher among GABA+OP+BZD and GABA+OP users when compared to OP only users.
- H_3: The odds of substance-related overdose is higher among GABA+OP+BZD, GABA+BZD, and GABA+OP users when compared to GABA only users and
- H_4: The odds of any adverse drug-related event is higher among GABA+OP+BZD, GABA+BZD, and GABA+OP users when compared to GABA only users

These hypotheses were tested separately for disabled individuals with acute pain, chronic pain, and mental health disorders. To test these hypotheses listed above using a nested case control design, the following models were examined:

$$\text{Logit}[\Pr(_{\text{respiratory depression}})] = \beta_0 + \beta^*(\text{concurrent use category}) + \beta^*(\text{unmatched covariates})$$

$$\text{Logit}[\Pr(_{\text{opioid related overdose}})] = \beta_0 + \beta^*(\text{concurrent use category}) + \beta^*(\text{unmatched covariates})$$

$$\text{Logit}[\Pr(_{\text{substance related overdose}})] = \beta_0 + \beta^*(\text{concurrent use category}) + \beta^*(\text{unmatched covariates})$$

$$\text{Logit}[\Pr(_{\text{adverse drug event}})] = \beta_0 + \beta^*(\text{concurrent use category}) + \beta^*(\text{unmatched covariates})$$

The interpretation of parameters in the equations are summarized below:

$\text{Logit}[\Pr(_{\text{respiratory depression}})]$ refers to the probability of respiratory depression

$\text{Logit}[\Pr(_{\text{opioid related overdose}})]$ refers to the probability of opioid related overdose

$\text{Logit}[\Pr(_{\text{substance related overdose}})]$ refers to the probability of substance related overdose

$\text{Logit}[\Pr(_{\text{adverse drug event}})]$ refers to the probability of an adverse drug event

β^*(concurrent use category) is a parameter for concurrent use categories

β^*(unmatched variables) is a set of parameters for variables not matched on

Sensitivity analyses

To account for varying interval periods of gabapentin, opioid, and benzodiazepine, utilization, we varied the definitions of concurrent use. Tighter definitions requiring overlap of at least 7 days for days supplied of all medications and continuous use of all medications for at least 30 days (without the requirement of overlap) in the 90-day time window were incorporated. Looser definitions including any gabapentin, opioid, and

benzodiazepine exposure in the 90-days prior to the index date (without requirement of overlap) were examined.

In additional sensitivity analyses, we completed separate analyses focused on an opioid naive population by excluding beneficiaries with prior opioid utilization. By excluding beneficiaries who may have utilized opioids in the past and for whom opioids were later discontinued due to side effects, we will gain a more accurate assessment of any observed association. Since gabapentin is considered fairly-safe compared to opioids and benzodiazepines, it is unlikely that prescribers are aware of potential adverse effects associated with gabapentin use; as a result, gabapentin is less likely to be discontinued due to side effects. Compared to the documented time dependent overdose risk associated with opioids, there is little evidence suggesting a time dependent risk of overdose and respiratory depression with gabapentin and benzodiazepines; hence the focus on newly initiated opioid users.

Finally, we completed a dose response analysis where we stratified opioid users into low dose (<50MME), medium dose (50-90MME), high dose (91-150MME), and very high dose (>150MME) and gabapentin users into low dose (<900mg daily), medium dose (900-1,799mg daily), high dose (1,800-2,699mg daily) and very high dose (>2,700mg daily) users.

CHAPTER IV: AIM 1 RESULTS

Chapter IV addresses the first aim of the study: **To describe and compare the patterns of gabapentin, opioids, and benzodiazepine use among SSDI eligible Medicare beneficiaries overall, and those with: 1) acute pain; 2) chronic pain; and 3) mental health conditions.** The results for aim 1 analyses are discussed in this chapter under the following headings: Section A, Section B and Section C. The results for overall beneficiaries are presented in **Section A**. Results for sub-cohort analyses are presented in **Section B** and the results of our secondary analyses are discussed in **Section C**.

Section A. Overall Medicare SSDI eligible beneficiaries

Results for overall beneficiaries are discussed under study sample, types of medication therapy, patterns of switching and augmentation, and time to switch/augmentation

Section A.1. Study Sample

We identified 151,552 disabled beneficiaries who met study inclusion and exclusion criteria **(Figure 5).** Of those, 102,794 (68%) also had diagnoses of chronic pain, 84,600 (55.8%) had diagnoses of acute pain, and 53,751 (36%) were diagnosed with mental health conditions (**Figure 5**.)

Section A.2. Types of medication therapy

Among disabled beneficiaries who initiated therapy, 19,642 (13%) initiated on gabapentin, 93,309 (61.5%) started on opioids, and the remaining 38,601 (25.5%) started on benzodiazepines (**Table IV.A.2**). Monotherapy was the most common type of overall therapy within our sample. Gabapentin users were significantly more likely to be dual-

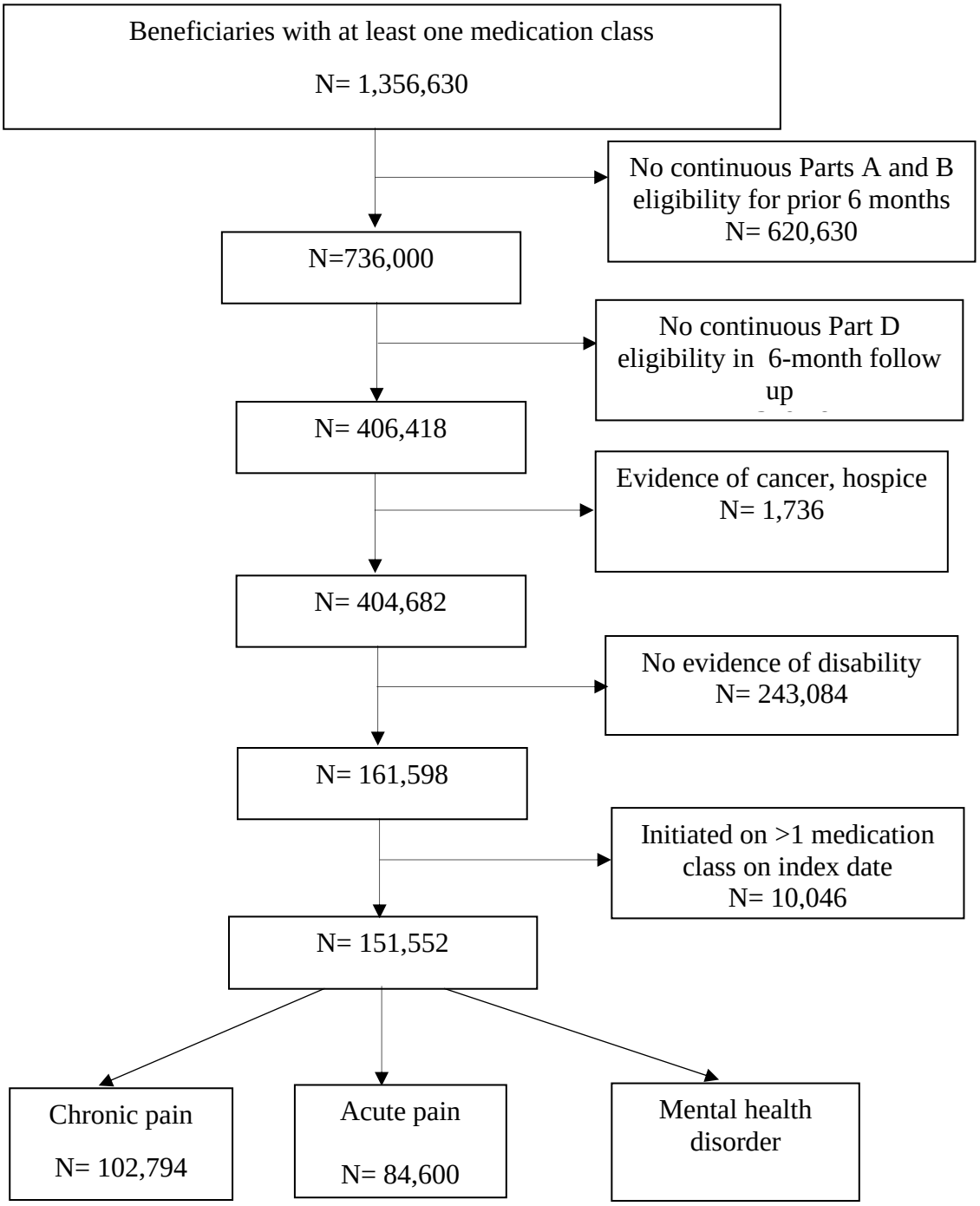
(39.8%) and tri- (17.7%) therapy users than were beneficiaries who initiated with opioids (26.7% and 6.2%) or benzodiazepines (36.2% and 7.5%; $p<0.01$.)

Overall, augmentation was the most common pattern noted among disabled beneficiaries; this pattern was significantly higher among gabapentin initiators (50.1%) than among opioid (28.7%) and benzodiazepine (38.7%) initiators ($p<0.01$; **Table IV.A.2**). Only a small proportion of beneficiaries switched therapies; this proportion was highest among gabapentin initiators (7.4%) and lowest among opioid initiators (4.1%; **Table IV.A.2**). Similarly, only 7.6% of beneficiaries discontinued therapy during follow-up—gabapentin initiators were significantly less likely to have discontinued therapy than were opioid or benzodiazepine initiators ($p<0.01$).

Section A.3. Patterns of switching and augmentation

Switching and augmenting among dual-therapy gabapentin users more commonly involved opioids (82.9% and 86.1%) than benzodiazepines (17.1% and 13.9%; **Table IV.A.3.)**. Among dual-therapy opioid users who switched/augmented, a higher proportion of both patterns involved benzodiazepines (62.2% and 61.7%), though gabapentin (37.8% and 38.3%) was also fairly common. Gabapentin tri-therapy users were more likely to augment with opioids and then benzodiazepines (59.2%) when compared to augmentation with benzodiazepines first (40.8%). Similarly, benzodiazepine initiators were more likely to add opioids before gabapentin (61.9%) than to add gabapentin first (38.1%). Among opioid initiators, however, augmentation was comparable between benzodiazepines then gabapentin (57.5%) and gabapentin then benzodiazepines (42.5%).

Figure 5. Analytic cohort for main analyses



Section A.4. Time to switching and augmentation

Overall, switching of therapies among 45%-60% of dual-therapy beneficiaries occurred within 3 to 4 months of initial therapy and was higher among those who switched from gabapentin to opioids during the first few months of follow-up (**Figure 6**). Among dual-therapy users, nearly half of those who augmented had done so within the first month after initial therapy, and up to 75% had augmented by the second month of follow-up. In the first few months of follow-up, augmentation with gabapentin among opioid and benzodiazepine initiators was lower than augmentation with the other therapies. Similar to dual-therapy users, by the second month of follow-up, more than half of tri-therapy users had augmented therapy. Among these augmenters, the addition of opioids and then benzodiazepines or benzodiazepines and then opioids among gabapentin initiators was the most common pattern observed during each month of follow-up.

Table IV.A.2. Types and patterns of therapy among disabled Medicare beneficiaries with specific initial therapy

Therapy pattern	Initial therapy			
	Gabapentin (N = 19,642)	**Opioids (N = 93,909)**	**Benzodiazepines (N = 38,601)**	***P* value**
Monotherapy, N (%)	8,356(42.5)	62,650(67.1)	21,718(56.3)	<0.001
Dual therapy, N (%)	7,822(39.8)	24,876(26.7)	13,989(36.2)	<0.001
Tri-therapy, N (%)	3,464(17.7)	5,783(6.2)	2,894(7.5)	<0.001
Augmenters, N (%)	9,833(50.1)	26,809(28.7)	14,942(38.7)	<0.001
Switchers, N (%)	1,453(7.4)	3,850(4.1)	1,941(5)	<0.001
Discontinuers, N (%)	560 (2.9)	8,830(9.5)	2,127(5.5)	<0.001

Percentages are column percentages

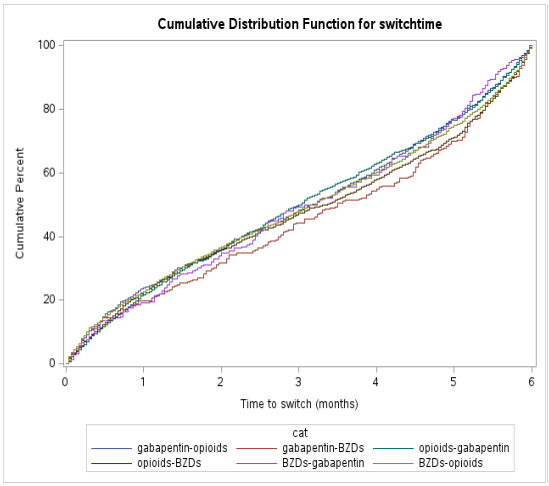
Table IV.A.3. Patterns of therapy among disabled Medicare beneficiaries with dual and tri-therapy

Therapy pattern	Initial therapy		
	Gabapentin, N (%)	Opioids, N (%)	Benzodiazepines, N (%)
Switched (dual therapy)			
Gabapentin	———	1,456 (37.8)	209 (10.8)
Opioids	1,204 (82.9)	———	1,732 (89.2)
Benzodiazepines	249 (17.1)	2,394 (62.2)	———
Augmented (dual therapy)			
Gabapentin	———	8,047 (38.3)	1,039 (8.6)
Opioids	5,485 (86.1)	———	11,009 (91.4)
Benzodiazepines	884 (13.9)	12,979 (61.7)	———
Augmented (tri-therapy)			
Opioids then benzodiazepines	1,930(59.2)	———	———
Benzodiazepines then opioids	1,332(40.8)	———	———
Gabapentin then benzodiazepines	———	2,389(42.5)	———
Benzodiazepines then gabapentin	———	3,229(57.5)	———
Gabapentin then opioids	———	———	1,031(38.1)
Opioids then gabapentin	———	———	1,677(61.9)

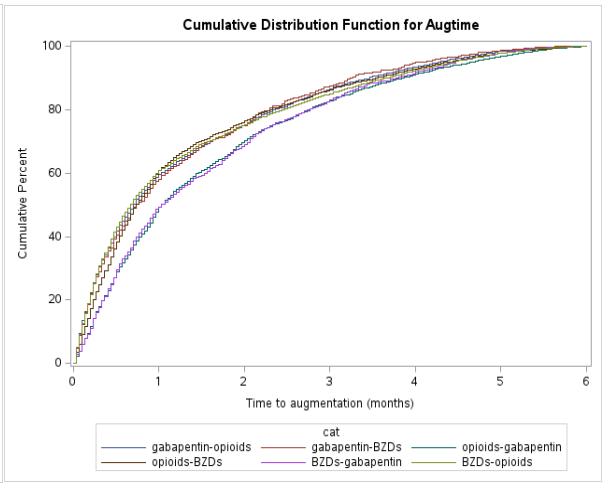
Percentages are column percentages

Patterns of switching for tri-therapy users not presented due to low sample sizes

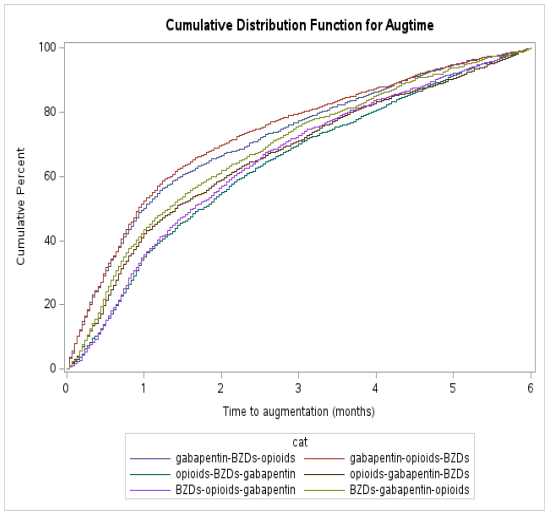
Figure 6. Cumulative distribution function curves for time to switching and augmentation among disabled Medicare beneficiaries. (A) Time to switching among dual-therapy users. (B) Time to augmentation among dual-therapy users. (C) Time to augmentation among tri-therapy users



A.



B.



C.

Section B. Sub-cohort analyses

Results for overall beneficiaries are discussed under types of medication therapy, patterns of switching and augmentation, and time to switch/augmentation.

Section B.1 Types of therapy among disabled beneficiaries with acute pain, chronic pain and mental health conditions

Overall, disabled beneficiaries diagnosed with acute pain conditions were more likely to be monotherapy users and to initiate on opioids **(Table IV.B.1).** Gabapentin initiators were significantly more likely to be dual and tri-therapy users (65.1%) when compared to opioid (36.1%) and benzodiazepine (55.6%) initiators. Among gabapentin initiators, the proportion of dual therapy users was the highest. Augmentation was the most common overall pattern observed in this sub-group of disabled beneficiaries diagnosed with acute pain conditions (**Table IV.B.1**); however the proportion of augmenters among gabapentin (57.6%) initiators was significantly higher than among opioid (31.7%) and benzodiazepine(49.7%) initiators. Overall, only a small proportion of beneficiaries switched or discontinued therapy. While the proportion of switchers was highest among gabapentin (7.5%) initiators, the proportion of discontinuers was lowest among gabapentin (2.5%) initiators.

Disabled beneficiaries with chronic pain were more likely to utilize gabapentin, opioids, and benzodiazepines as monotherapy; however, there were differences noted in therapies based on the specific medication initiated. Beneficiaries who initiated on gabapentin were significantly more likely to be dual and tri-therapy users when compared to those who initiated on opioids and benzodiazepines (63.9% vs. 37.4% and 57.4%). When compared to mono and tri-therapy, dual therapy users had the highest proportions

among gabapentin and benzodiazepine initiators. Augmentation was the most common pattern noted among disabled beneficiaries with chronic pain and this was consistent across all initiators (**Table IV.B.1**). Nonetheless, gabapentin initiators (56.3%) were significantly more likely to augment therapy when compared to opioid (33.3%) and benzodiazepine (51.7%) initiation. Only a small proportion of beneficiaries switched or discontinued therapy. While switching was more common among gabapentin initiators, discontinuation was least common among beneficiaries who initiated on gabapentin.

Disabled beneficiaries diagnosed with mental health conditions were significantly more likely to initiate on opioids and to use a single therapy in the 6-month follow up period ($p<0.01$). The proportion of dual and tri-therapy users was highest among gabapentin (65%) initiators when compared to opioid (48%) and benzodiazepine (44.8%) initiators (**Table IV.B.1**). When compared to opioid (11.3%) and benzodiazepine (8.2%) initiators, gabapentin initiators were significantly more likely to be tri-therapy users (27.5%). Augmentation was the most common pattern observed within this sub-cohort; though consistent across all initiators, the proportion of augmenters was highest among gabapentin initiators (58.6%) when compared to opioid (42.9%) and benzodiazepine (40.6%) initiators (**Table IV.B.1**). Across all initiators, only a small proportion of beneficiaries switched or discontinued therapy among beneficiaries with mental health conditions. The proportion of beneficiaries who switched was highest among gabapentin initiators (6.4%) and lowest among benzodiazepine initiators (4.2%). For discontinuation, the proportion was highest among opioid initiators (7.4%) and lowest among gabapentin initiators (2.1%).

Section B.2. Patterns of switching and augmentation

In the acute pain sub-cohort, the most common pattern noted among dual therapy users was switching to or augmentation with opioids among benzodiazepine initiators (**Table IV.B.2**). A large proportion of gabapentin initiators also switched to and augmented with opioids. Switching and augmentation among gabapentin initiators was more likely to involve opioids (85.3% and 88.5%) rather than benzodiazepines (14.7% and 11.5%). The proportion of opioid initiators who switched to or augmented with benzodiazepines (61.9% and 60.8%) was higher than those who switched to or augmented with gabapentin (38.1% and 39.2%); this pattern was also consistent for benzodiazepine initiators. Among tri-therapy users who initiated gabapentin, the proportion of beneficiaries who augmented with opioids and then benzodiazepines (59.2%) was higher than those who augmented with benzodiazepines and then opioids (40.8%) (**Table IV.B.2**). For benzodiazepine initiators, augmentation with opioids and then gabapentin (62.7%) was more common than with gabapentin and then opioids (37.3%.) Among opioid initiators, however, the proportion of those who added on gabapentin and then benzodiazepines (42.7%) was more similar to those who added on benzodiazepines and then gabapentin (57.3%).

In the chronic pain sub-cohort, the most common pattern noted among dual therapy users was switching and augmentation to/with opioids among gabapentin initiators; although for augmentation, the proportion of beneficiaries who added on opioids among benzodiazepine users was slightly higher than those who added on opioids while on gabapentin (**Table IV.B.2**). Gabapentin initiators who switched or augmented were more likely to switch to or add on opioids (85.4% and 89.2%) rather than

benzodiazepines (14.6% and 10.8%). Switching and augmentation among dual therapy users who initiated on opioids and benzodiazepines was more likely to involve both opioids and benzodiazepines, though to a lesser extent for opioid initiators. Gabapentin initiators with tri-therapy were more likely to add-on opioids and then benzodiazepines (60%) when compared to augmentation with benzodiazepines then opioids (40%) (**Table IV.B.2**). While benzodiazepine initiators were more likely to augment with opioids and then gabapentin, augmentation among opioid initiators was more comparable between gabapentin and benzodiazepines.

The most common pattern of switching and augmenting among dual therapy users noted in the mental health sub-cohort was between opioids and benzodiazepines, and vice-versa (**Table IV.B.2**). Among gabapentin initiators, the proportion of switching and augmentation was highest for opioids (73.8% and 76.9%) when compared to benzodiazepines (26.2% and 23.1%). Opioid initiators were more likely to switch to/augment with benzodiazepines (73% and 73%) than gabapentin (27% and 27%). Similarly, the proportion of beneficiaries who switched to/augmented with opioids (88.1% and 91.2%) was higher than those who switched to/augmented with gabapentin (11.9% and 8.8%) among benzodiazepine initiators. Among gabapentin initiators with tri-therapy, the proportion of beneficiaries who augmented on opioids and then benzodiazepines (54.9%) was slightly higher than those who added on benzodiazepines before opioids (45.1%) (**Table IV.B.2**). For opioid initiators, the proportion who added on benzodiazepines before gabapentin (59.4%) was higher than those who added on gabapentin before benzodiazepines (40.6%). Benzodiazepine users with tri-therapy were

more likely to augment with opioids before gabapentin (63.1%) rather than gabapentin before opioids (36.9%).

Section B.3. Time to switch and augmentation

In the acute pain sub-cohort, dual therapy users switched therapies within three to four months following initial therapy—those who switched from gabapentin to opioids, often did so the quickest similar to the pattern noted among disabled beneficiaries with chronic pain (**Figure 7**). Augmentation among dual therapy users, on the other hand, occurred within two months for majority of beneficiaries(**Figure 8**). Dual therapy users who augmented with benzodiazepines took the shortest time to augment, regardless of initial therapy. Augmentation with gabapentin among benzodiazepine and opioid users took the longest time, on average more than a month. More than 50% of tri-therapy users who augmented therapy did so within two-months following initial therapy—gabapentin initiators who augmented on opioids and then benzodiazepines had the shortest time to augmentation (**Figure 9**.)

Switching among majority of dual therapy users in the chronic pain sub-cohort occurred within three to four months; although switching to opioids from gabapentin and from benzodiazepines to opioids occurred sooner for majority of beneficiaries. Most dual therapy users who augmented therapy did so within two months- this pattern occurred earliest for augmentation with benzodiazepines among gabapentin and opioid initiators (up to 80% had done so by the second month of follow up) and latest for augmentation with gabapentin among benzodiazepine and opioid initiators (less than 70% had

augmented by the second month of follow up) (**Figure 8**). Augmentation among tri-therapy users occurred within two months for majority of beneficiaries—quickest among gabapentin initiators who added on opioids and then benzodiazepines (more than 60% of gabapentin initiators had augmented with both medications by the second month of follow up).

In the mental health sub-cohort, switching between therapies occurred within three to four months for more than 50% of these beneficiaries; On average, time to switching was shortest for switching between opioids and gabapentin, and opioids and benzodiazepines but longest for benzodiazepine switching to gabapentin or opioids (**Figure 7**). Augmentation among majority of dual therapy users occurred within two months; by the second month of follow up almost 80% of gabapentin and opioid initiators who augmented with benzodiazepines had augmented. Augmentation with gabapentin among benzodiazepine initiators took almost a month longer. Similar to the pattern observed among dual therapy users, augmentation among tri-therapy users typically occurred within two months. Time to augmentation was shortest among gabapentin initiators who augmented with opioids and benzodiazepines (60% had augmented by the first month of follow up.)

Table IV.B.1. Types of therapy among disabled beneficiaries with acute pain, chronic pain, and mental health disorders

	Gabapentin (N=19, 642)			Opioids (N=93, 909)			Benzodiazepines (N=38, 601)		
	Acute pain (N=10,710)	Chronic pain (N=13,986)	Mental health (N=6,416)	Acute pain (N=56,086)	Chronic pain (N=67,952)	Mental health (N=26,098)	Acute pain (N=17,804)	Chronic pain (N=20,856)	Mental health (N=21,237)
Monotherapy, N (%)	3,734 (34.9)	5,046 (36.1)	2,245 (35)	35,813 (63.9)	42,543 (62.6)	13,566 (52)	7,907 (44.4)	8,883 (42.6)	11,724 (55.2)
Dual therapy, N (%)	4,670 (43.6)	6,017 (43)	2,406 (37.5)	16,149 (28.8)	20,245 (29.8)	9,576 (36.7)	7,931 (44.6)	9,529 (45.7)	7,772 (36.6)
Tri-therapy, N (%)	2,306 (21.5)	2,923 (20.9)	1,765 (27.5)	4,124 (7.3)	5,164 (7.6)	2,956 (11.3)	1,966 (11)	2,444 (11.7)	1,741 (8.2)
Augmenters, N (%)	6,169 (57.6)	7,868 (56.3)	3,759 (58.6)	17,766 (31.7)	22,622 (33.3)	11,202 (42.9)	8,852 (49.7)	10,777 (51.7)	8,616 (40.6)
Switchers, N (%)	807 (7.5)	1,072 (7.7)	412 (6.4)	2,507 (4.5)	2,787 (4.1)	1,330 (5.1)	1,045 (5.9)	1,196 (5.7)	897 (4.2)
Discontinuers, N (%)	266 (2.5)	343 (2.5)	132 (2.1)	5,296 (9.4)	5,862 (8.6)	1,917 (7.4)	789 (4.4)	912 (4.4)	985 (4.6)

Percentages are column percentages

Table IV.B.2. Patterns of Switching and Augmenting among SSDI eligible beneficiaries with acute pain, chronic pain and mental health conditions

Switched (Dual therapy)									
	Gabapentin			**Opioids**			**Benzodiazepines**		
	Acute pain	**Chronic pain**	**Mental health**	**Acute pain**	**Chronic pain**	**Mental health**	**Acute pain**	**Chronic pain**	**Mental health**
Gabapentin, N (%)	____	____	____	955 (38.1)	1,111 (39.9)	359 (27)	117 (11.2)	142 (11.9)	107 (11.9)
Opioids, N (%)	689 (85.3)	915 (85.4)	304 (73.8)	____	____	____	928 (88.8)	1,054 (88.1)	790 (88.1)
Benzodiazepines, N (%)	118 (14.7)	157 (14.6)	108 (26.2)	1,552 (61.9)	1,676 (60.1)	971 (73)	____	____	____
Augmented (Dual therapy)									
	Gabapentin			**Opioids**			**Benzodiazepines**		
	Acute pain	**Chronic pain**	**Mental health**	**Acute pain**	**Chronic pain**	**Mental health**	**Acute pain**	**Chronic pain**	**Mental health**
Gabapentin, N (%)	____	____	____	5,352 (39.2)	6,928 (39.7)	2,230(27)	509 (7.4)	609 (7.3)	608 (8.8)
Opioids, N (%)	3,420 (88.5)	4,410 (89.2)	1,533 (76.9)	____	____	____	6,377 (92.6)	7,724 (92.7)	6,267 (91.2)
Benzodiazepines, N (%)	443 (11.5)	535 (10.8)	461 (23.1)	8,290 (60.8)	10,530 (60.3)	6,016 (73)	____	____	____

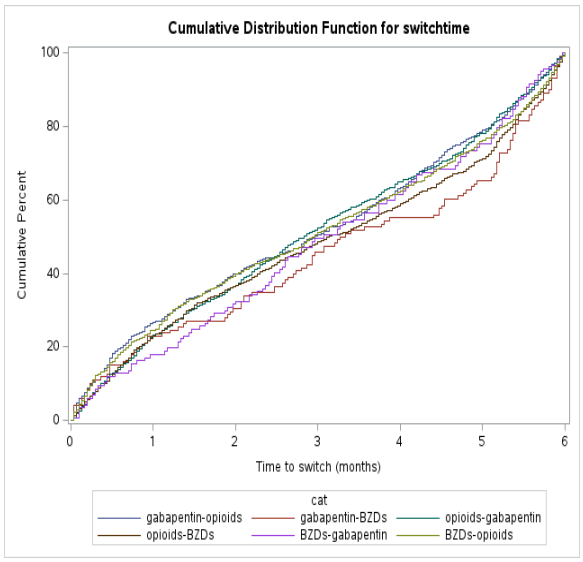
Percentages are column percentages

Table IV. B.2. Patterns of Switching and Augmentation among SSDI eligible Medicare beneficiaries with acute pain, chronic pain, and mental health conditions continued

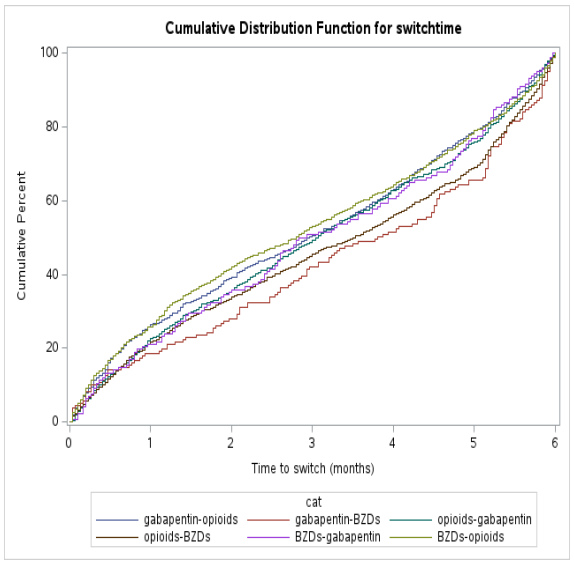
Augmented (Tri-therapy)									
	Gabapentin			Opioids			Benzodiazepines		
	Acute pain	Chronic pain	Mental health	Acute pain	Chronic pain	Mental health	Acute pain	Chronic pain	Mental health
Opioids, Benzodiazepines, N (%)	1,284 (59.2)	1,659 (60)	918 (54.9)	____	____	_____	_____	_____	_____
Benzodiazepines, Opioids, N (%)	886 (40.8)	1,101 (40)	755 (45.1)	____	____	_____	_____	_____	_____
Gabapentin, Benzodiazepines, N (%)	____	____	____	1,710 (42.7)	2,152 (42.8)	1,168 (40.6)	_____	_____	_____
Benzodiazepines, Gabapentin, N (%)	____	____	____	2,295 (57.3)	2,880 (57.2)	1,708 (59.4)	_____	_____	_____
Gabapentin, opioids, N (%)	____	____	____	____	_____	_____	687 (37.3)	843 (36.8)	612 (36.9)
Opioids, Gabapentin, N (%)	____	____	____	____	_____	_____	1,155 (62.7)	1,448 (63.2)	1,047 (63.1)

Percentages are column percentages
Patterns of switching for tri-therapy users not presented due to low sample sizes

Figure 7. Cumulative distribution function curves for time to switching among dual therapy users. A) Acute pain B) Chronic pain C) Mental health disorders



A.



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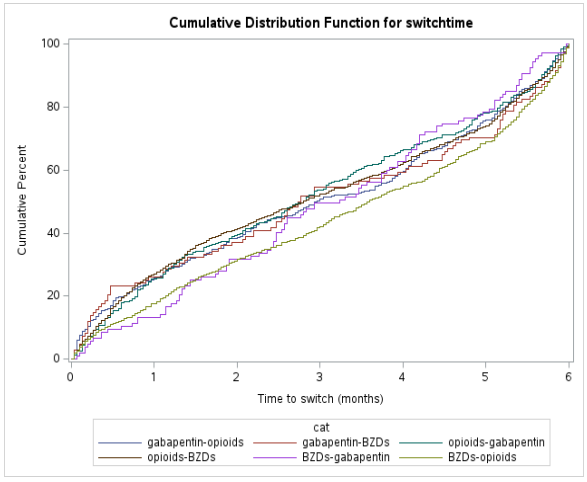
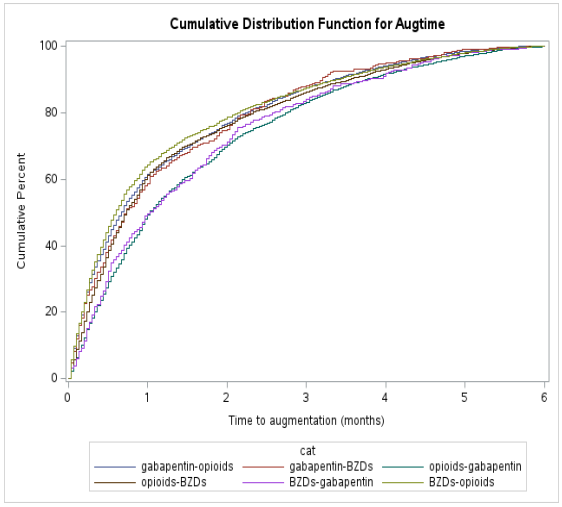
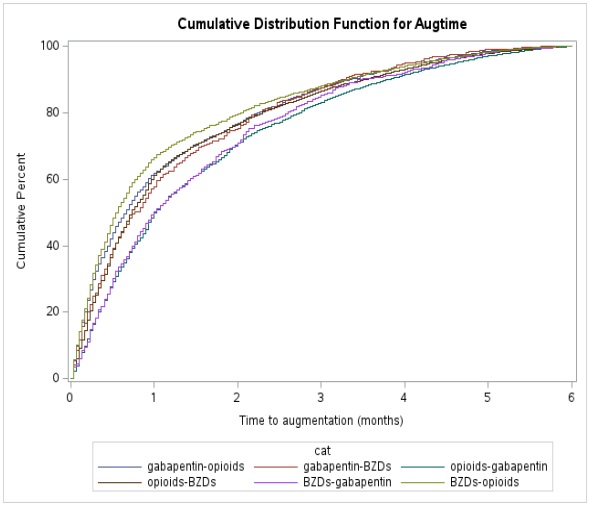


C.

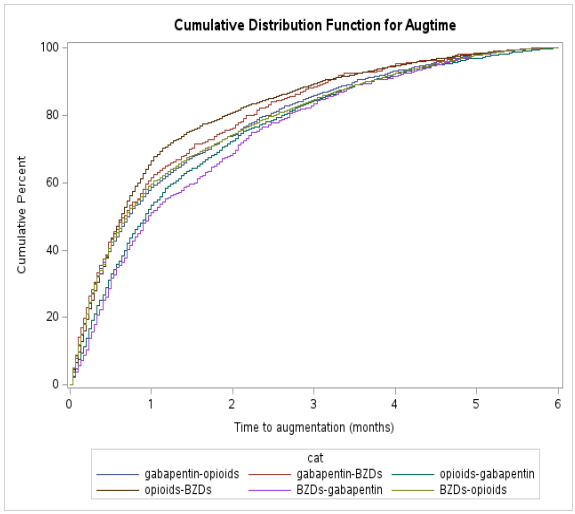
Figure 8. Cumulative distribution function curves for time to augmentation among dual therapy users. A) Acute pain B) Chronic pain C) Mental health disorders



A.

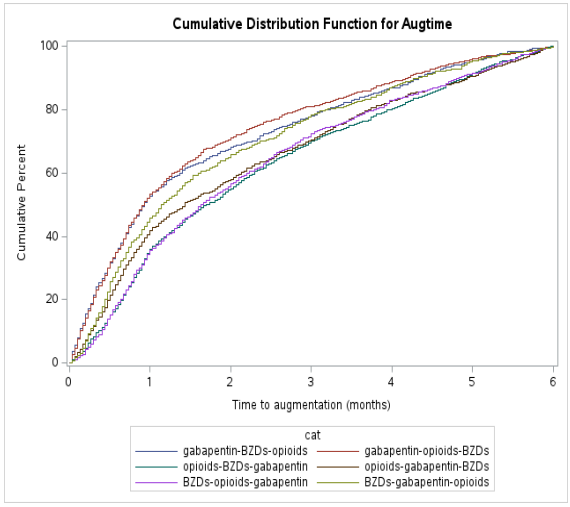


B.

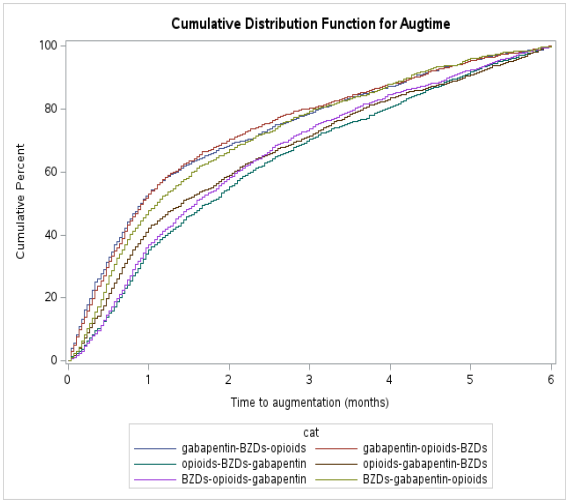


C.

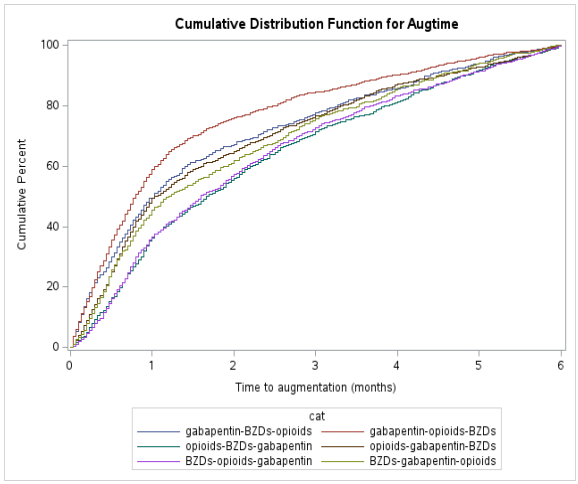
Figure 9. Cumulative distribution function curves for time to augmentation among tri- therapy users. A) Acute pain B) Chronic pain C) Mental health disorders



A.



B.



C.

B.4. Comparisons across sub-cohorts

This section compares findings across sub-cohorts of disabled beneficiaries diagnosed with acute pain, chronic pain or mental health conditions. Across our three sub-cohorts, multiple therapy was highest among disabled beneficiaries with mental health conditions (**Table IV.B.1**). The proportions of dual- and tri-therapy users were highest among benzodiazepine initiators in the chronic pain sub-cohort and among gabapentin initiators in the mental health sub-cohort (**Table IV.B.1**).

Overall, augmentation was highest among disabled beneficiaries with mental health conditions—specifically among gabapentin initiators. Across sub-cohorts, the proportion of switchers was highest among gabapentin initiators in the chronic pain sub-cohort and discontinuation was lowest among gabapentin initiators in the mental health sub-cohort (**Table IV.B.1**). Among dual therapy users across sub-cohorts, switching and augmenting between opioids and gabapentin was higher among beneficiaries diagnosed with chronic pain; however, switching to/augmenting with benzodiazepines was higher within the mental health sub-cohort (**Table IV.B.2**).

When compared to the other sub-cohorts, the time between initiation and switching from benzodiazepines was longer for most beneficiaries in the mental health sub-cohort (**Figure 7**). Among dual therapy users who augmented, most gabapentin and benzodiazepine initiators augmented with opioids much sooner in the chronic pain sub-cohort than did those in the other sub-cohorts (**Figure 8**). Similarly, a majority of gabapentin and opioid initiators in the mental health sub-cohort took less time to augment with benzodiazepines. Although a similar overall augmentation pattern was observed among tri-therapy users across sub-cohorts, a larger proportion of benzodiazepine users

augmented with gabapentin and then opioids more quickly in the chronic pain sub-cohort **Figure 9**). Majority of gabapentin initiators in the mental health sub-cohort augmented with opioids and then benzodiazepines sooner than they did in other sub-cohorts.

Section C. Secondary analyses

Results for overall beneficiaries are discussed under study sample and patterns of therapy.

Section C.1. Study sample

In secondary analysis, we identified 22, 313 beneficiaries who were newly initiated on gabapentin (**Figure 10**). Among these gabapentin initiators, 9193 (41.2%) were disabled, 11, 030 (49.4%) had diagnoses of chronic pain and 14, 050 (62.9%) and 3,293 (14.8%) had diagnoses of acute pain and mental health disorders, respectively.

Section C.2. Patterns of therapy among disabled beneficiaries overall, and by specific conditions

The results of the secondary analyses are presented in **Table IV.C.2.** Majority of beneficiaries who previously used opioids continued opioid utilization in the 6-months following gabapentin initiation, and this was consistent across all diagnoses. The proportion of new gabapentin users who continued opioid use was highest among disabled beneficiaries (87.5%) and those diagnosed with mental health conditions (85.7%). Overall, only a small proportion of beneficiaries discontinued opioid use after initiating gabapentin—similar to the pattern noted among continuers, this proportion was lowest among the disabled (12.6%) and those with mental health conditions (14.3%).

Figure 10. Analytic cohort for secondary analysis

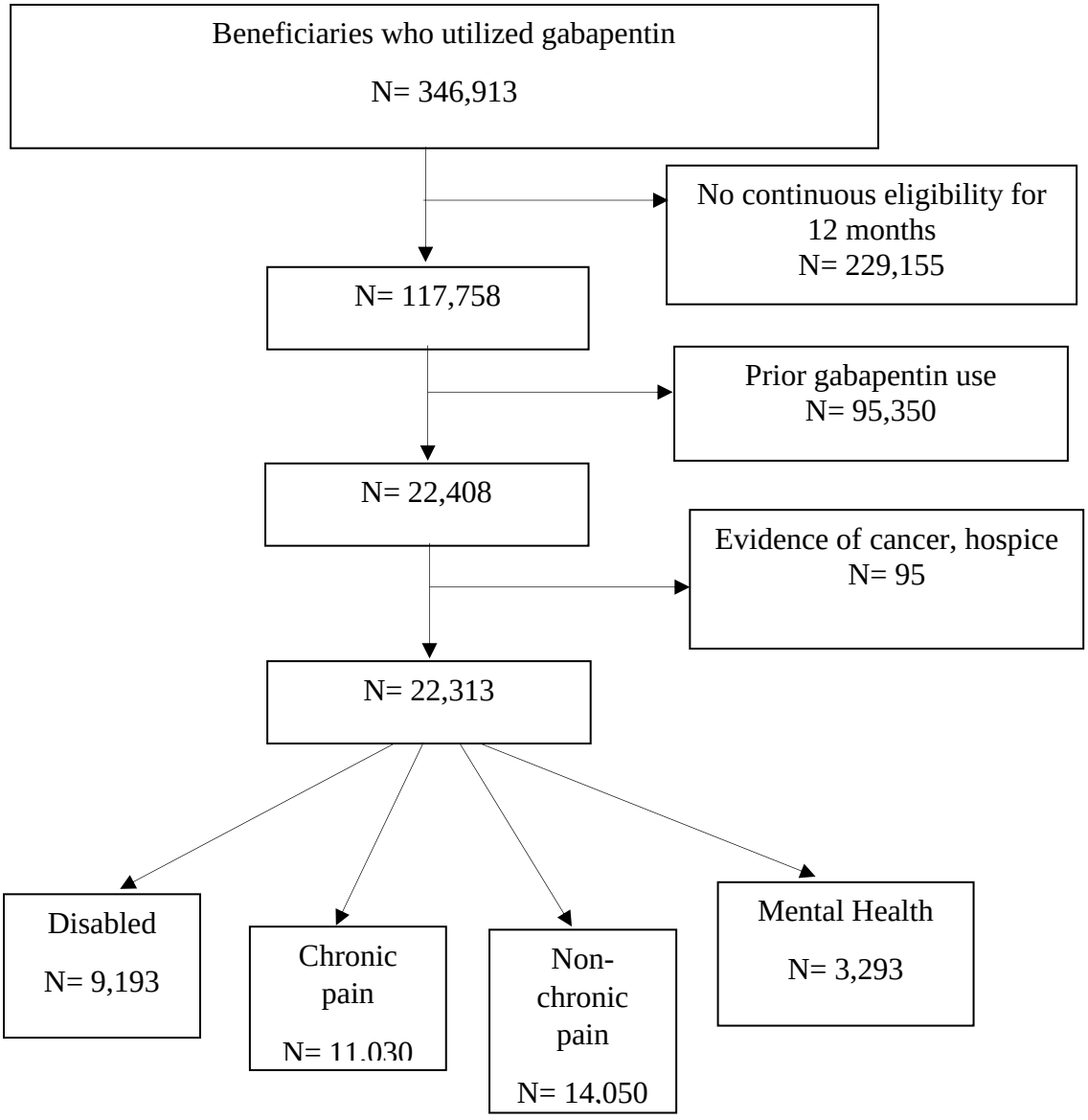


Table IV.C.2 Patterns of opioid and/or benzodiazepine utilization after gabapentin initiation

	Opioid use in prior 6-months		No opioid use in prior 6-months
	Continued use, N(%)	**Discontinued use, N(%)**	**Started use, N (%)**
Disabled	5,559(87.5)	798(12.6)	833(29.4)
Chronic pain	5,979(83)	1,224(17)	1,044(29.6)
Non-chronic pain	4,624(81.8)	1,026(18.2)	761(31.1)
Mental health	1,924(85.7)	321(14.3)	274(30)
	BZD use in prior 6-months		**No BZD use in prior 6-months**
	Continued use, N(%)	**Discontinued use, N(%)**	**Started use, N (%)**
Disabled	2,504(82.5)	531(17.5)	581(9.4)
Chronic pain	2,416(79.4)	628(20.6)	694(9)
Non-chronic pain	1,905(80)	476(20)	545(9.5)
Mental health	1,363(84.4)	252(15.6)	221(14.3)
	Opioid and BZD use in prior 6-months		**No opioid and BZD use in prior 6-months**
	Continued use, N(%)	**Discontinued use, N(%)**	**Started use, N (%)**
Disabled	1,816(75.5)	589(24.5)	648(9.6)
Chronic pain	1,758(72.3)	673(27.7)	663(8)
Non-chronic pain	1,384(72.1)	537(27.9)	529(8.6)
Mental health	959(76.5)	295(23.5)	249(13.1)

Across all diagnoses, more than a quarter of beneficiaries who had not used opioids in the prior six months, started opioids following gabapentin initiation. Majority of beneficiaries who had previously utilized benzodiazepines continued benzodiazepine utilization following gabapentin initiation, though to a lesser extent than was observed among opioid continuers. Similar to the pattern noted among opioid continuers, disabled (82.5%) beneficiaries and those with mental health conditions (84.4%) were more likely to continue benzodiazepine use when compared to beneficiaries with chronic (79.4%) and non-chronic pain (80%) conditions. When compared to the pattern noted among opioid discontinuers, a slightly larger proportion of beneficiaries discontinued benzodiazepine use following gabapentin initiation. Discontinuation was highest within the chronic (20.6%) and acute pain (20%) cohorts. The proportion of new gabapentin initiators with no prior benzodiazepine use who started benzodiazepine use was much lower than the proportion noted for opioid starters. Despite this lower proportion, beneficiaries with mental health conditions (14.3%) remained more likely to initiate benzodiazepine use after gabapentin initiation.

Almost three-quarters of beneficiaries with prior opioid and benzodiazepine use continued use of both medication classes following gabapentin initiation. While this proportion was slightly lower than the proportions noted for the individual therapies, a similar pattern of utilization was noted among opioid and benzodiazepine continuers—disabled beneficiaries (75.5%) and those with mental health conditions(76.5%) remained more likely to continue utilization of both medication classes. Across all cohorts, a quarter of beneficiaries who previously used both opioids and benzodiazepines discontinued utilization of both medications—this proportion was lowest among those

with mental health conditions (23.5%) and disabled beneficiaries (24.5%). While only a small proportion of beneficiaries without prior opioid and benzodiazepine started use following gabapentin utilization, the proportion of whose who started use of both medication classes was much higher within the mental health cohort when compared to the disabled and those with pain conditions.

CHAPTER V: AIM 2 RESULTS

Chapter V addresses the second aim of the study: **To describe and compare the prevalence of and factors associated with concurrent tri-therapy, dual therapy, and single therapy.** The results for aim 2 analyses are discussed in this chapter under the following headings: Section A, Section B, Section C, Section D, and Section E. Study sample is presented in **Section A**. Prevalence estimates are presented in **Section B**. Descriptive analyses are discussed in **Section C**; Multinomial logistic regression results are presented in **Section D** and sensitivity analyses are discussed in **Section E**.

Section A. Study sample

We included 214,722 disabled beneficiaries who met our initial study inclusion and exclusion criteria for prevalence estimation (**Figure 11**) and 142,709 who met additional criteria for inclusion in our characterization cohort (**Figure 11**).

Section B. Prevalence of concurrent therapy among Medicare SSDI eligible beneficiaries

Among 214, 722 disabled beneficiaries who initiated at least one therapy, 74,235 (34.6%) utilized gabapentin in the follow-up period (**Figure 12**). Of these gabapentin users, 72.6% used both gabapentin and opioids and 35.2% used both gabapentin and benzodiazepines in the follow-up period. Among the 53, 929 who used gabapentin and opioids during follow up, 43,214 (80%) had evidence of concurrent use of both medications; similarly, 16,929 (65%) of gabapentin and benzodiazepine users used both medications concurrently. More than three quarters of gabapentin and benzodiazepine users and almost a fourth of gabapentin and opioid users used all three medications

during follow-up. Among the 21,165 beneficiaries who used all three medications, 17,511 (82.7%) had evidence of concurrent use of all three medications.

Figure 11. Analytic cohort

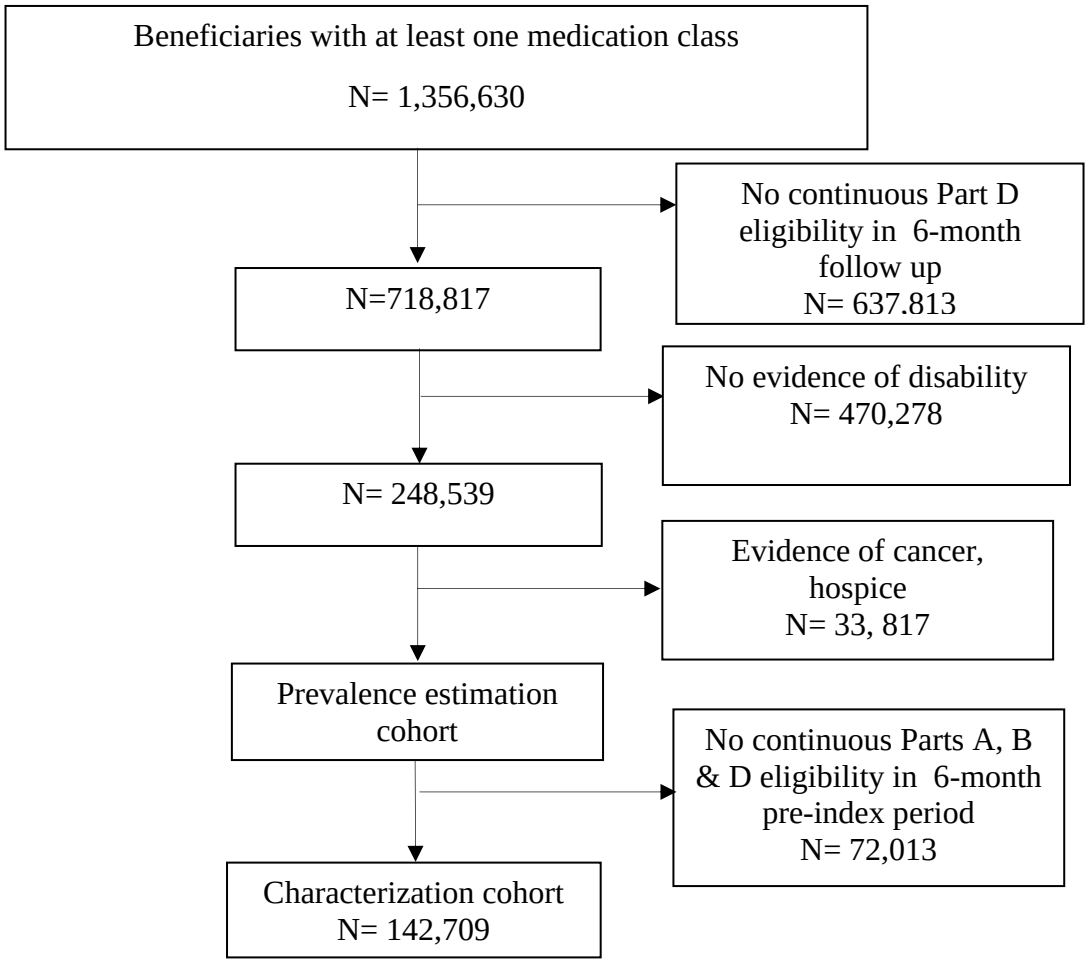
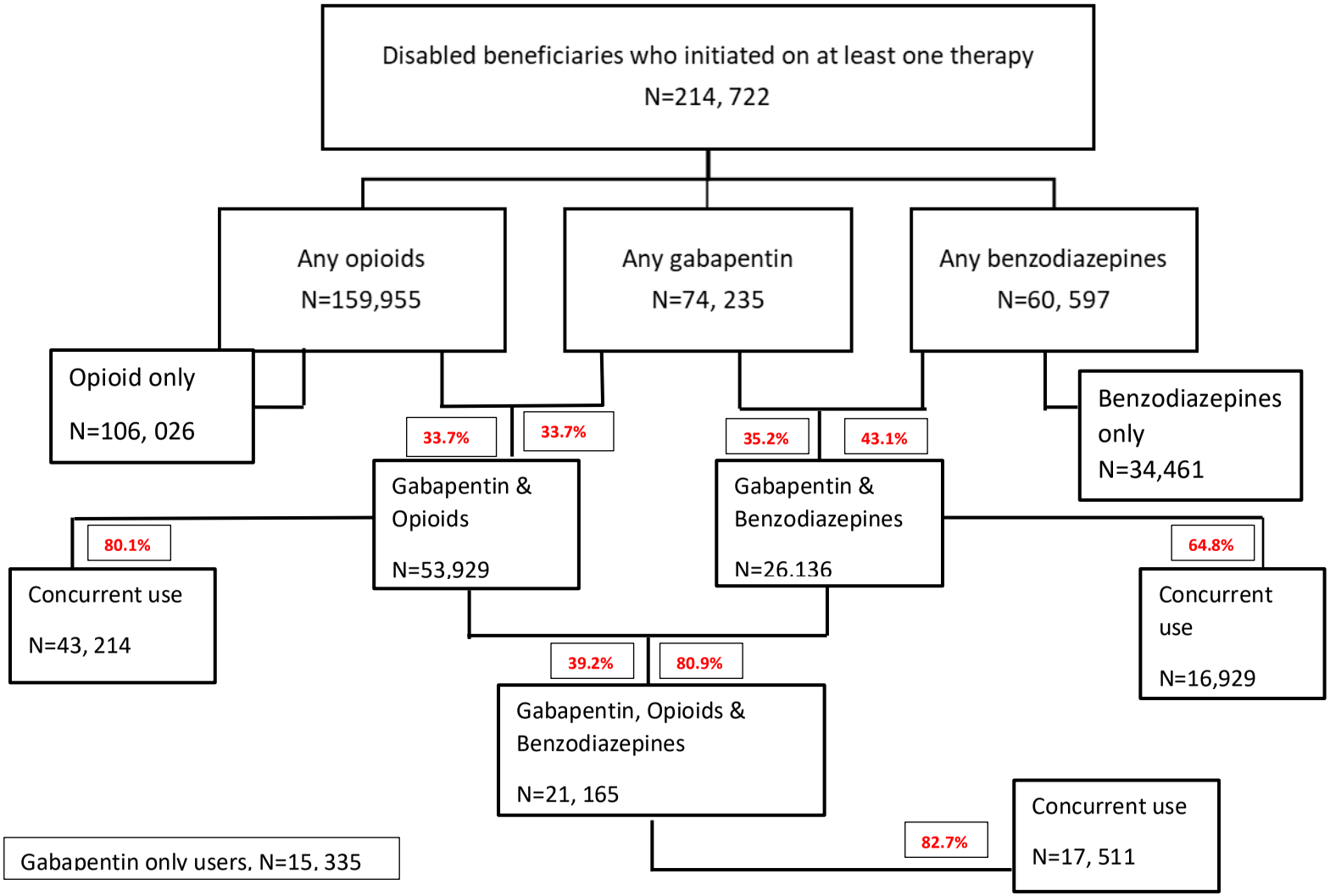


Figure 12. Prevalence of concurrent therapy among Medicare SSDI eligible beneficiaries



Section C. Descriptive and Bivariate analyses

Table V.C.1 describes the baseline characteristics of our sample. The majority of beneficiaries within our sample were aged <65(72%), female (58.2%), non-Hispanic white (76.3%), and Medicare-Medicaid dually eligible (63%). Joint and back pain were the most common chronic pain conditions in the sample and were significantly higher among beneficiaries whose longest concurrent use involved gabapentin, opioids and benzodiazepines when compared to the other concurrent use categories ($p<.01$). With the exception of neuropathic pain, which was highest among GABA+OP users, other chronic pain conditions were significantly higher among beneficiaries in the GABA+OP+BZD category when compared to the GABA+OP, GABA+BZD, GABA only, OP only, and BZD only categories ($p<0.01$;**Table V.C.1**). Acute pain and mental health conditions also were significantly higher among beneficiaries whose longest episode involved multiple medications (vs. single medications; $p<.01$).

When compared to other concurrent use categories, beneficiaries in the GABA+OP+BZD category had significantly higher average daily opioid dose (65.3MME vs. 56.2MME for GABA+OP, 13.5MME for GABA+BZD, 11.7MME for GABA only, 50.4MME for OP only and 12.5MME for BZD only; **Table V.C.1**). Chronic opioid and benzodiazepine use was highest among beneficiaries whose longest concurrent use involved gabapentin, opioids and benzodiazepines (59.3% and 91.1% vs. 55.9% and 2.2% for GABA+OP, 1.1% and 86.5% for GABA+BZD, 0.5% and 1% for GABA only, 35.1% and 9.2% for OP only and 3.9% and 71.4% for BZD only). Beneficiaries in the

GABA+OP+BZD category also were significantly more likely to have utilized muscle relaxants and non-benzodiazepine sedatives ($p<0.01$).

The average length of the longest concurrency episodes for beneficiaries included in our sample was 55 days (**Table V. C.2**.) On average the length of longest concurrency episodes was longest among GABA only users (67 days) and GABA+OP users (62 days) and shortest for OP only users (52 days).

Table V.C.1. Sample characteristics of SSDI eligible Medicare Beneficiaries by longest concurrent use

	Overall sample N=142,709	GABA+OP +BZD N=5,747	GABA+OP N=8,795	GABA+BZD N=2,625	GABA only N=16,466	OP only, N=71,354	BZD only N=37,722	p-value
Socio-demographic factors								
Age, N (%)								<.01
<65	102,791 (72)	4,611(80.2)	6,382 (72.6)	1,900 (72.4)	10,785 (65.5)	51,057 (71.6)	28,056(74.4)	
65+	39,918 (28)	1,136(19.8)	2,413 (27.4)	725(27.6)	5,681 (34.5)	20,297 (28.5)	9,666 (25.6)	
Gender, N (%)								<.01
Females	83,110 (58.2)	3,834 (66.7)	5,166 (58.7)	1,679 (64)	9,531 (57.9)	40,057 (56.1)	22,843(60.6)	
Males	59,599 (41.8)	1,913 (33.3)	3,629 (41.3)	946 (36)	6,935(42.1)	31,297 (43.9)	14,879(39.4)	
Ethnicity, N (%)								<.01
White	108,904 (76.3)	4,948(86.1)	6,779 (77.1)	2,267 (86.4)	11,928(72.4)	51,753 (72.5)	31,229(82.8)	
Black	24,747 (17.3)	552(9.6)	1,501 (17.1)	211(8)	3,215 (19.5)	15,177 (21.3)	4,091 (10.9)	
Hispanic	4672(3.3)	108(1.9)	226 (2.6)	91(3.5)	676 (4.1)	2,235(3.1)	1,336 (3.5)	
Others	4386 (3.1)	139 (2.4)	289 (3.2)	56(2.1)	647 (4)	2,189 (3.1)	1,066 (2.8)	
Health insurance, N (%)								<.01
Dual eligibility	89,872 (63)	3,970 (69.1)	5,516 (62.7)	1,715(65.3)	9,823(59.7)	44,183 (61.9)	24,665 (65.4)	
Clinical factors, N (%)								
Chronic pain	99,050 (69.4)	5,074 (88.3)	7,570 (86.1)	1,774 (67.6)	11,052 (67.1)	53,351(74.8)	20,229 (53.6)	<.01
Back	48,246 (33.8)	3,356(58.4)	4,621 (52.5)	730 (27.8)	4,113(25)	27,335 (38.3)	8,091 (21.5)	<.01
Neck	17,037 (11.9)	1,288 (22.4)	1,614 (18.4)	288(11)	1,513 (9.2)	9,293 (13)	3,041 (8.1)	<.01
Headache	4,655(3.3)	344(6)	295(3.4)	132 (5)	425(2.6)	2,207 (3.1)	1,252 (3.3)	<.01
Joint	78,382 (54.9)	3,955 (68.8)	5,863 (66.7)	1,461 (55.7)	8,826 (53.6)	41,812 (58.6)	16,465 (43.7)	<.01
Chronic	17,783 (12.46)	1,669 (29)	2,050 (23.3)	216(8.2)	914 (5.6)	10,584 (14.8)	2,350 (6.2)	<.01
Neuropathic	20,037 (14)	1,406 (24.5)	2,403 (27.3)	482(18.4)	3,873 (23.5)	9,119 (12.8)	2,754 (7.3)	<.01
Acute pain	77,945 (54.6)	3,800 (66.1)	5,475 (62.2)	1,443 (55)	8,624 (52.4)	41,531(58.2)	17,072 (45.3)	<.01
Mental Health conditions	50,864(35.6)	3,188 (55.5)	2,556 (29.1)	1,549 (59)	4,676(28.4)	18,381 (25.8)	20,514(54.4)	<.01

Table V.C.1. Sample characteristics of SSDI eligible Medicare Beneficiaries continued

Substance Use disorder	1307 (0.9)	65 (1.1)	107 (1.2)	28 (1.1)	161 (1)	676(1)	270 (0.7)	<.01
Co-morbid condition count								
None	46,373 (32.5)	1,604 (27.9)	2,342 (26.6)	759 (28.9)	4,160 (25.3)	23,176 (32.5)	14,332 (38)	<.01
1	37,794 (26.5)	1,475 (25.7)	2,252 (25.6)	685 (26.1)	4,052 (24.6)	19,107 (26.8)	10,223(27.1)	<.01
2	27,701 (19.4)	1,190 (20.7)	1,791 (20.4)	547 (20.8)	3,597 (21.9)	13,818 (19.4)	6,758 (17.9)	<.01
3	15,937 (11.2)	690 (12)	1,178 (13.4)	333 (12.7)	2,300 (14)	7,952 (11.1)	3,484 (9.2)	<.01
4+	14,904 (10.4)	788 (13.7)	1,232 (14)	301 (11.5)	2,357 (14.3)	7,301 (10.2)	2,925 (7.8)	<.01
Pharmacologic factors, N (%)								
Muscle relaxants	30,924 (21.7)	2,367 (41.2)	3,053 (34.7)	611 (23.3)	2,883 (17.5)	16,425 (23)	5,585 (14.8)	<.01
Benzodiazepines	64,694 (45.3)	5,747 (100)	1,421 (16.2)	2,625 (100)	1,889 (11.5)	15,290 (21.4)	37,722 (100)	<.01
Gabapentin	39, 941 (30)	5,747 (100)	8,795 (100)	2,625 (100)	16,466 (100)	4,782 (6.7)	1,526 (4.1)	<.01
Pregabalin	8,309 (5.8)	296(5.2)	369(4.2)	74 (2.8)	411 (2.5)	5,484 (7.7)	1,675 (4.4)	<.01
Non-benzodiazepine sedatives	18,698 (13.1)	1,199 (20.9)	1,335 (15.2)	457 (17.4)	1,594 (9.7)	8,934 (12.5)	5,179 (13.7)	<.01
Gabapentin dose, mean (std)	304(694)	1352 (939)	1180 (908)	1383 (954)	1035 (843)	36 (264)	18 (189)	<.01
Opioid dose, mean (std)	36.17 (59)	65.34 (70)	56.20 (64.21)	13.47 (29.35)	11.69 (26.24)	50.35(65.13)	12.50 (36.82)	
Opioid duration, N (%)								
None	39,576 (27.7)	———————	———————	1,692 (64.5)	10,993(66.8)	202 (0.3)	26,689 (70.8)	<.01
Acute	67,567 (47.4)	2340 (40.7)	3,880 (44.1)	902 (34.4)	5,384 (32.7)	45,501 (63.8)	9,560 (25.3)	<.01
Chronic	35,566 (24.9)	3,407 (59.3)	4,915 (55.9)	31 (1.1)	89 (0.5)	25,561 (35.9)	1,473 (3.9)	<.01
Gabapentin duration, N (%)								
None	102,768 (72)	———————	———————	———————	———————	66,572 (93.3)	36,196 (96)	<.01
Acute	15,012 (10.5)	1,635 (28.5)	1,849 (21)	468 (17.8)	5,530 (33.6)	4,196 (5.9)	1,334 (3.5)	<.01
Chronic	24, 929 (17.5)	4,112 (71.6)	6,946(79)	2,157(82.2)	10,936 (66.4)	586 (0.8)	192 (0.5)	<.01
BZD duration, N (%)								

Table V.C.1 Sample characteristics of SSDI eligible Medicare Beneficiaries continued

None	78,241 (54.8)	————	7,374(83.8)	————	14,577 (88.5)	56,064(78.6)	226(0.6)	<.01
Acute	23,165 (16.2)	514 (8.9)	1,232 (14)	355 (13.5)	1,728 (10.5)	8,764 (12.3)	10,572(28)	<.01
Chronic	41, 303 (28.94)	5,233 (91.1)	189 (2.2)	2,270 (86.5)	161 (1)	6,526 (9.2)	26,924 (71.4)	<.01

All percentages are column percentages

Table V.C.2. Distribution of length (in days) of longest concurrency episodes

	Mean (std)	Median	Range
Concurrent use category			
Overall sample	55 (45.7)	40	1-180
GAB+OP+BZD	52(31.9)	43	2-180
GAB+OP	62 (35.1)	56	3-180
GAB+BZD	58(33.3)	53	5-180
OP only	52(49.2)	30	1-180
BZD only	56 (43.8)	42	1-180
GAB only	67 (42.3)	58	3-180

Section D. Multivariable results

Among disabled beneficiaries, back pain and chronic pain were the strongest predictors of longest concurrent use of gabapentin, opioids and benzodiazepines [AOR(95%CI): 1.23(1.07-1.41) and 1.27 (1.07-1.51);**Table V.D.1**], when compared to GABA only users. Having a mental health condition[1.16(1.02-1.33)], higher opioid dose[1.05(1.03-1.06)], longer opioid duration[1.07(1.06-1.07)], and longer benzodiazepine duration[1.06(1.05-1.06)] also were significantly and positively associated with longest concurrent use of GABA+OP+BZD. Except for mental health, these factors also significantly predicted GABA+OP concurrent use. When compared to GABA only users, GABA+OP and GABA+OP+BZD users had lower odds of neuropathic pain.

Although age was not a significant predictor of other concurrent use categories, the odds of longest concurrent use involving GABA+BZD [1.40(1.14-1.72)] and BZD only [1.19(1.06-1.33)] were higher among beneficiaries aged 65 and older. Having a mental health condition also significantly predicted GABA+BZD [1.62(1.35-1.95)] and BZD only [1.54(1.38-1.72)] use; the odds for these associations were higher than those noted for GAB+OP+BZD users. Non-benzodiazepine sedatives was a significant predictor of longest concurrent use involving gabapentin and benzodiazepines [1.27(1.02-1.58)] but not for other concurrent use categories. Pregabalin use also was only a significant predictor of longest concurrent use involving OP only [1.73(1.38-2.15)] and BZD only [1.61(1.27-2.05)] users.

Table V.D. Results of multinomial logistic regression analyses for the association between factors and longest concurrent use category

	GABA+OP+ BZD AOR (95%CI)	**GABA+OP AOR (95%CI)**	**GABA+ BZD AOR (95%CI)**	**OP only AOR (95%CI)**	**BZD only AOR (95%CI)**
Socio-demographic factors					
Age					
<65	reference	reference	Reference	reference	reference
65+	1.06 (0.90-1.24)	0.94 (0.84-1.04)	**1.40 (1.14-1.72)**	0.99 (0.90-1.10)	**1.19 (1.06-1.33)**
Gender					
Males	reference	reference	Reference	reference	reference
Females	1.01 (0.88-1.17)	0.92 (0.84-1.01)	0.97 (0.81-1.17)	0.94 (0.86-1.03)	**1.14 (1.03-1.26)**
Ethnicity					
White	reference	reference	Reference	reference	reference
Black	0.96 (0.79-1.15)	0.98 (0.87-1.10)	0.86 (0.65-1.13)	**0.89 (0.79-0.98)**	**0.82 (0.72-0.93)**
Hispanic	0.92 (0.62-1.38)	1.00 (0.78-1.29)	0.75 (0.44-1.28)	**0.74 (0.56-0.92)**	0.94 (0.73-1.21)
Others	1.42 (0.97-2.08)	**1.33 (1.04-1.71)**	1.36 (0.79-2.33)	0.99 (0.79-1.27)	1.03 (0.78-1.35)
Health insurance					
Dual eligibility	1.05 (0.92-1.21)	1.09 (0.99-1.20)	1.00 (0.83-1.20)	1.06 (0.96-1.16)	0.91 (0.82-1.01)
Clinical factors					
Chronic pain					
Back	**1.23 (1.07-1.41)**	**1.20 (1.08-1.32)**	0.98 (0.82-1.18)	0.94 (0.85-1.03)	**0.71 (0.64-0.79)**
Neck	1.16 (0.97-1.39)	1.09 (0.95-1.24)	0.97 (0.76-1.24)	1.11 (0.97-1.27)	1.04 (0.89-1.21)
Headache	0.83 (0.61-1.12)	0.80 (0.62-1.03)	1.15 (0.79-1.65)	0.77 (0.62-0.98)	0.95 (0.74-1.23)
Joint	0.95 (0.80-1.12)	0.99 (0.88-1.12)	0.94 (0.76-1.18)	**0.87 (0.78-0.97)**	**0.76 (0.67-0.86)**
Chronic	**1.27 (1.07-1.51)**	**1.34 (1.17-1.54)**	**0.67 (0.53-0.86)**	1.15 (0.99-1.33)	**0.67 (0.57-0.78)**
Neuropathic	**0.85 (0.72-0.99)**	0.90 (0.81-1.00)	**0.79 (0.64-0.98)**	**0.67 (0.60-0.74)**	**0.59 (0.52-0.67)**

Table V.D. Results of multinomial logistic regression analyses for the association between factors and longest concurrent use category continued

Acute pain	0.98 (0.83-1.15)	0.91 (0.81-1.02)	1.14 (0.91-1.42)	0.91 (0.82-1.01)	1.08 (0.96-1.22)
Mental Health conditions	**1.16 (1.02-1.33)**	0.95 (0.86-1.06)	**1.62 (1.35-1.95)**	**0.84 (0.76-0.92)**	**1.54 (1.38-1.72)**
Substance Use disorder	0.61 (0.30-1.11)	0.60 (0.39-1.03)	1.26 (0.54-2.83)	**0.32 (0.22-0.48)**	0.79 (0.50-1.23)
Co-morbid condition count					
None	reference	reference	reference	reference	reference
1	**0.79 (0.66-0.94)**	**0.81 (0.71-0.93)**	0.83 (0.65-1.06)	**0.83 (0.73-0.94)**	**0.85 (0.74-0.98)**
2	**0.79 (0.65-0.95)**	**0.76 (0.66-0.87)**	0.85 (0.66-1.09)	**0.79 (0.69-0.90)**	0.87 (0.75-1.00)
3	0.81 (0.65-1.01)	**0.76 (0.65-0.89)**	0.95 (0.71-1.27)	**0.72 (0.62-0.83)**	**0.75 (0.64-0.89)**
4+	0.84 (0.67-1.04)	**0.71 (0.61-0.83)**	0.94 (0.71-1.26)	**0.64 (0.55-0.74)**	**0.76 (0.64-0.90)**
Pharma-cologic factors					
Muscle relaxants	1.06 (0.92-1.23)	1.08 (0.97-1.20)	0.90 (0.75-1.10)	1.04 (0.93-1.16)	0.84 (0.74-0.95)
Pregabalin	1.04 (0.78-1.40)	1.01 (0.79-1.27)	0.70 (0.46-1.08)	**1.73 (1.38-2.15)**	**1.61 (1.27-2.05)**
Other sedatives/ hypnotics	1.14 (0.96-1.36)	0.98 (0.85-1.11)	**1.27 (1.02-1.58)**	1.01 (0.88-1.16)	1.02 (0.88-1.18)
Opioid dose	**1.05 (1.03-1.06)**	**1.05 (1.03-1.06)**	1.01 (0.99-1.03)	**1.05 (1.04-1.06)**	**1.03 (1.02-1.04)**
Opioid duration	**1.07 (1.06-1.07)**	**1.06 (1.05-1.06)**	**1.01 (1.01-1.02)**	**1.06 (1.05-1.06)**	**1.04 (1.03-1.04)**
Gabapentin dose	1.01 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	0.99 (0.99-1.00)	0.99 (0.99-1.00)
Gabapentin duration	0.99 (0.99-1.00)	0.99 (0.99-1.00)	1.00 (0.99-1.00)	**0.94 (0.93-0.94)**	**0.94 (0.93-0.94)**
BZD duration	**1.06 (1.05-1.06)**	**1.01 (1.01-1.02)**	**1.06 (1.05-1.06)**	**1.02 (1.02-1.03)**	**1.05 (1.04-1.05)**

Adjusted for all variables included in table
Significant findings are highlighted in bold
Gabapentin is the reference category

Section E. Results from sensitivity analyses comparing factors associated with longest concurrent use to those associated with any concurrent use

In sensitivity analyses, the majority of chronic pain conditions were significant positive predictors of any concurrent use of GABA+OP+BZD, and GABA+OP (see **table V.E.1**.) Specifically, back pain, joint pain, neck pain, chronic pain and neuropathic pain were significantly associated with any concurrent use of GABA+OP+BZD. However, back pain and chronic pain were the only pain conditions positively associated with higher odds of longest concurrent use involving GABA+OP+BZD. Similarly, with the exception of headache, all pain conditions examined were significantly associated with higher odds of any concurrent use involving GABA+OP; however, back pain and chronic pain were the only pain conditions significantly associated with higher odds of longest concurrent use involving GABA+OP. Prior mental health diagnoses was a stronger predictor among longest concurrent GABA+BZD [1.62(1.35-1.95)] users than any concurrent GABA+BZD users [1.53(1.39-1.68)]

Sex, prior use of non-benzodiazepine sedatives, gabapentin and benzodiazepines also were significant predictors across all concurrent use categories (GABA+OP+BZD, GABA+OP, GABA+BZD) for any concurrent use; however, sex was not a significant predictor of any longest concurrent use category and prior non-benzodiazepine sedative use was only a predictor of longest concurrent use involving GABA+BZD. Although having multiple co-morbid conditions and use of muscle relaxants increased the odds of any concurrent use of GABA+OP+BZD, and GABA+OP, these factors were not significant predictors of concurrent GABA+BZD use.

Table V.E. : Results of sensitivity analysis for the association between factors and any concurrent use category

	GABA+OP+BZD AOR(95%CI)	GABA+OP AOR(95%CI)	GABA+BZD AOR(95%CI)
Socio-demographic factors			
Age			
<65	reference	reference	Reference
65+	**0.82 (0.75-0.89)**	**0.92 (0.88-0.97)**	0.98 (0.88-1.09)
Gender			
Males	reference	reference	Reference
Females	**1.32 (1.23-1.41)**	**1.13 (1.08-1.19)**	**1.17 (1.07-1.28)**
Ethnicity			
White	reference	reference	Reference
Black	**0.59 (0.54-0.65)**	0.95 (0.89-1.01)	**0.68 (0.59-0.79)**
Hispanic	**0.53 (0.44-0.65)**	**0.83 (0.73-0.94)**	1.13 (0.91-1.41)
Others	**0.64 (0.53-0.77)**	0.91 (0.80-1.03)	0.95 (0.74-1.22)
Health insurance			
Dual eligibility	1.06 (1.00-1.13)	0.99 (0.95-1.04)	**0.89 (0.81-0.97)**
Clinical factors			
Chronic pain			
Back	**1.81(1.69-1.94)**	**1.58 (1.50-1.66)**	**0.84 (0.75-0.94)**
Neck	**1.12 (1.02-1.22)**	**1.15 (1.08-1.24)**	0.87 (0.74-1.03)
Headache	1.16 (0.99-1.35)	1.07(0.93-1.22)	0.85 (0.66-1.09)
Joint	**1.22 (1.12-1.32)**	**1.15 (1.09-1.22)**	0.99 (0.88-1.11)
Chronic	**1.90 (1.74-2.08)**	**1.54 (1.44-1.65)**	**0.61 (0.50-0.75)**
Neuropathic	**1.26 (1.16-1.37)**	**1.28 (1.20-1.35)**	1.13 (0.99-1.29)
Acute pain	1.07 (0.99-1.17)	**1.12 (1.06-1.18)**	1.08 (0.97-1.21)
Mental Health conditions	**1.17 (1.10-1.25)**	**0.86 (0.82-0.91)**	**1.53 (1.39-1.68)**
Substance Use disorder	0.81 (0.54-1.22)	1.13 (0.83-1.54)	1.12 (0.58-2.19)
Co-morbid condition count			
None	reference	reference	Reference
1	1.06 (0.97-1.15)	1.06 (1.00-1.13)	1.06 (0.94-1.19)
2	**1.18 (1.08-1.30)**	**1.16 (1.09-1.24)**	1.10 (0.97-1.25)
3	**1.28 (1.15-1.43)**	**1.26 (1.17-1.36)**	1.14 (0.98-1.33)
4+	**1.54 (1.38-1.72)**	**1.50 (1.38-1.62)**	1.07 (0.90-1.27)
Pharmacologic factors			
Muscle relaxants	**1.69 (1.56-1.82)**	**1.43 (1.36-1.51)**	0.97 (0.87-1.10)
Pregabalin	**0.74 (0.64-0.85)**	**0.60 (0.55-0.67)**	**0.63 (0.48-0.83)**
Other sedatives/hypnotics	**1.47 (1.36-1.60)**	**1.29 (1.21-1.38)**	**1.17 (1.03-1.32)**

Table V.E. : Results of sensitivity analysis for the association between factors and any concurrent use category continued

Opioids	**4.45 (4.15-4.78)**	**4.17 (3.95-4.40)**	**0.35 (0.29-0.41)**
Gabapentin	**7.54 (6.28-7.72)**	**5.97 (5.63-6.32)**	**7.11 (6.37-7.95)**
Benzodiazepines	**5.88 (5.42-6.39)**	**1.09 (1.02-1.17)**	**4.62 (4.05-5.26)**

Adjusted for all variables included in table
Significant findings are highlighted in bold
No concurrent use is the reference category

CHAPTER VI: AIM 3 RESULTS

Chapter VI addresses the third aim of the study: **To examine the association between concurrent therapy and potential adverse public health outcomes (respiratory depression, opioid-related overdose, substance-related overdose, and adverse drug-related events) among SSDI eligible Medicare beneficiaries with: 1) acute pain; 2) chronic pain; and 3) mental health conditions.** The results for aim 3 analyses are discussed in this chapter under the following headings: Section A, Section B, Section C, Section D, Section E and Section F. The results for the overall nest cohort for this aim are presented in **Section A**. The results for respiratory depression are presented in **Section B**. Results for opioid-related overdose are presented in **Section C;** results for substance-related overdose are presented in **Section D** and the results of adverse drug-related events are discussed in **Section E**. Sensitivity analyses are discussed in **Section F.**

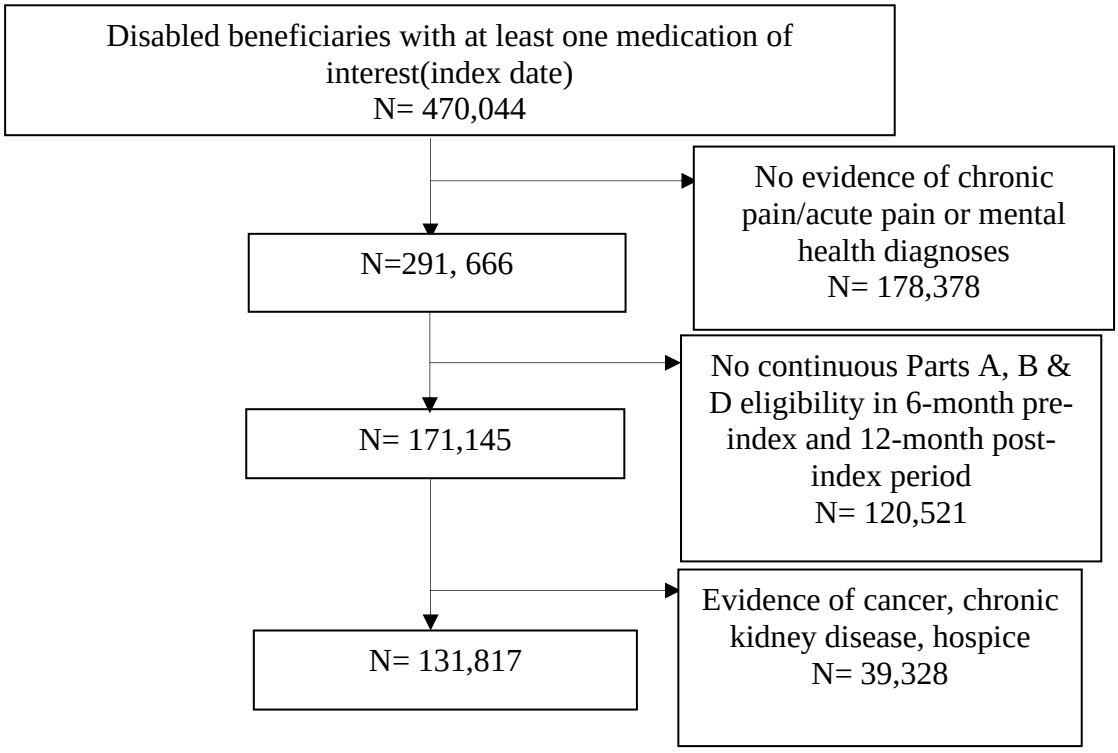
Section A. Overall nest cohort

There were 470,044 disabled beneficiaries who received at least one prescription for gabapentin, opioids or benzodiazepines during the entire study period. Of these, 131,817 beneficiaries met additional inclusion criteria for the overall nest cohort (**Figure 13.)**

Section B. Respiratory depression

Results for Section B are discussed under study sample, descriptive and bivariate analyses, and multivariable results.

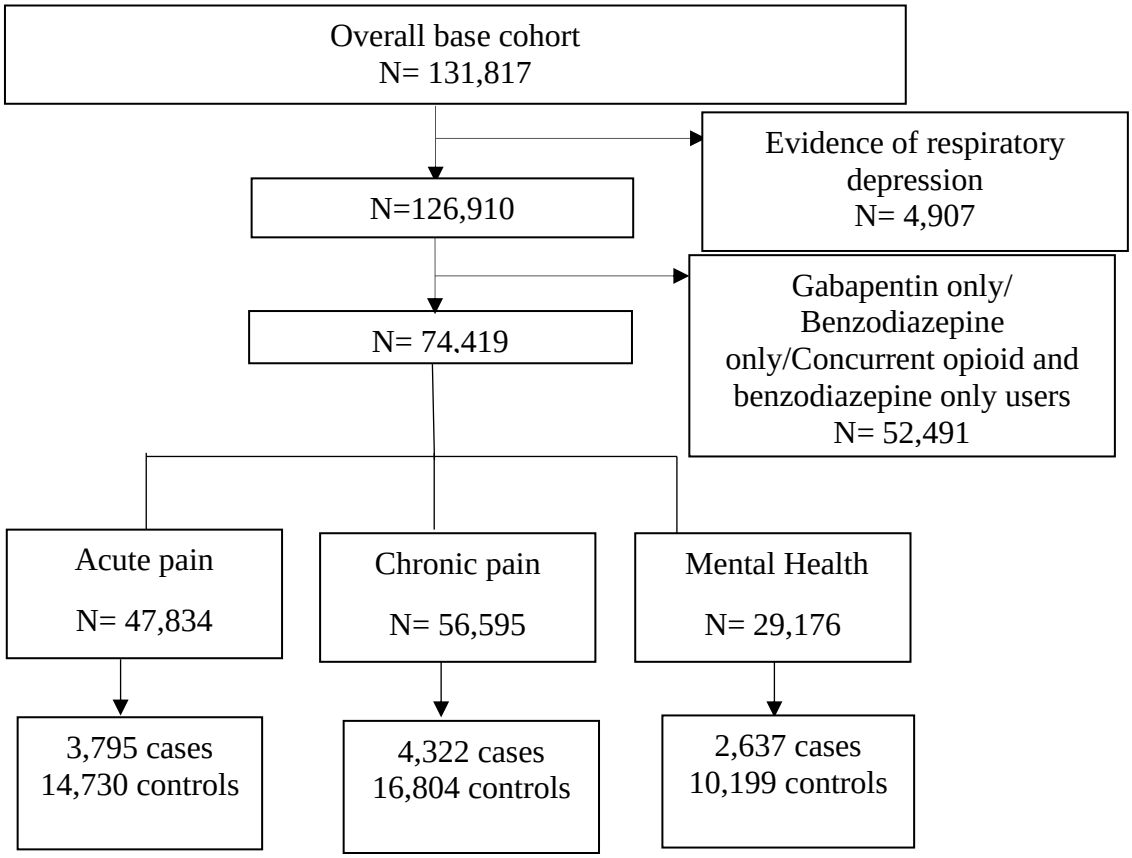
Figure 13. Overall base cohort



Section B.1. Study sample

Of the 131, 817 disabled beneficiaries who were included in our overall nest cohort, 4,907 beneficiaries who were previously diagnosed with a respiratory depression event were excluded. We identified 74,419 beneficiaries who were included in our final cohort for examining the association between respiratory depression and concurrent use (**Fig 14)**. Among these beneficiaries, 56,595 had diagnoses of chronic pain, 47,834 were diagnosed with acute pain, and 29,176 beneficiaries were included in our mental health sub-cohort. In our chronic pain sub-cohort, we identified 4322 cases who were matched to 16,804 controls. The acute pain sub-cohort included 3,795 cases and 14,730 controls and the mental health sub-cohort included 2,637 cases and 10,199 controls.

Figure 14. Nest cohort for respiratory depression



Section B.2. Descriptive and Bivariate results

Baseline characteristics of cases and controls included in each sub-cohort are presented in **Tables VI.B.2.1-VI.B.2.3.** Across all sub-cohorts, majority of cases and controls were younger than 65 (acute pain: cases 66.5% and controls 67%; chronic pain: cases 65.7% and controls 66.2%; mental health diagnoses: cases 71.2% and controls 71.8%), female (acute pain: cases 62% and controls 62.3%; chronic pain: cases 61.1% and controls 61.5%;; mental health diagnoses: cases 66.1% and controls 66.7%) and dually eligible (chronic pain: cases 65.7% and controls 66.2%; acute pain: cases 66.5% and controls 67%; mental health diagnoses: cases 71.2% and controls 71.8%). In addition, cases and controls tended to have been previously diagnosed with pain and mental health conditions and this pattern was consistent across all sub-cohorts examined. Overall, baseline characteristics did not differ significantly between cases and controls. Across all sub-cohorts, cases tended to utilize higher doses of opioids when compared to controls.

Table VI.B.2.1. Baseline characteristics of matched cases and controls with acute pain

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	2,524 (66.5)	9,869 (67)	0.57
>65+	1,271 (33.5)	4,861 (33)	
Gender			
Females	2,352 (62)	9,181 (62.3)	0.69
Males	1,443(38)	5,549 (37.7)	
Ethnicity			
White	3,027 (79.8)	111,879 (80.6)	0.35
Black	572(15.1)	2,162 (14.7)	
Others	196 (5.2)	689 (4.7)	
Health insurance			
Dual eligibility	2,517 (66.3)	9,792 (66.5)	0.9
Chronic pain	2,960 (78)	11,357 (77.1)	0.7
Acute pain	-------	--------	
Mental Health conditions	2,230 (58.8)	8,454 (57.4)	0.06
Substance Use disorder	297 (7.8)	1,081 (7.3)	0.3
Other Clinical factors			
Chronic lung disease	1,346(35.5)	4,992 (33.9)	0.06
Diabetes	1,403 (37)	5,216 (35.4)	0.07
Myocardial Infarction	120(3.2)	389 (2.6)	0.07
Congestive Heart Failure	430 (11.3)	1,338 (9.1)	0.06
Peripheral Vascular disease	351(9.3)	1,309 (8.9)	0.5
Connective tissue disease	234(6.2)	966 (6.6)	0.4
Cerebrovascular disease	291 (7.7)	1,056 (7.2)	0.3
Peptic ulcer disease	45 (1.2)	142 (1)	0.3
Liver disease	197 (5.2)	606 (4.1)	0.08
Hypertension	1,693 (44.6)	6,341 (43.1)	0.08
Hypothyroidism	473 (12.5)	1,866 (12.7)	0.7
Seizures	224 (5.9)	670 (4.6)	0.07

Table VI.B.2.1. Baseline characteristics of matched cases and controls with acute pain continued

Dementia	73 (1.9)	307 (2.1)	0.5
Pharmacologic factors			
Muscle relaxants	992 (26.1)	3,808 (25.9)	0.7
Benzodiazepines	1,167 (30.8)	4,256 (28.)	0.06
Gabapentin	986 (26)	3,535 (24)	0.05
Pregabalin	324 (8.5)	1,226 (8.3)	0.7
Non-benzodiazepine sedatives	575 (15.2)	2,104 (14.3)	0.2
Opioids	2,594 (68.4)	9,869 (67)	0.06
Opioid dose			<.01
<50MME	2,702 (71.8)	11,127 (76.2)	
51-90MME	608 (16.2)	2,058 (14.1)	
91MME-150MME	238 (6.3)	813 (5.6)	
>150MME	217 (5.8)	614 (4.2)	
Number of Outpatient visits			
None	15 (0.4)	72 (0.5)	0.06
1-5	254 (6.7)	1,093 (7.4)	
6-10	510 (13.4)	2,171 (14.7)	
>10	3,016 (79.5)	11,394 (77.4)	
Number of Inpatient visits			0.06
None	2,990 (78.8)	11,912 (80.9)	
1	563 (14.8)	2,128 (14.5)	
>1	242 (6.4)	690 (4.7)	

Table VI.B.2.2. Baseline characteristics of cases and controls with chronic pain

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	2,839 (65.7)	11,128 (66.2)	0.51
>65+	1,483 (34.3)	5,676 (33.8)	
Gender			
Females	2,639 (61.1)	10,328 (61.5)	0.62
Males	1,683(40)	6,476 (38.5)	
Ethnicity			
White	3,458 (80)	13,562 (80.7)	0.45
Black	651(15.1)	24,80 (14.8)	
Others	213 (4.9)	762 (4.5)	
Health insurance			
Dual eligibility	2,823 (65.3)	11,008 (65.5)	0.81
Chronic pain	----------	----------	
Acute pain	3,614 (83.6)	13,747 (81.8)	0.06
Mental Health conditions	2,501 (57.9)	9,410 (56)	0.07
Substance Use disorder	325 (7.5)	1,228 (7.3)	0.6
Other clinical factors			
Chronic lung disease	1,527(35.3)	5,713 (31.6)	0.07
Diabetes	1,582 (36.6)	5,881 (36)	0.07
Myocardial Infarction	133(3.1)	422 (2.5)	0.08
Congestive Heart Failure	481 (11.1)	1,512 (9)	0.05
Peripheral Vascular disease	383(8.9)	1,428 (8.5)	0.4
Connective tissue disease	263(6.1)	1,094 (6.5)	0.31
Cerebrovascular disease	326 (7.5)	1,187 (7.1)	0.28
Peptic ulcer disease	44 (1)	168 (1)	
Liver disease	206 (4.8)	729 (4.3)	0.2
Hypertension	1,905 (44.1)	7,124 (42.4)	0.06
Hypothyroidism	507 (11.7)	2,021 (12)	0.6
Seizures	238 (5.5)	765 (4.6)	
Dementia	80 (1.9)	266(1.6)	0.2

Table VI.B.2.2. Baseline characteristics of cases and controls with chronic pain continued

Pharmacologic factors			
Muscle relaxants	1,146 (26.5)	4,260 (25.4)	0.1
Benzodiazepines	1,341 (31)	4,957 (29.5)	0.07
Gabapentin	1,113 (25.8)	4,054 (24.1)	0.06
Pregabalin	362 (8.4)	1,354 (8.1)	0.5
Non-benzodiazepine sedatives	651 (15.1)	2,388 (14.2)	0.2
Opioids	3,003 (69.5)	11,427 (68)	0.06
Opioid dose			
0-50MME	3,063(71.4)	12,657 (75.7)	<.01
51-90MME	691 (6.1)	2,281 (13.6)	
91-150MME	279 (6.5)	972 (5.8)	
>200MME	257 (6)	808 (4.8)	
Number of Outpatient visits			
None	19 (0.4)	90 (0.5)	0.06
1-5	364 (8.4)	1,596 (9.5)	
6-10	649 (15)	2,705 (16)	
>10	3,290 (76.1)	12,434 (74)	
Number of Inpatient visits			
None	3,460 (80.1)	13,779 (82)	0.07
1	609 (14.1)	2,178 (13)	
>1	253 (5.9)	840 (5)	

Table VI.B.2.3. Baseline characteristics of cases and controls with mental health conditions

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	1,877 (71.2)	7,318 (71.8)	0.6
>65+	760 (28.8)	2,881 (28.3)	
Gender			
Females	1,743 (66.1)	6,800 (66.7)	0.6
Males	894 (33.9)	3,399 (33.3)	
Ethnicity			
White	2,218 (84.1)	8,649 (84.8)	0.6
Black	309(11.7)	1,155 (11.3)	
Others	110 (4.2)	395 (3.9)	
Health insurance			
Dual eligibility	1,846 (70)	7,159 (70.2)	0.8
Chronic pain	2,471 (93.7)	9,539 (93.5)	0.7
Acute pain	2,219 (84.2)	8,465 (83)	0.07
Mental Health conditions	----------	----------	
Substance Use disorder	241 (9.1)	856 (8.4)	0.2
Other Clinical factors			
Chronic lung disease	1,013(38.4)	3,733 (34.2)	0.05
Diabetes	914 (34.7)	3,365 (33)	0.06
Myocardial Infarction	82 (3.1)	283 (2.8)	0.4
Congestive Heart Failure	273 (10.4)	857 (8.4)	0.05
Peripheral Vascular disease	213(8.1)	774 (7.6)	0.4
Connective tissue disease	133(5)	499 (4.9)	0.7
Cerebrovascular disease	212 (8.0)	749 (7.3)	0.2
Peptic ulcer disease	30 (1.1)	91 (0.9)	0.2
Liver disease	138 (5.2)	425 (4.2)	0.07
Hypertension	1,167 (44.3)	4,366 (42.8)	0.2
Hypothyroidism	334 (12.7)	1,324 (13)	0.7
Seizures	182 (6.9)	558 (5.5)	

Table VI.B.2.3. Baseline characteristics of cases and controls with mental health conditions continued

Dementia	55 (2.1)	214 (2.1)	0.9
Pharmacologic factors			
Muscle relaxants	759 (28.8)	2,883 (28.3)	0.6
Benzodiazepines	1,063 (40.3)	3,908(38.3)	0.06
Gabapentin	749 (28.4)	2,727 (26.7)	0.08
Pregabalin	232 (8.8)	876 (8.6)	0.7
Non-benzodiazepine sedatives	486 (18.4)	1,731 (17)	0.08
Opioids	1,906 (72.3)	7,241 (71)	0.08
Opioid dose			<.01
<50MME	1,815 (69.3)	7.574 (74.6)	
51-90MME	456 (17.4)	1,491 (14.7)	
91MME-150MME	182 (7)	599 (5.9)	
>150MME	166(6.3)	491 (4.8)	
Number of Outpatient visits			
None	----------	36 (0.4)	0.3
1-5	----------	744 (7.3)	
6-10	324 (12.3)	1,359 (13.3)	
>10	2,127 (80.7)	8,060 (79)	
Number of Inpatient visits			
None	2,045 (77.6)	8,066 (79.1)	0.2
1	412 (15.6)	1,508 (14.8)	
>1	180 (6.8)	625 (6.1)	

Section B.3. Multivariable results

Conditional logistic regression

Among disabled Medicare beneficiaries with chronic pain, 486 (11.2%) of cases had concurrent utilization of GABA+OP+BZD, and 667 (15.4%) of cases had concurrent utilization of GABA+OP when compared to 9.5% and 15.5% of controls, respectively. In the acute pain cohort, 437 (11.5%) of cases had concurrent utilization of GABA+OP+BZD, and 568 (15%) of cases had concurrent utilization of GABA+OP when compared to 9.3% and 14.7% of controls, respectively. Within the mental health sub-cohort, 377 (14.3%) of cases had concurrent utilization of GABA+OP+BZD, and 382 (14.5%) of cases had concurrent utilization of GABA+OP when compared to 12.8% and 15% of controls, respectively.

Among disabled beneficiaries with chronic pain, we noted that the odds of respiratory depression were 56% higher among GABA+OP+BZD users and 22% higher among GABA+OP users when compared to OP only users. After adjusting for potential confounders, the odds of respiratory depression remained significantly higher among GABA+OP+BZD users [1.24(1.11-1.38)] but not among GABA+OP [1.02(1.00-1.12)] users. In unadjusted analyses, GABA+OP+BZD and GABA+OP use was associated with higher odds of respiratory depression among disabled beneficiaries with acute pain and our findings remained significant even after adjusting for all potential confounders previously described [GABA+OP+BZD: 1.34(1.19-1.52)] and GABA+OP [1.06(1.01-1.18)]. Among disabled beneficiaries with mental health conditions, after adjusting for all potential confounders, GABA+OP+BZD [1.16(1.02-1.32)] use remained significantly

associated with 16% higher odds of respiratory depression. However, GABA+OP use[0.98(0.86-1.12)] was no longer significantly associated with respiratory depression.

Table VI.B.3. Conditional logistic regression analysis: Association between concurrent use category and respiratory depression among disabled beneficiaries

		Unadjusted OR(95%CI)	**Adjusted OR(95%CI)**
Sub-group	**Concurrent use category**		
Acute Pain	GABA+OP+BZD	**1.62 (1.45-1.80)**	**1.35 (1.19-1.52)**
	GABA+OP	**1.23 (1.12-1.34)**	**1.10(1.03-1.18)**
	OP only	reference	Reference
Chronic Pain	GABA+OP+BZD	**1.56 (1.41-1.72)**	**1.24 (1.11-1.38)**
	GABA+OP	**1.22 (1.21-1.33)**	**1.06 (1.01-1.12)**
	OP only	reference	Reference
Mental Health conditions	GABA+OP+BZD	**1.37 (1.22-1.54)**	**1.16 (1.02-1.32)**
	GABA+OP	**1.27 (1.13-1.42)**	0.98 (0.86-1.12)
	OP only	reference	Reference

Significant findings are highlighted in bold
OP only is reference category

Section C. Opioid related overdose

Results for Section C are discussed under study sample, descriptive and bivariate analysis, and multivariable results.

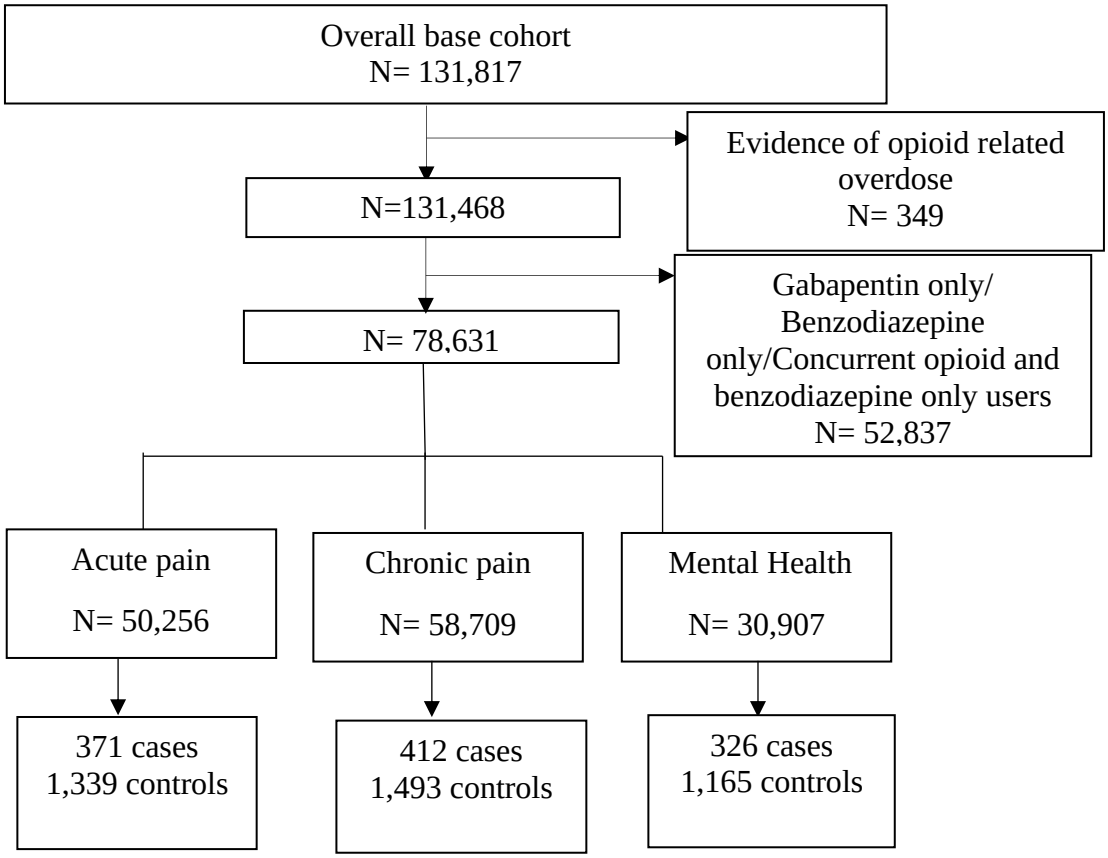
Section C.1. Study sample

Of the 131, 817 disabled beneficiaries who were included in our overall nest cohort, we excluded 349 beneficiaries who were previously diagnosed with an opioid related overdose. We identified 78,631 beneficiaries who were included in our final cohort for examining the association between opioid related overdose and concurrent use. Among these beneficiaries, 58,709 had diagnoses of chronic pain; 50,256 and 30,907 beneficiaries were included in our acute pain and mental health sub-cohort, respectively. In our chronic pain sub-cohort, we identified 412 cases who were matched to 1,493 controls. In our acute pain sub-cohort, 371 cases and 1,339 controls were included and 326 cases matched to 1,165 controls were included in our mental health sub-cohort **(Figure 15.)**

Section C.2. Descriptive and Bivariate results

Baseline characteristics of cases and controls included in each sub-cohort are presented in Tables **VI.C.2.1-VI.C.2.3.** Across all sub-cohorts, majority of cases and controls were younger than 65 (acute pain: cases 83% and controls 83.6%; chronic pain: cases 83.7% and controls 84%; mental health diagnoses: cases 84.7% and controls 86.1%), female (acute pain: cases 62% and controls 62.9%; chronic pain: cases 62.9% and controls 62.6%; mental health diagnoses: cases 63.2% and controls 63.9%) and

Figure 15. Nest cohort for opioid related overdose



dually eligible (acute pain: cases 70.4% and controls ; chronic pain: cases 68.7% and controls 70.1%; 71.4%; mental health diagnoses: cases 73.3% and controls 73.7%). In addition, cases and controls tended to have been previously diagnosed with pain and mental health conditions and this pattern was consistent across all sub-cohorts examined. Overall, baseline characteristics did not differ significantly between cases and controls. Across all sub-cohorts, cases utilized higher opioid doses than controls.

Table VI.C.2.1. Baseline characteristics of matched cases and controls with acute pain

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	308(83)	1,120 (83.6)	0.8
>65+	63 (17)	219 (17)	
Gender			
Females	230 (62)	842 (62.9)	0.7
Males	141(38)	497 (37.1)	
Ethnicity			
White	326 (87.9)	1,201 (89.7)	0.6
Black	----------	110 (8.2)	
Others	----------	28 (2.1)	
Health insurance			
Dual eligibility	261 (70.4)	956 (71.4)	0.7
Chronic pain	360 (97)	1,291 (96.4)	0.6
Acute pain	----------	----------	0.6
Mental Health conditions	282 (76)	951 (71)	0.08
Substance Use disorder	142(38.3)	428 (32)	0.07
Other Clinical factors			
Chronic lung disease	110 (29.7)	367 (27.4)	0.4
Diabetes	102 (27.5)	329 (24.6)	0.3
Myocardial Infarction	----------	30 (2.2)	0.6
Congestive Heart Failure	25 (6.7)	83 (6.2)	0.7
Peripheral Vascular disease	21(5.7)	69 (5.2)	0.7
Connective tissue disease	16 (4.3)	63 (4.7)	0.8
Cerebrovascular disease	20 (5.4)	72 (5.4)	0.9
Peptic ulcer disease	----------	17 (1.3)	0.2
Liver disease	24 (6.5)	93 (7)	0.7
Hypertension	153 (41.2)	485 (36.2)	0.08
Hypothyroidism	47(12.8)	181 (13.5)	0.7

Table VI.C.2.1. Baseline characteristics of matched cases and controls with acute pain continued

Seizures	24 (6.5)	71 (5.3)	0.4
Dementia	----------	----------	0.9
Pharmacologic factors			
Muscle relaxants	155 (41.8)	511 (38.2)	0.2
Benzodiazepines	187 (50.4)	603(45)	0.07
Gabapentin	131 (35.3)	409 (30.6)	0.08
Pregabalin	36 (9.7)	139 (10.4)	0.7
Non-benzodiazepine sedatives	83 (22.4)	244 (18.2)	0.07
Opioids	301 (81.1)	1,053 (78.6)	0.3
Opioid dose			<.001
<50MME	174 (47.3)	928(69.7)	
51-90MME	79 (21.5)	220 (16.5)	
91MME-150MME	59 (16)	105(7.9)	
>150MME	56 (15.2)	79(5.9)	
Number of Outpatient visits			
None	----------	----------	0.06
1-5	----------	----------	
6-10	27(7.3)	147 (11)	
>10	321 (86.5)	1,085 (81)	
Number of Inpatient visits			
None	266 (71.7)	1,037 (77.5)	0.06
1	71 (19.1)	209 (15.6)	
>1	34 (9.2)	93 (7)	

Table VI.C.2.2. Baseline characteristics of cases and controls with chronic pain

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	345 (83.7)	1,254 (84)	0.9
>65+	67 (16.3)	5239(16)	
Gender			
Females	259 (62.9)	1935 (62.6)	0.9
Males	153(37.1)	558 (37.4)	
Ethnicity			
White	361 (87.6)	1,331 (89.2)	0.6
Black	----------	132 (8.8)	
Others	----------	30 (2)	
Health insurance			
Dual eligibility	283 (68.7)	1,046 (70.1)	0.6
Chronic pain			
Acute pain	364 (88.4)	1,290 (86.4)	0.3
Mental Health conditions	301 (73.1)	1,054 (70.5)	0.2
Substance Use disorder	155 (37.6)	507 (33.6)	0.08
Other clinical factors			
Chronic lung disease	119(28.9)	367 (24.6)	0.07
Diabetes	108 (26.2)	390 (26.1)	0.9
Myocardial Infarction	----------	30 (2)	0.6
Congestive Heart Failure	28 (6.8)	105 (7)	0.9
Peripheral Vascular disease	25 (6.1)	86 (5.8)	0.8
Connective tissue disease	16(3.9)	76 (5.1)	0.3
Cerebrovascular disease	22 (5.3)	61 (4.1)	0.3
Peptic ulcer disease	44 (1)	168 (1)	
Liver disease	23 (5.6)	83 (5.6)	0.9
Hypertension	153 (40)	553 (37)	0.4
Hypothyroidism	52 (12.6)	199 (13.3)	0.7
Seizures	20 (4.9)	66 (4.4)	0.7
Dementia	----------	----------	0.1

Table VI.C.2.2. Baseline characteristics of cases and controls with chronic pain continued

Pharmacologic factors			
Muscle relaxants	174 (42.2)	553 (37)	0.06
Benzodiazepines	209 (50.7)	684 (45.8)	0.06
Gabapentin	139 (33.7)	435 (29.1)	0.07
Pregabalin	40 (9.7)	150 (10.1)	0.8
Non-benzodiazepine sedatives	89 (21.6)	259 (17.4)	0.05
Opioids	335 (81.3)	1,167 (78.2)	0.2
Opioid dose			<.001
0-50MME	197 (48.3)	1,009(68.1)	
51-90MME	89 (21.8)	254 (17.1)	
91-150MME	62 (15.2)	118(8)	
>200MME	60 (14.7)	101(6.8)	
Number of Outpatient visits			0.06
None	----------	----------	
1-5	29 (7)	136 (9.1)	
6-10	37 (9)	179 (12)	
>10	345 (83.7)	1,194 (80)	
Number of Inpatient visits			0.03
None	302 (73.3)	1,183 (79.2)	
1	74 (18)	224 (13.3)	
>1	36 (8.7)	112 (7.5)	

Table VI.C.2.3. Baseline characteristics of cases and controls with mental health conditions

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	276 (84.7)	1,003 (86.1)	0.5
>65+	50 (15.3)	162(13.9)	
Gender			
Females	206 (63.2)	744 (63.9)	0.8
Males	120 (36.8)	421 (36.1)	
Ethnicity			
White	297 (91.1)	1,085 (84.8)	0.9
Black	29(8.9)	80 (16.2)	
Others			
Health insurance			
Dual eligibility	239 (73.3)	858 (73.7)	0.8
Chronic pain	307 (94.2)	1,070 (92)	0.2
Acute pain	288 (88.3)	988 (84.8)	0.1
Mental Health conditions	----------	----------	
Substance Use disorder	133 (40.8)	419(36)	0.08
Other Clinical factors			
Chronic lung disease	102 (31.3)	322 (27.6)	0.2
Diabetes	83 (25.5)	281 (24.1)	0.6
Myocardial Infarction	----------	30 (2.6)	0.9
Congestive Heart Failure	23 (7.1)	100 (8.6)	0.8
Peripheral Vascular disease	17 (5.2)	41 (3.5)	0.2
Connective tissue disease	13(4)	64 (5.5)	0.3
Cerebrovascular disease	14 (4.3)	56 (4.8)	0.7
Peptic ulcer disease	----------	18 (1.6)	0.2
Liver disease	20 (6.1)	74 (6.4)	0.9
Hypertension	130 (40)	434 (37.3)	0.4
Hypothyroidism	45 (13.8)	155 (13.3)	0.8
Seizures	19 (5.9)	56(4.9)	0.5

Table VI.C.2.3. Baseline characteristics of cases and controls with mental health conditions continued

Dementia	----------	----------	-------
Pharmacologic factors			
Muscle relaxants	133 (40.8)	408 (35)	0.05
Benzodiazepines	181 (55.5)	593 (50.9)	0.1
Gabapentin	107 (32.8)	333 (28.6)	0.1
Pregabalin	36 (11)	110 (9.4)	0.4
Non-benzodiazepine sedatives	83 (25.5)	281 (24.1)	0.6
Opioids	261 (80.1)	899 (77.2)	0.3
Opioid dose	164 (51.6)	791(70)	<.001
<50MME	70 (22)	179 (15.8)	
51-90MME	46 (14.5)	82 (7.2)	
91MME-150MME	38 (12)	82 (7.2)	
>150MME			
Number of Outpatient visits			
None	----------	----------	0.2
1-5	----------	----------	
6-10	27 (8.3)	139 (11.9)	
>10	278 (85.3)	944 (81)	
Number of Inpatient visits			
None	230 (70.6)	868 (74.5)	0.4
1	64 (19.6)	196 (16.8)	
>1	32 (9.8)	101 (8.7)	

Section C.3. Multivariable results

Conditional logistic regression

Among disabled Medicare beneficiaries with chronic pain, 81 (19.7%) of cases had concurrent utilization of GABA+OP+BZD, and 68(16.5%) of cases had concurrent utilization of GABA+OP when compared to 15.4% and 14.7% of controls, respectively. In the acute pain cohort, 78 (21%) of cases had concurrent utilization of GABA+OP+BZD, and 63 (16.9%) of cases had concurrent utilization of GABA+OP when compared to 15.9% and 15.3% of controls, respectively. Within the mental health sub-cohort, 74 (22.7%) of cases had concurrent utilization of GABA+OP+BZD, and 48 (14.7%) of cases had concurrent utilization of GABA+OP when compared to 17.8% and 12.9% of controls, respectively.

Among disabled beneficiaries with chronic pain, we noted that crude the odds of opioid related overdose were 3.24 times higher among GABA+OP+BZD users and 43% higher among GABA+OP users when compared to OP only users. After adjusting for potential confounders, the odds of opioid related overdose remained significantly higher among GABA+OP+BZD users [1.47(1.07-2.00)] and GABA+OP [1.23(1.01-1.68)] users. Among disabled beneficiaries with acute pain and mental health disorders, though crude analyses suggested higher odds of opioid related overdose for both exposure groups (compared to OP only), after adjusting for potential confounding only GABA+OP+BZD use was significantly associated with opioid related overdose (acute pain: [1.43(1.04-1.98)] and mental health [1.44 (1.04-2.00)].

Table VI.C.3. Conditional logistic regression analysis: Association between concurrent use category and opioid overdose among Medicare disabled beneficiaries

		Unadjusted OR(95%CI)	Adjusted OR(95%CI)
Sub-group	**Concurrent use category**		
Acute Pain	GABA+OP+BZD	**3.51 (2.75-4.47)**	**1.43 (1.04-1.98)**
	GABA+OP	**1.60 (1.23-2.08)**	1.21 (0.90-1.70)
	OP only	reference	Reference
Chronic Pain	GABA+OP+BZD	**3.24 (2.56-4.09)**	**1.47 (1.07-2.00)**
	GABA+OP	**1.63 (1.27-1.95)**	**1.23 (1.04-1.48)**
	OP only	reference	Reference
Mental Health conditions	GABA+OP+BZD	**2.56 (1.99-3.28)**	**1.44 (1.04-2.00)**
	GABA+OP	**1.48 (1.10-2.00)**	1.29 (0.90-1.85)
	OP only	reference	Reference

Significant findings are highlighted in bold
OP only is reference category

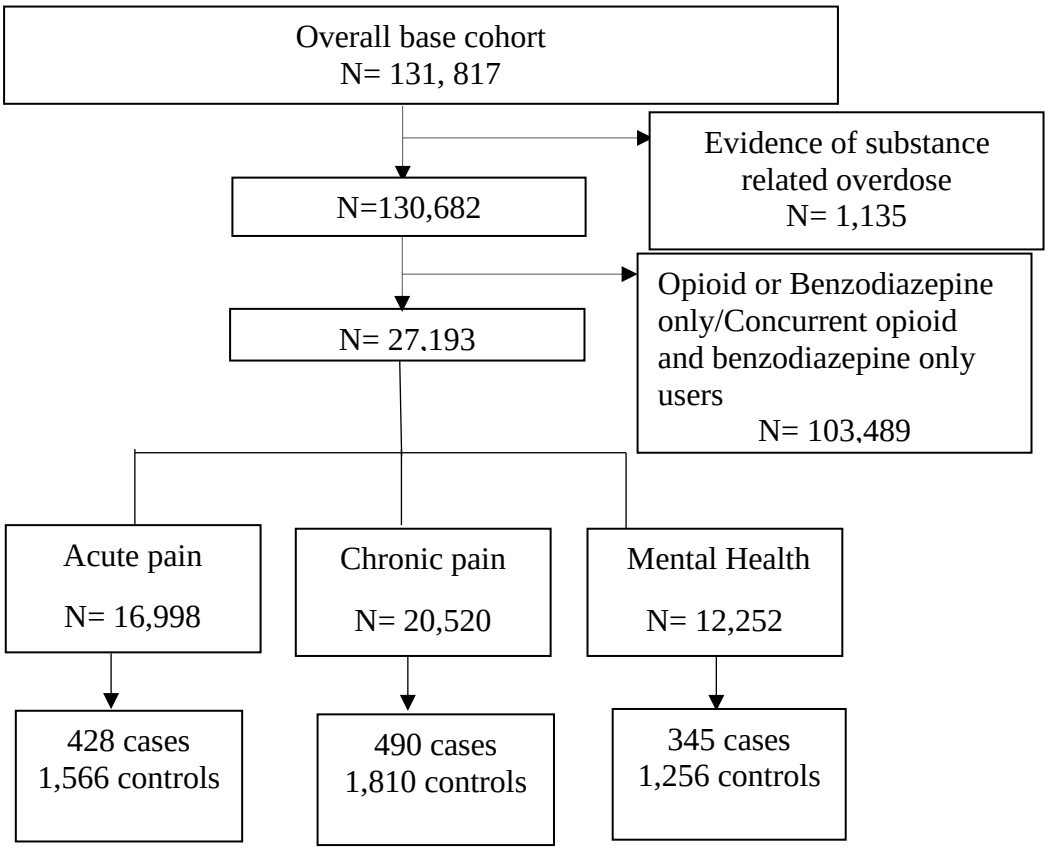
Section D. Substance-related overdose

Results for Section D are discussed under study sample, descriptive and bivariate analyses, and multivariable results.

Section D.1 Study sample

After excluding 1,135 beneficiaries who were previously diagnosed with a substance-related overdose, we identified 27,193 beneficiaries who were included in our final cohort for examining the association between substance related overdose and concurrent use . Among these beneficiaries, 20,520 had diagnoses of chronic pain;

Figure 16. Nest cohort for substance related overdose



16998 and 12,252 beneficiaries were included in our acute pain and mental health sub-cohort, respectively. Among disabled beneficiaries with chronic pain, we identified 490 cases who were matched to 1,810 controls. In our acute pain sub-cohort, 428 cases were matched to 1,566 controls and in our mental health sub-cohort, 345 cases were matched to 1,256 controls (**Figure 16.)**

Section D.2.Descriptive and Bivariate results

Baseline characteristics of cases and controls included in each sub-cohort are presented in Tables **VI.D.2.1-VI.D.2.3**. Across all sub-cohorts, majority of cases and controls were younger than 65 (chronic pain: cases 84.9% and controls 84.7%; acute pain: cases 85.3% and controls 84.7%; mental health diagnoses: cases 86.1% and controls 86.1%), female (chronic pain: cases 63.1% and controls 63%; acute pain: cases 64% and controls 64.2%; mental health diagnoses: cases 63.2% and controls 63.9%) and dually eligible (chronic pain: cases 75.3% and controls 75.4%; acute pain: cases 77.8% and controls 78%; mental health diagnoses: cases 78.3% and controls 78.5%). In addition, cases and controls tended to have been previously diagnosed with pain and mental health conditions and this pattern was consistent across all sub-cohorts examined. Overall, baseline characteristics were similar between cases and controls. In the acute and chronic pain sub-cohort, cases tended to utilize higher gabapentin doses (very high category) than controls; however, in the mental health sub-cohort, gabapentin dose did not differ significantly between cases and controls.

Table VI.D.2.1. Baseline characteristics of matched cases and controls with acute pain

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	365 (85.3)	1,326 (84.7)	0.8
>65+	63 (14.7)	240 (15.3)	
Gender			
Females	274 (64)	1,006 (64.2)	0.9
Males	154 (36)	560 (35.8)	
Ethnicity			
White	381 (89)	1,392 (88.9)	0.9
Black	33 (7.7)	125 (8)	
Others	14 (3.3)	49 (3.1)	
Health insurance			
Dual eligibility	333 (77.8)	1,221 (78)	0.9
Chronic pain	412 (96.3)	1,492 (95.3)	0.4
Acute pain	----------	----------	
Mental Health conditions	344 (80.4)	1,238 (79.1)	0.6
Substance Use disorder	83 (19.4)	251 (16)	0.06
Other Clinical factors			
Chronic lung disease	126 (29.4)	442 (28.2)	0.6
Diabetes	121 (28.3)	490 (31.3)	0.2
Myocardial Infarction	12 (2.8)	40 (2.6)	0.8
Congestive Heart Failure	26 (6.1)	99 (6.3)	0.9
Peripheral Vascular disease	24 (5.6)	88 (5.6)	0.9
Connective tissue disease	17 (4)	59 (3.8)	0.8
Cerebrovascular disease	26 (6.1)	101 (6.5)	0.8
Peptic ulcer disease	8 (1.9)	20 (1.3)	0.4
Liver disease	27(6.3)	80(5.1)	0.3
Hypertension	161 (37.6)	607(38.8)	0.7
Hypothyroidism	59 (13.8)	196 (12.5)	0.5
Seizures	48 (11.2)	141 (9)	0.2

Table VI.D.2.1. Baseline characteristics of matched cases and controls with acute pain continued

Dementia	8 (1.9)	31 (2)	0.9
Pharmacologic factors			
Muscle relaxants	173 (40.4)	596 (38.1)	0.4
Benzodiazepines	226 (52.8)	786 (50.2)	0.3
Gabapentin	305 (71.3)	1,080 (69)	0.4
Gabapentin dose			0.03
<900mg	183 (43.3)	781 (50.5)	
901-1799mg	123 (29.1)	356 (23)	
1800-2699mg	87 (20.6)	320 (20.7)	
>2700mg	30 (7.1)	90 (5.8)	
Pregabalin	21 (4.9)	65 (4.2)	0.5
Non-benzodiazepine sedatives	84 (19.6)	266 (17)	0.2
Opioids	323 (75.5)	1,147 (73.2)	0.4
Number of Outpatient visits			
None	1 (0.2)	6 (0.4)	0.9
1-5	19 (4.4)	68 (4.3)	
6-10	48 (11.2)	191 (12.2)	
>10	360 (84.1)	1,301 (83.1)	
Number of Inpatient visits			
None	325 (75.93)	1,207 (77.08)	0.8
1	67 (15.65)	237 (15.13)	
>1	36 (8.41)	122 (7.79)	

Table VI.D.2.2. Baseline characteristics of cases and controls with chronic pain

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	416 (84.9)	1533 (84.7)	0.9
>65+	74 (15.1)	277 (15.3)	
Gender			
Females	309 (63.1)	1,138 (62.9)	0.9
Males	181(36.9)	672 (37.1)	
Ethnicity			
White	439 (89.6)	1619 (89.5)	0.9
Black	33 (6.7)	125 (6.9)	
Others	18 (3.7)	66 (3.7)	
Health insurance			
Dual eligibility	369 (75.3)	1364 (75.4)	0.9
Chronic pain	----------	----------	
Acute pain	418 (85.3)	1,494 (82.5)	0.1
Mental Health conditions	393 (80.2)	1,415 (78.2)	0.3
Substance Use disorder	92 (18.8)	291 (16.1)	0.1
Other clinical factors			
Chronic lung disease	139 (28.4)	502 (27.7)	0.8
Diabetes	137 (28)	519 (28.7)	0.8
Myocardial Infarction	14 (2.9)	59 (3.3)	0.7
Congestive Heart Failure	27 (5.5)	112 (6.2)	0.6
Peripheral Vascular disease	25 (5.1)	97 (5.4)	0.8
Connective tissue disease	20 (4.1)	73 (4.)	0.9
Cerebrovascular disease	32 (6.5)	118 (6.5)	0.9
Peptic ulcer disease	8 (1.6)	27 (1.5)	0.8
Liver disease	30 (6.1)	100 (5.5)	0.6
Hypertension	185 (37.8)	677 (37.4)	0.9
Hypothyroidism	64 (13.1)	246 (13.6)	0.8
Seizures	58 (11.8)	199 (11)	0.1
Dementia	9 (1.84)	32 (1.77)	0.9

Table VI.D.2.2. Baseline characteristics of cases and controls with chronic pain continued

Pharmacologic factors			
Muscle relaxants	200 (40.8)	688 (38)	0.3
Benzodiazepines	260 (53.1)	928 (51.3)	0.5
Gabapentin	347 (70.8)	1,216 (67.2)	0.1
Gabapentin dose			0.2
<900mg	216 (44.5)	888 (49.6)	
901-1799mg	129 (26.6)	435 (24.3)	
1800-2699mg	103 (21.2)	358 (20)	
>2700mg	37 (7.6)	109 (6.1)	
Pregabalin	22 (4.5)	86 (4.8)	0.8
Non-benzodiazepine sedatives	95 (19.4)	311 (17.2)	0.3
Opioids	359 (73.3)	1,259 (69.6)	0.1
Number of Outpatient visits			
None	1 (0.2)	4 (0.2)	0.9
1-5	23 (4.7)	89 (4.9)	
6-10	57 (11.6)	219 (12.1)	
>10	409 (83.5)	1,498 (82.8)	
Number of Inpatient visits			
None	375 (76.5)	1,417 (78.3)	0.6
1	73 (14.9)	259 (14.3)	
>1	42 (8.6)	134 (7.4)	

Table VI.D.2.3. Baseline characteristics of cases and controls with mental health conditions

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	297 (86.1)	1,081 (86.1)	0.9
>65+	48 (13.9)	175 (13.9)	
Gender			
Females	218 (63.2)	802 (63.9)	0.8
Males	127 (36.8)	454 (36.2)	
Ethnicity			
White	316 (91.6)	1,155 (91.9)	0.9
Black	19 (5.5)	67 (5.3)	
Others	10 (2.9)	34 (2.7)	
Health insurance			
Dual eligibility	270 (78.3)	986 (78.5)	0.9
Chronic pain	331 (95.9)	1,177 (93.7)	0.1
Acute pain	335 (97.9)	1,210 (96.3)	0.1
Mental Health conditions	----------	----------	
Substance Use disorder	70 (20.3)	203 (16.2)	0.07
Other Clinical factors			
Chronic lung disease	111 (32.2)	365 (29.1)	0.3
Diabetes	89 (25.1)	311 (24.8)	0.7
Myocardial Infarction	9 (2.6)	38 (3)	0.7
Congestive Heart Failure	21 (6.1)	73 (5.8)	0.9
Peripheral Vascular disease	15 (4.6)	44 (3.5)	0.5
Connective tissue disease	12 (3.5)	51 (4.1)	0.6
Cerebrovascular disease	23 (6.7)	75 (6)	0.6
Peptic ulcer disease	6 (1.7)	16 (1.3)	0.5
Liver disease	22 (6.4)	68 (5.4)	0.5
Hypertension	135 (39.1)	450 (35.8)	0.3
Hypothyroidism	50 (14.5)	149 (11.9)	0.2
Seizures	58 (13.7)	146 (11.7)	0.1

Table VI.D.2.3. Baseline characteristics of cases and controls with mental health conditions continued

Dementia	6 (1.7)	28 (2.2)	0.6
Pharmacologic factors			
Muscle relaxants	138 (40)	480 (38.2)	0.6
Benzodiazepines	191 (55.4)	676 (53.9)	0.6
Gabapentin	248 (71.9)	880 (70.1)	0.5
Gabapentin dose			0.5
<900mg	191 (45.7)	770 (50.1)	
901-1799mg	105 (25.1)	347 (22.6)	
1800-2699mg	95(22.7)	334 (21.7)	
>2700mg	27(6.5)	86 (5.6)	
Pregabalin	14 (4.06)	45 (3.6)	0.7
Non-benzodiazepine sedatives	71 (20.6)	244 (19.4)	0.6
Opioids	260 (75.4)	894 (71.2)	0.1
Number of Outpatient visits			
None	---------	--------	0.6
1-5	----------	58 (4.6)	
6-10	30 (8.7)	128 (10.2)	
>10	303 (87.8)	1,069 (85.1)	
Number of Inpatient visits			
None	253 (73.3)	961 (76.5)	0.4
1	61 (17.7)	205 (16.3)	
>1	31 (9)	90 (7.2)	

Section D.3. Multivariable results

Conditional Logistic regression

Among disabled Medicare beneficiaries with chronic pain, 190 (38.8%) of cases had concurrent utilization of GABA+OP+BZD, 154 (31.4%) of cases had concurrent utilization of GABA+OP, and 58 (11.8%) had concurrent utilization of GABA+BZD when compared to 33.6%, 32.4% and 10% of controls, respectively. Within the acute pain cohort, 167 (39%) of cases had concurrent utilization of GABA+OP+BZD, 140 (32.7%) of cases had concurrent utilization of GABA+OP, and 49 (11.5%) had concurrent utilization of GABA+BZD when compared to 35%, 30.6% and 8.2% of controls, respectively. Among disabled beneficiaries in the mental health sub-cohort, 143 (41.4%) of cases had concurrent utilization of GABA+OP+BZD, 99 (28.7%) of cases had concurrent utilization of GABA+OP, and 42 (12.2%) had concurrent utilization of GABA+BZD when compared to 40%, 28.1% and 11.7% of controls, respectively.

Among disabled beneficiaries with chronic pain, GABA+OP+BZD use was associated with a more than threefold increased odds of substance-related overdose. Similarly, when compared to GABA only, GABA+BZD and GABA+OP use were associated with higher odds of substance-related overdose. After adjusting for potential confounders, the odds of substance-related overdose remained significantly higher among GABA+OP+BZD [1.70(1.24-2.34)], GABA+BZD [1.68(1.14-2.47)], and GABA+OP [1.39(1.03-1.89)] users. Similarly, among disabled beneficiaries with acute pain and mental health disorders, GABA+OP+BZD, GABA+OP, and GABA+OP+BZD were significantly associated with higher odds of substance-related overdose (compared to

GABA only). Even after adjusting for potential confounding the odds of substance-related overdose was significantly higher among GABA+OP+BZD (acute pain [1.77(1.26-2.50)] and mental health [1.92 (1.31-2.82)]), GABA+BZD (acute pain [2.19(1.43-3.34)] and mental health [1.63 (1.03-2.58)]), and GABA+OP (acute pain [1.74(1.25-2.41)] and mental health [1.64 (1.12-2.39)]) users when compared to GABA only users.

Table VI.D.3. Conditional logistic regression analysis: Association between concurrent use category and substance-related overdose among Medicare disabled beneficiaries

		Unadjusted OR(95%CI)	Adjusted OR(95%CI)
Sub-group	**Concurrent use category**		
Acute Pain	GABA+OP+BZD	**3.28 (2.52-4.27)**	**1.77 (1.26-2.50)**
	GABA+BZD	**2.79 (1.97-3.97)**	**2.19 (1.43-3.34)**
	GABA+OP	**1.98 (1.36-2.06)**	**1.74 (1.25-2.41)**
	GABA only	reference	Reference
Chronic Pain	GABA+OP+BZD	**3.16 (2.49-4.03)**	**1.70 (1.24-2.34)**
	GABA+BZD	**2.76 (2.00-3.82)**	**1.68 (1.14-2.47)**
	GABA+OP	**1.43 (1.11-1.83)**	**1.39 (1.03-1.89)**
	GABA only	reference	Reference
Mental Health conditions	GABA+OP+BZD	**2.04 (1.60-2.61)**	**1.92 (1.31-2.82)**
	GABA+BZD	**1.65 (1.20-2.27)**	**1.63(1.03-2.58)**
	GABA+OP	**1.81 (1.34-2.08)**	**1.64 (1.12-2.39)**
	GABA only	reference	Reference

Significant findings are highlighted in bold
GABA only is reference category

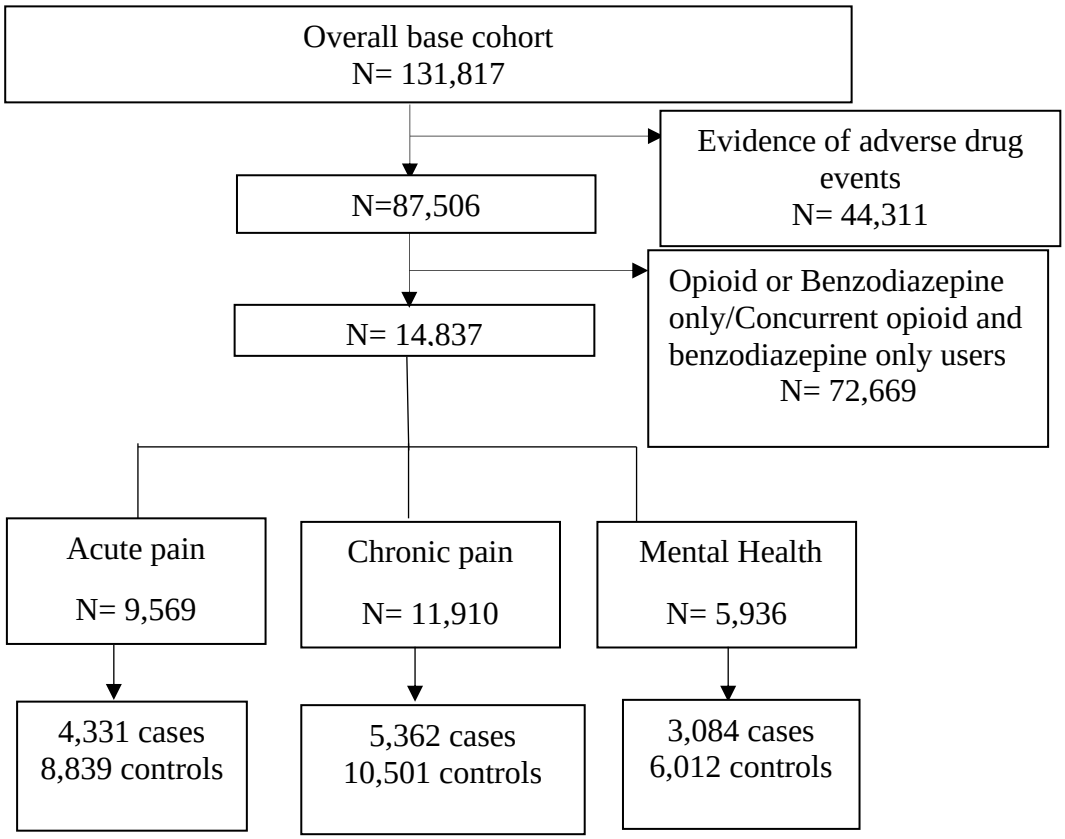
Section E. Adverse drug-related events

Results for Section E are discussed under study sample, descriptive and bivariate analyses, and multivariable results.

Section E.1. Study sample

There were 14,537 beneficiaries in our final cohort for examining the association between substance related overdose and concurrent use. Among these beneficiaries, 11,910 had diagnoses of chronic pain; 9,569 and 5,936 had diagnoses of acute pain and mental health, respectively. Among disabled beneficiaries with chronic pain, we identified 5,362 cases who were matched to 10, 501 controls. In our acute pain sub-

Figure 17. Nest cohort for adverse drug events



cohort, 4,331 cases were matched to 8,839 controls and in our mental health sub-cohort, 3,084 cases were matched to 6,012 controls.

Section E.2. Descriptive and Bivariate results

Baseline characteristics of cases and controls included in each sub-cohort are presented in Tables **VI.E.2.1-VI.E.2.3.** Across all sub-cohorts, majority of cases and controls were younger than 65 (chronic pain: cases 73.4% and controls 73.6%; acute pain: cases 74.2% and controls 74.6%; mental health diagnoses: cases 82.2% and controls 82.8%), female (chronic pain: cases 62.4% and controls 62.5%; acute pain: cases 64.1% and controls 64.3%; mental health diagnoses: cases 64.6% and controls 64.9%) and dually eligible (chronic pain: cases 64.3% and controls 64.6%; acute pain: cases 65.8% and controls 66.3%; mental health diagnoses: cases 70.8% and controls 71.2%). In addition, cases and controls tended to have been previously diagnosed with pain and mental health conditions and this pattern was consistent across all sub-cohorts examined. Overall, baseline characteristics were similar between cases and controls.

Table VI.E.2.1. Baseline characteristics of matched cases and controls with acute pain

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	3363 (74.2)	6,594 (74.6)	0.6
>65+	1,168 (25.8)	2,245 (25.4)	
Gender			
Females	2,906 (64.1)	5,682 (64.3)	0.9
Males	1,625 (35.9)	3157 (35.7)	
Ethnicity			
White	3,632 (80.2)	7,130 (80.7)	0.8
Black	665 (14.7)	1,264 (14.3)	
Others	234 (5.2)	445 (5.1)	
Health insurance			
Dual eligibility	2,982 (65.8)	5,856 (66.3)	0.6
Chronic pain	4,350 (96)	8,526 (96.5)	0.2
Acute pain	---------	--------	
Mental Health conditions	2,445 (54)	4,630 (52.4)	0.1
Substance Use disorder	228 (5)	360 (4.1)	0.1
Other Clinical factors			
Chronic lung disease	913 (20.2)	1,573 (17.8)	0.1
Diabetes	1,619 (35.7)	3,159 (35.7)	0.9
Myocardial Infarction	68 (1.5)	133 (1.5)	0.9
Congestive Heart Failure	226 (5)	303 (3.4)	0.1
Peripheral Vascular disease	331 (7.3)	546 (6.2)	0.1
Connective tissue disease	218 (4.8)	350 (4)	0.1
Cerebrovascular disease	187 (4.1)	363 (4.1)	0.9
Peptic ulcer disease	37 (0.8)	40 (0.5)	0.1
Liver disease	157 (3.5)	251 (2.8)	0.5
Hypertension	1,632 (36)	2,912 (32.9)	0.1
Hypothyroidism	537 (11.9)	938 (10.6)	0.1
Seizures	183(4.1)	311 (3.6)	0.1

Table VI.E.2.1. Baseline characteristics of matched cases and controls with acute pain continued

Dementia	14 (0.31)	22 (0.25)	0.53
Pharmacologic factors			
Muscle relaxants	1,322 (29.2)	2,560 (29)	0.8
Benzodiazepines	1,530 (33.8)	2,908 (32.9)	0.3
Gabapentin	3,182 (70.2)	5,884 (66.6)	0.1
Gabapentin dose			0.00
<900mg	2425(55)	2954 (50.3)	
901-1799mg	911(20.7)	1259 (21.4)	
1800-2699mg	822 (18.6)	1357 (23.1)	
>2700mg	251 (5.7)	308(5.2)	
Pregabalin	169 (3.7)	339 (3.8)	0.8
Non-benzodiazepine sedatives	586 (12.9)	1,001 (11.3)	0.1
Opioids	2,916 (64.4)	5,421 (61.3)	0.1
Number of Outpatient visits			
None	27 (0.6)	40 (0.5)	0.6
1-5	427 (9.4)	813 (9.2)	
6-10	828 (18.3)	1,663 (18.8)	
>10	3,249 (71.7)	6,323 (71.5)	
Number of Inpatient visits			
None	4,056 (89.5)	8,138 (92.1)	0.1
1	389 (8.6)	583 (6.6)	
>1	86 (1.9)	118 (1.3)	

Table VI.E.2.2. Baseline characteristics of cases and controls with chronic pain

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	3,933 (73.3)	7,727 (73.6)	0.8
>65+	1,429 (26.7)	2,774 (26.4)	
Gender			
Females	3,344 (62.7)	6,567 (62.5)	0.8
Males	2,018 (37.6)	3,934 (37.5)	
Ethnicity			
White	4,315 (80.5)	8,503 (81)	0.7
Black	766 (14.3)	1,466 (14)	
Others	281 (5.2)	532 (5.1)	
Health insurance			
Dual eligibility	3,447 (64.3)	6,778 (64.5)	0.8
Chronic pain	----------	----------	
Acute pain	4,344 (81)	8,266 (78.7)	0.1
Mental Health conditions	2,798 (52.2)	5,430 (51.7)	0.6
Substance Use disorder	250 (4.7)	367 (3.5)	0.1
Other clinical factors			
Chronic lung disease	1,011 (189)	1,889 (18)	0.2
Diabetes	1,890 (35.6)	3,576 (34.1)	0.1
Myocardial Infarction	79 (1.5)	141 (1.3)	0.5
Congestive Heart Failure	264 (4.9)	355 (3.4)	0.1
Peripheral Vascular disease	374 (7)	655 (6.2)	0.1
Connective tissue disease	251 (4.7)	481 (4.6)	0.8
Cerebrovascular disease	217 (4.1)	389 (3.7)	0.3
Peptic ulcer disease	36 (0.7)	49 (0.5)	0.1
Liver disease	165 (3.1)	291 (2.8)	0.3
Hypertension	1,873 (34.9)	3,440 (32.8)	0.1
Hypothyroidism	612 (11.4)	1,118 (10.7)	0.1
Seizures	212(4)	303 (2.9)	0.1
Dementia	19 (0.4)	35 (0.3)	0.8

Table VI.E.2.2. Baseline characteristics of cases and controls with chronic pain continued

Pharmacologic factors			
Muscle relaxants	1,552 (28.9)	3,024 (28.8)	0.9
Benzodiazepines	1,770 (33)	3,406 (32.4)	0.5
Gabapentin	3,766 (70)	7,190 (68.5)	0.2
Gabapentin dose			
<900mg	2882 (54.9)	5786 (56.2)	0.1
901-1799mg	1088 (20.7)	2101 (20.4)	
1800-2699mg	984(18.7)	1,913(18.6)	
>2700mg	296(5.6)	495 (4.8)	
Pregabalin	176 (3.3)	408 (3.9)	0.1
Non-benzodiazepine sedatives	670 (12.5)	1,265 (12.1)	0.4
Opioids	3,426 (63.9)	6,516 (62.1)	0.1
Number of Outpatient visits			
None	35 (0.7)	32 (0.3)	0.1
1-5	658 (12.3)	1,326 (12.6)	
6-10	1,056 (19.7)	2,244 (21.4)	
>10	3,613 (67.4)	6,899 (65.7)	
Number of Inpatient visits			
None	4,849 (90.4)	9,752 (92.9)	0.1
1	425 (7.9)	639 (6.1)	
>1	88 (1.6)	110 (1.1)	

Table VI.E.2.3. Baseline characteristics of cases and controls with mental health conditions

	Cases, N(%)	Controls, N(%)	p-value
Socio-demographic factors			
Age			
<65	2,536 (82.2)	4,975 (82.8)	0.5
>65+	548 (17.8)	1,037 (17.3)	
Gender			
Females	1,992 (64.6)	3,899 (64.9)	0.8
Males	1,092 (35.4)	2,113 (35.6)	
Ethnicity			
White	2,609 (84.6)	5,133 (85.4)	0.6
Black	329 (10.7)	611 (10.2)	
Others	146 (4.7)	268 (4.5)	
Health insurance			0.5
Dual eligibility	2,184 (70.8)	4,282 (71.2)	0.9
Chronic pain	2,764 (82.2)	5,433 (90.4)	0.3
Acute pain	2,420 (78.5)	4,687 (78)	0.6
Mental Health conditions	----------	----------	
Substance Use disorder	223 (7.2)	361(6)	0.1
Other Clinical factors			
Chronic lung disease	629 (20.4)	1,094 (18.2)	0.1
Diabetes	903 (29.3)	1,681 (28)	0.2
Myocardial Infarction	47 (1.5)	60 (1)	0.2
Congestive Heart Failure	113 (3.7)	154 (2.6)	0.2
Peripheral Vascular disease	167 (5.4)	257 (4.3)	0.1
Connective tissue disease	115 (3.7)	255 (4.2)	0.2
Cerebrovascular disease	102 (3.3)	206 (3.4)	0.8
Peptic ulcer disease	21 (0.7)	38 (0.6)	0.8
Liver disease	104 (3.4)	181 (3)	0.4
Hypertension	1,004 (32.6)	1821 (30.3)	0.1
Hypothyroidism	379 (12.3)	653 (10.9)	0.1
Seizures	128 (4.2)	214 (3.6)	0.2

Table VI.E.2.3. Baseline characteristics of cases and controls with mental health conditions continued

Dementia	12 (0.4)	13 (0.2)	0.1
Pharmacologic factors			
Muscle relaxants	897 (29.1)	1,784 (29.7)	0.6
Benzodiazepines	1,367 (44.3)	2,543 (42.3)	0.1
Gabapentin	2,237 (72.5)	4,267 (71)	0.1
Gabapentin dose			0.00
<900mg	1,582 (52.6)	2954 (50.3)	
901-1799mg	648 (21.6)	1259 (21.4)	
1800-2699mg	603 (20.1)	1357 (23.1)	
>2700mg	173 (5.8)	308 (5.2)	
Pregabalin	106 (3.4)	173 (2.9)	0.1
Non-benzodiazepine sedatives	459 (14.9)	800 (13.3)	0.1
Opioids	1,908 (61.9)	3,658 (60.8)	0.3
Number of Outpatient visits			
None	24 (0.8)	31 (0.5)	0.1
1-5	336 (10.9)	569 (9.5)	
6-10	541 (17.5)	1,070 (17.8)	
>10	2,183 (70.8)	4,342 (72.2)	
Number of Inpatient visits			
None	2,741 (89)	5,568 (92.6)	0.1
1	276 (8.9)	367 (6.1)	
>1	67 (2.1)	77 (1.3)	

Section E.3 Multivariable results

Conditional logistic regression

In disabled Medicare beneficiaries with chronic pain, 1,192 (22.2%) of cases had concurrent utilization of GABA+OP+BZD, 2,089(38.6%) of cases had concurrent utilization of GABA+OP, and 421 (7.9%) had concurrent utilization of GABA+BZD when compared to 21.9%, 38.3% and 7.1% of controls, respectively. Within the acute pain cohort, 1,021 (22.8%) of cases had concurrent utilization of GABA+OP+BZD, 1,751 (38.6%) of cases had concurrent utilization of GABA+OP, and 368 (8.1%) had concurrent utilization of GABA+BZD when compared to 21.3%, 37.5% and 7.8% of controls, respectively. Among disabled beneficiaries in the mental health sub-cohort, 874 (28.3%) of cases had concurrent utilization of GABA+OP+BZD, 920 (29.8%) of cases had concurrent utilization of GABA+OP, and 391 (12.6%) had concurrent utilization of GABA+BZD when compared to 28.6%, 29.5% and 9.8% of controls, respectively.

Among disabled beneficiaries with chronic pain, the odds of an adverse drug-related event was 1.51, 1.46, and 1.16 times higher among GABA+OP+BZD, GAB+BZD, and GAB+OP users, respectively (when compared to GABA only). After adjusting for potential confounders, the odds of an adverse drug-related event remained significantly higher among GABA+OP+BZD [1.23(1.10-1.36)], GABA+BZD [1.19(1.06-1.27)], and GABA+OP [1.06(1.03-1.19)] users. A similar pattern was noted among disabled beneficiaries with acute pain and mental health conditions. When compared to GABA only, the odds of an adverse drug-related event was significantly higher among GABA+OP+BZD (acute pain [1.23(1.10-1.36)] and mental health [1.15 (1.02-1.30)]), GABA+BZD (acute pain [1.19(1.06-1.27)] and mental health [1.49 (1.28-

1.74)]), and GABA+OP (acute pain [1.06(1.03-1.19)] and mental health [1.16 (1.02-1.30)]) users.

Table VI.E.3. Conditional logistic regression analysis: Association between concurrent use category and adverse drug related events among Medicare disabled beneficiaries

		Unadjusted OR(95%CI)	Adjusted OR(95%CI)
Sub-group	**Concurrent use category**		
Acute Pain	GABA+OP+BZD	**1.51 (1.35-1.70)**	**1.23 (1.10-1.36)**
	GABA+BZD	**1.46 (1.24-1.72)**	**1.19 (1.06-1.27)**
	GABA+OP	**1.16 (1.10-1.39)**	**1.06 (1.03-1.19)**
	GABA only	reference	Reference
Chronic Pain	GABA+OP+BZD	**1.70 (1.24-2.34)**	**1.36 (1.22-1.50)**
	GABA+BZD	**1.68 (1.14-2.47)**	**1.61 (1.38-1.89)**
	GABA+OP	**1.39 (1.10-1.89)**	**1.19 (1.04-1.51)**
	GABA only	reference	Reference
Mental Health conditions	GABA+OP+BZD	**1.41 (1.23-1.61)**	**1.15 (1.02-1.30)**
	GABA+BZD	**1.69 (1.41-1.98)**	**1.49 (1.28-1.74)**
	GABA+OP	**1.26 (1.11-1.44)**	**1.16 (1.02-1.30)**
	GABA only	reference	Reference

Significant findings are highlighted in bold
GABA only is reference category

Section F. Results of sensitivity analyses

Results of Section F are presented under each outcome.

Section F.1. Respiratory depression

Concurrent 7-day exposure: When we required an overlap of at least 7 days to define exposure categories, we noted higher odds among GABA+OP+BZD and GABA+OP users in the acute pain sub-cohort. Although the odds among GABA+OP in the chronic pain cohort was also higher than in our main analyses, it remained non-significant **(Table VI.F.1.)**

Continuous 30-days exposure: When our medications of interest were used for more than 30 days, GABA+OP+BZD and GABA+OP use were associated with significantly higher odds of respiratory depression. This was consistent across all sub-cohort categories except for GABA+OP use in the mental health sub-cohort where our findings were non-significant **(Table VI.F.1.)**

Any exposure in the prior 90 days: When we loosened our definition of exposure to capture any medication utilization in the prior 90-days before the index date, GABA+OP+BZD use was significantly associated with higher odds of respiratory depression **(Table VI.F.1.)**

Opioid Naive population: After excluding prior opioid users in sensitivity analyses, we noted no significant associations between GABA+OP+BZD and GABA+OP use and respiratory depression **(Appendix F.)**

Section F.2. Opioid-related overdose

Concurrent 7-day exposure: When we required an overlap of at least 7 days to define exposure categories, we noted that GABA+OP use was associated with significantly higher odds of opioid overdose across all sub-cohorts. However, GABA+OP+BZD use was only significantly associated with opioid-related overdose among disabled beneficiaries with mental health conditions **(Table VI.F.2.)**

Continuous 30-days exposure: When our exposure categories were varied to capture medication utilization for more than 30 days, GABA+OP+BZD use was associated with significantly higher odds of opioid-related overdose among disabled beneficiaries across all sub-cohorts. GABA+OP use was only significantly associated with higher odds of opioid-related overdose among disabled beneficiaries with mental health conditions **(Table VI.F.2.)**

Any exposure in the prior 90 days: When we loosened our definition of exposure to capture any medication utilization in the prior 90-days before the index date, we noted significantly higher odds of opioid-related overdose among GABA+OP+BZD and GABA+OP users across all three sub-cohorts examined. In fact, the odds were higher than those previously noted in our main analyses **(Table VI.F.2.)**

Opioid Naive population: After excluding prior opioid users in sensitivity analyses, we noted significant associations between GABA+OP+BZD and opioid-related overdose **(Appendix F.)**

Section F.3. Substance-related overdose

Concurrent 7-day exposure: When we required an overlap of at least 7 days to define exposure categories, no significant associations were noted between ―GABA+OP+BZD, GABA+BZD, or GABA+OP use and substance-related overdose within all sub-cohorts, except within the acute pain sub-cohort where GABA+OP+BZD was significantly associated with higher odds of substance-related overdose. **(Table VI.F.3.)**

Continuous 30-days exposure: When we varied exposure definitions to capture medication utilization for at least 30-days in the pre-index period, GABA+OP+BZD and GABA+BZD use were associated with significantly higher odds of substance-related overdose among disabled beneficiaries within all sub-cohorts examined. However, across all sub-cohorts, we noted no significant association between GABA+OP use and substance related overdose **(Table VI.F.3.)**

Any exposure in the prior 90 days: When we loosened our definition of exposure to capture any medication utilization in the prior 90-day pre-index period, GABA +OP+BZD, GABA+BZD and GABA+OP use were all significantly associated with higher odds of substance-related overdose among disabled beneficiaries with chronic or acute pain. However, among disabled beneficiaries with mental health, only GABA +BZD use was associated with significantly higher odds of substance related overdose **(Table VI.F.3.)**

Opioid Naive population: After excluding prior opioid users in sensitivity analyses, we noted no significant associations between GABA+OP+BZD, GABA+BZD, and GABA+OP use and substance-related overdose **(Appendix F.)**

Section F.4. Adverse drug-related event

Concurrent 7-day exposure: When we required an overlap of at least 7 days to define exposure categories, we noted no significant associations between exposure categories-GABA+OP+BZD, GABA+BZD, and GABA+OP and adverse drug-related events within our sub-cohorts, with the exception of the mental health sub-cohort. Among disabled beneficiaries with mental health conditions, GABA+BZD use was associated with significantly higher odds of an adverse drug-related event **(Table VI.F.4.)**

Continuous 30-days exposure: When we varied exposure definitions to capture medication utilization for at least 30-days in the pre-index period, GABA+OP+BZD, GABA+BZD, and GABA+OP use were associated with significantly higher odds of adverse drug-related events among disabled beneficiaries with chronic or acute pain. Among disabled beneficiaries with mental health conditions, we noted no significant association between GABA+OP use and adverse drug-related events but significantly higher odds of adverse drug-related events among GABA+OP+BZD and GABA+BZD users **(Table VI.F.4.)**

Any exposure in the prior 90 days: When we loosened our definition of exposure to capture any medication utilization in the prior 90-day pre-index period, GABA +OP+BZD, GABA+BZD and GABA+OP use were all significantly associated with higher odds of adverse drug-related events. This is similar to our findings from our main analyses **(Table VI.F.4.)**

Opioid Naive population: After excluding prior opioid users in sensitivity analyses, we noted no significant associations between GABA+OP+BZD and GABA+OP use and

adverse drug-related events. However, GABA+BZD use was associated with significantly higher odds of an adverse drug-related event across all sub-cohorts.

Table VI.F.1. Sensitivity analyses: Association between concurrent use category and respiratory depression among Medicare disabled beneficiaries

		7-day overlap	Continuous 30-day use	Any use
Sub-group	**Concurrent use category**			
Acute Pain	GABA+OP +BZD	**1.37 (1.21-1.56)**	**1.39 (1.18-1.64)**	**1.35 (1.20-1.53)**
	GABA+OP	**1.10(1.02-1.22)**	**1.14(1.01-1.31)**	1.01(0.91-1.13)
	OP only	reference	reference	Reference
Chronic Pain	GABA+OP +BZD	**1.20 (1.06-1.3)**	**1.37 (1.18-1.60)**	**1.12 (1.01-1.26)**
	GABA+OP	1.07 (0.99-1.19)	**1.14 (1.01-1.29)**	1.02 (0.92-1.12)
	OP only	reference	reference	Reference
Mental Health conditions	GABA+OP +BZD	1.09 (0.95-1.26)	**1.19 (1.01-1.43)**	1.13 (1.00-1.30)
	GABA+OP	1.00 (0.88-1.14)	1.10 (0.93-1.31)	0.96 (0.85-1.10)
	OP only	reference	reference	Reference

Significant findings are highlighted in bold
OP only is reference category

Table VI.F.2. Sensitivity analyses: Association between concurrent use category and opioid-related overdose among Medicare disabled beneficiaries

		7-day overlap	Continuous 30-day use	Any use
Sub-group	**Concurrent use category**			
Acute Pain	GABA+OP +BZD	1.27 (0.90-1.80)	**1.97 (1.22-3.19)**	**1.84 (1.26-2.69)**
	GABA+OP	**1.44 (1.05-1.97)**	1.39 (0.92-2.09)	**1.48 (1.03-2.14)**
	OP only	reference	reference	reference
Chronic Pain	GABA+OP +BZD	1.29 (0.93-1.79)	**1.70(1.07-2.70)**	**2.62 (1.89-3.79)**
	GABA+OP	**1.50 (1.10-2.04)**	1.47 (0.99-2.19)	**1.83 (1.28-2.63)**
	OP only	reference	reference	reference
Mental Health conditions	GABA+OP +BZD	**1.52 (1.06-2.16)**	**1.94 (1.17-3.21)**	**2.42 (1.62-3.62)**
	GABA+OP	**1.81 (1.25-2.62)**	**1.61 (1.01-2.57)**	**1.67 (1.08-2.57)**
	OP only	reference	reference	reference

Significant findings are highlighted in bold
OP only is reference category

Table VI.F.3. Sensitivity analyses: Association between concurrent use category and substance-related overdose among Medicare disabled beneficiaries

		7-day overlap	Continuous 30-day use	Any use
Sub-group	**Concurrent use category**			
Acute Pain	GABA+OP +BZD	**1.24 (1.26-2.50)**	**1.89 (1.27-2.81)**	**1.78 (1.25-2.55)**
	GABA+BZD	1.60 (0.90-1.70)	**1.96 (1.21-3.18)**	**2.27 (1.44-3.57)**
	GABA+OP	1.27 (0.94-1.71)	1.34 (0.93-1.95)	**1.66 (1.18-2.35)**
	GABA only	reference	reference	reference
Chronic Pain	GABA+OP +BZD	1.24 (0.92-1.67)	**1.62 (1.13-2.31)**	**1.83 (1.32-2.54)**
	GABA+BZD	1.33 (0.94-1.89)	**1.81 (1.19-2.76)**	**1.77 (1.18-2.63)**
	GABA+OP	1.11(0.84-1.47)	1.19 (0.85-1.67)	**1.47 (1.07-2.02)**
	GABA only	Reference	reference	reference
Mental Health conditions	GABA+OP +BZD	1.01 (0.74-1.36)	1.35 (0.91-1.97)	1.37 (0.97-1.92)
	GABA+BZD	1.25(0.87-1.79)	**1.64(1.07-2.50)**	**1.56 (1.04-2.34)**
	GABA+OP	0.87 (0.64-1.19)	1.10 (0.74-1.64)	1.02 (0.72-1.44)
	GABA only	reference	reference	reference

Significant findings are highlighted in bold
GABA only is reference category

Table VI.F.4. Sensitivity analyses: Association between concurrent use category and adverse drug events among Medicare disabled beneficiaries

		7-day overlap	Continuous 30-day use	Any use
Sub-group	**Concurrent use category**			
Acute Pain	GABA+OP +BZD	1.04 (0.93-1.16)	**1.22 (1.06-1.39)**	**1.30 (1.17-1.44)**
	GABA+BZD	0.98 (0.86-1.13)	**1.35 (1.14-1.61)**	**1.17 (1.01-1.37)**
	GABA+OP	0.98 (0.90-1.07)	**1.19 (1.07-1.39)**	**1.20 (1.08-1.30)**
	GABA only	reference	reference	reference
Chronic Pain	GABA+OP +BZD	0.94 (0.86-1.03)	**1.12 (1.01-1.27)**	**1.24 (1.13-1.37)**
	GABA+BZD	0.95 (0.84-1.07)	**1.32 (1.12-1.55)**	**1.21 (1.05-1.40)**
	GABA+OP	0.94 (0.88-1.01)	**1.13 (1.02-1.25)**	**1.13 (1.04-1.23)**
	GABA only	Reference	reference	reference
Mental Health conditions	GABA+OP +BZD	0.98 (0.87-1.10)	**1.16 (1.01-1.34)**	**1.21 (1.07-1.36)**
	GABA+BZD	**1.24 (1.08-1.44)**	**1.37 (1.15-1.64)**	**1.36 (1.16-1.59)**
	GABA+OP	1.01 (0.90-1.13)	1.10 (0.96-1.28)	**1.15 (1.02-1.30)**
	GABA only	reference	reference	reference

Significant findings are highlighted in bold
GABA only is reference category

CHAPTER VII: DISCUSSION

Chapter VII discusses the findings of the study and addresses specific issues related to each study aim. The strengths and limitations of the study are also discussed under each specific aim. Finally, relevant conclusions and implications for practice, policy and public health are discussed.

Discussion for aim 1

In this study, we found that medication augmentation was common in the disabled population, especially among those who initiated gabapentin. Our findings support the previously documented high prevalence of polypharmacy among gabapentin users, especially related to opioid and benzodiazepine use. We also noted low prevalence of switching and discontinuation of these medications in this vulnerable population.

When examined within the context of higher augmentation, our findings suggest that gabapentin may not be prescribed as an alternative to opioids and/or benzodiazepines, but rather as an adjunct to potentiate the effectiveness of either therapy, potentially at lower doses. The current culture of pain medicine involves the utilization of multimodal analgesia.[73-75] This approach involves the concurrent use of analgesics from two or more drug classes to mediate effects via different mechanisms of action, targeting different (peripheral or central) pain pathways, and achieving a synergistic effect at lower analgesic doses.[73-75] This potentiation hypothesis is also supported by results from our secondary analyses, which indicate that most of the beneficiaries who previously used opioids and/or benzodiazepines continued to do so after initiating gabapentin.

To our knowledge, our study is among the first to directly tease out specific patterns of gabapentin, opioid, and/or benzodiazepine co-utilization. It is plausible that the switching pathway from gabapentin to opioids reflects suboptimal pain management, which often requires the introduction of opioids or benzodiazepines as part of the previously described multimodal approach, though at lower doses than would have been prescribed otherwise. This multimodal approach is also evident by the substantial augmentation with opioids among gabapentin initiators. Longer time to augmentation with gabapentin suggests the use of gabapentin to assist with the gradual weaning from opioids or benzodiazepines. Since our study did not directly examine dose changes for any of our medications of interest, further exploration of the dosing patterns associated with gabapentin, opioid and benzodiazepine utilization is warranted.

The common patterns identified among tri-therapy users highlight the complex interactions between pain and mental health treatment—with poor pain management exacerbating sleep disorders, anxiety, and other mental health conditions, and exacerbations in mental health diagnoses requiring more focused pain management. Though the specific underlying mechanisms through which pain affects mental health (and vice versa) are not well understood, previous studies have suggested that individuals with mental health diagnoses may be more likely to rate their pain more severely and, thus, be more likely to receive opioids than those without mental health conditions.[54,76] Higher rates of augmentation among disabled beneficiaries with mental health conditions and those with chronic pain are also consistent with the hypothesis that psychiatric diagnoses and pain treatment are closely linked.

Discussion for aim 2

In this retrospective cohort study, we noted concurrent opioid and benzodiazepine utilization among gabapentin users is common in the Medicare population. While the majority of gabapentin users also used opioids, a smaller proportion of them used benzodiazepines. Nevertheless, the majority of gabapentin users who used benzodiazepine also used opioids at some point during follow-up. Our study found most beneficiaries who used multiple medications of interest used them concurrently.

Our study highlighted vulnerable subgroups of beneficiaries with back pain, chronic pain, and mental health conditions among whom concurrent use of all three medications was longer in duration than any dual or single episodes of medication utilization. This finding is consistent with previous studies that suggest chronic pain and mental health conditions are closely related.[54,76-79] Indeed, individuals with chronic pain and mental health disorders are not only more likely to receive higher opioid doses but are also more likely to utilize opioids chronically.[54] This is supported by our finding that higher average daily opioid dose and longer duration of opioids or benzodiazepines increased the odds of longest concurrent use involving all three medication classes. Furthermore, the majority of beneficiaries whose longest concurrent use involved all three medications had used opioids or benzodiazepines for longer than ninety days. Chronic opioid and benzodiazepine use among gabapentin users with chronic pain or mental health conditions is particularly worrisome not only because these individuals are more likely to use other psychotropic or analgesic medications but also because they are potentially at higher risk for adverse consequences related to this combination therapy.[80-84] In the Medicare population, concurrent opioid and benzodiazepine use is associated

with a five-fold increase in the risk of opioid related overdose.[30] Co-utilization of gabapentin with opioids has also been recently linked to increased odds of opioid-related death;[21] the addition of gabapentin to opioids and benzodiazepines thus potentially heightens the risk for these negative consequences.

While acute pain, non-benzodiazepine sedatives, and muscle relaxants were not predicators of longest concurrent use involving gabapentin+opioids+benzodiazepines, these factors were associated with higher odds of any concurrent use of all three medications. This suggests that although these factors may not be related to longer term use of these medications, they are however related to some concurrent use of all three medications and as such, are also important in understanding this at-risk population. Although previous work has noted prior substance use disorders, specifically opioid use disorders, increases the risk for gabapentin and opioid overuse[22], we observed no significant association between substance use disorders and longest concurrent use categories. This is likely because we used a composite measure of alcohol, opioid, and non-opioid related substance use disorders. Additionally, substance use disorder diagnoses were fairly infrequent in our population.

Discussion for aim 3

In this study, we noted that in the Medicare disabled population, concurrent utilization of gabapentin, opioids and benzodiazepines is associated with increased risk of adverse public health outcomes including respiratory depression, opioid and substance related overdose, and adverse drug-related events. Concurrent utilization of gabapentin and opioids or gabapentin and benzodiazepines also increased the potential for substance related overdose and adverse drug-related events in this population. Although we noted

no association between concurrent use of gabapentin and opioids with respiratory depression and opioid related overdose within some of our sub-cohorts, when our definition of concurrent use was varied we noted an increased risk of both outcomes within this population.

Our findings regarding opioid related overdose are consistent with previous studies that have examined the association between gabapentinoids (gabapentin and pregabalin) and opioid related overdose. A previous study conducted in the Canadian population noted that the use of gabapentin with opioids was associated with a 49% higher risk of fatal opioid overdose. Similarly, Zhou and colleagues noted that in the Medicare population, consistent use of gabapentinoids and opioids was associated with a more than two-fold increase in opioid related overdose. While these prior studies have examined gabapentin using a composite gabapentinoid category which also captures pregabalin, our study is among the first to directly tease out the association between opioid related overdose and gabapentin, specifically. Further, since previous studies have suggested that gabapentin use with both opioids and benzodiazepines is common, we also examined the additional impact of concurrent benzodiazepine use among concurrent gabapentin and opioid users. The mechanism through which gabapentin potentially increases opioid related overdose is not fully understood; however, it has been linked to increased respiratory depression as well as increased bioavailability of gabapentin with concurrent opioid administration.[21-22]

We noted that concurrent gabapentin and opioid use was not strongly associated with respiratory depression except when benzodiazepines were added on or when these medications were used for more than thirty days. This suggests that duration of therapy

may be closely linked to a respiratory event when these medications are used in combination therapy. In addition, previous work has suggested that gabapentin is typically used in combination with opioids and benzodiazepines; hence, the increased risk of respiratory depression associated with all three medications is a relevant public health concern. A prior study noted that combination gabapentinoid and opioid use was associated with increased respiratory depression only among hospitalized patients who recently had surgery and those 65 years and older. While results from this study were significantly impacted by small sample sizes and limited available information on patient characteristics, it suggests that perhaps, there may be some heterogeneity in our findings among disabled beneficiaries 65 and older. In addition, since we noted significant associations between concurrent gabapentin and opioid use in the acute pain sub-cohort, further investigation of combination therapy within this sub-group is warranted.

Our finding that concurrent gabapentin, opioids, and benzodiazepines, gabapentin and benzodiazepines, and gabapentin and opioids was associated with increased risk of adverse drug-related events is consistent with findings from a previous study conducted in the commercially insured population. In this prior study, Alyssa Peckham and colleagues noted that concomitant gabapentin and opioid use is associated with 64% higher odds of a drug-related event. The magnitude of the association between concurrent gabapentin and opioids and adverse drug-related event noted in our study differed from those reported by Peckham et al. based on differences across our cohorts and exposure/outcome definitions. Nevertheless, we expanded on this previous study by incorporating exposure groups which take into account the influence of benzodiazepine

on gabapentin utilization. In addition, we adjust for multiple confounding factors that have not been previously considered in analyses.

Our study is among the first to examine the association between concurrent gabapentin, opioids, and benzodiazepines and substance related overdose. While previous studies have focused on gabapentin use with opioids, our finding that the odds of substance related overdose was especially high among GABA+BZD users suggests that gabapentin and benzodiazepine users are also a high risk group who are potentially also susceptible to adverse outcomes. Not only that, since there has been limited research on this population, they represent a subgroup among whom further research is warranted.

Overall discussion

Using our specific aims, our study set out to address three main questions regarding the co-utilization of gabapentin, opioids, and benzodiazepines. In Aim 1, we addressed how individuals end up on combined therapy involving our three medication classes of interests. For this aim, we identified treatment trajectories which lead to co-prescriptions for gabapentin, opioids, and benzodiazepines. In addition, we described the more common patterns of co-utilization noted among Medicare disabled beneficiaries. In Aim 2, we identified the beneficiaries who are likely to utilize these medications concurrently. We identified high-risk factors associated with concurrent therapy involving these medications and further, described how these factors change based on specific combination patterns. In Aim 3, we addressed the significance of concurrent gabapentin, opioids, and benzodiazepine utilization. We noted increased risk of multiple adverse outcomes when gabapentin is used concurrently with opioids and/or benzodiazepines.

Limitations

Our study had several limitations. First, given the widespread off-label prescription of gabapentin for a variety of conditions, there is potential for confounding by indication, especially because administrative claims data do not include information on the actual indications for prescribed medications. To address this limitation, we conducted analyses in separate sub-cohorts of individuals diagnosed with chronic pain, acute pain, and mental health conditions. We did not apply a new-user design to define medication utilization in Aim 1; however, because this is the first study to assess patterns of utilization of all three medication classes and no specific first- or second-line recommendations exist for pain and mental health conditions using all three medication classes, we believe the chosen design reflects medication utilization patterns seen within clinical practice. In addition, we applied a new-user design in our secondary analyses to directly examine the impact of new gabapentin initiation on opioid and benzodiazepine use.

There is a potential for selection bias resulting from capturing only those who seek care. In addition, we were unable to capture beneficiaries who obtained prescriptions for any of our medications of interest via cash, other payor, or illicit sources. Since gabapentin, opioids and benzodiazepines are often used illicitly, it is possible our estimates of co-utilization of these medications are underestimated. We believe the characteristics of beneficiaries who use these medications illicitly potentially differ from those captured in our population; however, since the focus of this paper is not on abuse or misuse of these substances, we believe our study findings are relevant to the general disabled Medicare population. We did not have a measure of pain severity which raises

the potential for channeling bias, as people with more severe pain are channeled to the more complex concurrent use categories. To address this, we included proxy measures for pain severity including both acute and chronic pain measures, co-morbidities, prior pain therapies, and previous health care utilization. To address the potential for detection bias related to our exposure groups, we used an opioid only or gabapentin only reference group rather than a no use category. In addition, since gabapentin utilization has only recently become scrutinized, it is likely that prescriber monitoring/ follow up was similar across our exposure groups. Finally, reimbursement for benzodiazepines in the Medicare program only began in 2013, which limits the number of available years for our study.

Strengths

Our study provides valuable information on the combined use of three medications that have been independently linked to adverse CNS effects. We focused on disabled Medicare beneficiaries, a population who, due to high rates of pain and psychiatric diagnosis, are more likely to be prescribed gabapentin, opioids, and benzodiazepines. To our knowledge, our study is among the first to characterize the prevalence and risk factors associated with concurrent gabapentin, opioids, and benzodiazepine use in the Medicare disabled population. Our study provides invaluable information on high-risk subgroups, who due to their increased odds of long-term concurrent gabapentin, opioids and benzodiazepine use, are potentially more susceptible to opioid-related overdose and other adverse consequences. Rather than select cutoffs for identification of long-term concurrent use of gabapentin, opioids and benzodiazepines, our study takes into account that patient specific factors influence decision-making on long term medication

management, and further, the identification of factors associated with individuals' longest concurrent episode provides more clinically meaningful information on drug utilization in this population. To assess the robustness of our findings, we also incorporated a more standardized measure of any concurrent use in our sensitivity analyses.

Our study utilizes a methodologically rigorous approach to examine the association between commonly co-prescribed medications and several public health outcomes. Our nested case control approach provides the advantage of minimized bias related to control selection as well as more precise estimates of the association between infrequent outcomes (such as opioid related overdose) and exposure. We utilize a disease risk score to summarize multiple confounders into one score which allowed for simplification of our model. In addition, given the widespread off-label use of gabapentin, the variation in prescriber preferences associated with our exposure categories is high. As a result, the DRS is a more useful approach than a PS in this setting. We address any potential for misclassification of exposure by incorporating multiple sensitivity analyses where our exposure definitions are varied. Our study also accounts for the potential influence of prescribing policies by matching on year of cohort entry.

Conclusion

Our study identified patterns of co-prescriptions of gabapentin, opioids and benzodiazepines that typically occur in clinical practice and further highlighted vulnerable subgroups who are more likely to be co-prescribed combination(s) of these therapies. We also noted the associations between concurrent utilization of gabapentin,

opioids, and benzodiazepines with several public health adverse outcomes including respiratory depression, opioid and substance related overdose and adverse drug-related events. Given these documented adverse consequences associated with combination therapy and the highlighted subgroups at greatest risk for these outcomes, further research into the benefits and risks of combining gabapentin with other sedating medications, is warranted. In the United States, the number of opioid related overdose deaths has increased by 120% between 2010 and 2018.[85] In addition, rising national health care costs associated with inpatient and outpatient health care utilization continues to be a significant challenge in the United States. In light of this, efforts which hope to curb this ongoing crisis must incorporate measures which address concurrent gabapentin, opioids and benzodiazepine utilization. At the practice level, there is a need for increased education of providers/clinicians on the risks associated with combined use of these medications. In addition, in the instances of prescribing, increased monitoring of high-risk sub-groups especially those with pain and mental health conditions may be crucial to mitigating these adverse outcomes. At the state and national levels, there is a need for more stringent legislature focused on gabapentin prescribing within the nation including—a change in gabapentin scheduled status or perhaps, more widespread incorporation of gabapentin in prescription drug monitoring programs.

APPENDIX

Appendix A. Relevant ICD-9-CM and ICD-10-CM codes for cohort selection

Conditions	ICD-9-CM codes	ICD-10-CM codes
Chronic pain	**Arthritis:** 710,711,712,713,714,715,716,717,718,719, 725,726,727,728, 729,730,731,732,733,734,735, 736,737,738,739 **Back pain:** 721.2-721.9 ,722.1,722.2, 722.30,722.32, 722.33,722.70,722.72,722.73, 722.80,722.82,722.83,722.90,722.92,722.93,724,737.1,737.3,737.4 ,737.5,739.2,739.4,756.10,756.11 ,756.12,756.13, 75619,8054, 8058, 8392,83942,846, 8471, 8472, 8473,8479 **Headache:** 346,30781 **Neuropathic pain:** 250.6, 353, 354, 355**,** 337.0, 356.x, 357, 357.2,357.3, 531.3, 723.4, 727.2 **Neck pain:** 7210,7211,7220,72231,72271, 72281,72291,723, 8390,8391,8470 **Chronic pain**: 3382,3384	**Arthritis:** E08.61 E10.61 E11.61 M05 M06 M07 M08 M12 M13 M14 M15 M16 M17 M18 M19 M20 M21 M22 M23 M24 M25 M1A, M11, M65, M66, M67, M70, M71, M75, M76, M77, M79.0, M94 **Back/neck pain:** M45.x-M55.x, S134XXA **Headache**: G43.x, G44.x **Neuropathic pain** E08.4 E09.4 E10.4 E11.4 G50 G51 G52 G53 G54 G55 G56 G57 G58 G59 G60 G61 G62 G63 G64 G65 O26.82 B02.23, G99.0, G90.5x, G35.x, G37.9, M79.2, S04.50XA, S14.x, S24.x, S34.x **Chronic pain:** G89.0, G89.2x, G89.4
Acute pain	**TMJ:** 524.6x **Extremity pain**: 274.0,274.9,354.0,717.x,726.x,727.3,729.5,735.x,836.x,840.x,841.9,843.8,843.9, 844.x, 848.5, 707.15,717.40,718.31, 719.4x, 726.1x, 726.3x,726.6x, 726.70, 726.71,727.0x, 727.41, 727.61, 728.71,729.82, 831.00,842.00, 842.10,845.x **Abdominal pain**: 533.90, 535.00,535.50, 541, 540.9, 550.90, 550.92, 553.x, 564.1,577.0,590.80,789.0x **Chest pain**: 786.50, 786.59, 413.9	**TMJ:** M26.6, S03.0, S03.4 **Extremity pain:** G56.4x, G57.7x, M79.6x **Abdominal pain:** K27.4-K27.9, K40.x-K46.x, K50.x, K51.x (except K51.4x), K58.x, K62.89, K86.0, K86.1, N11.x, R10.1x-R10.8 **Chest pain: :** R07 **Kidney pain:** N200, N201, N209, N210, K8018, K8020, K819 **Pelvic pain:** N946, R102, N9489, N921, N925, N938, N950, N951 **Fractures:** M843, M844 M846 M847 S72 **Fibromyalgia:** M797, M791 **Restless leg syndrome:** G2581

	Kidney pain: 592.x, 594.1, 574.10, 574.20, 575.10 **Pelvic pain:** 625.3, 625.9, 626.6, 626.8, 627.1, 627.2 **Fractures**: V5413 V5423 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 819 V5410 V5411 V5412 V5420 V5421 V5422 820 821 822 823 824 825 826 827 828 829 V5414 V5415 V5416 V5424 V5425 V5426 V1352 V540 V5401 V5402 V5409 V5417 V5419 V5427 V5429 V664 V674 **Fibromyalgia:** 729.1 **Restless leg syndrome:** 333.94 **Sprain:** 840.0 - 840.9, '8410'-841.9, 842.01-842.02, 842.09-842.19, 843.0-843.9, 844.0-844.9, 845.00, 845.1x, 846.x, 847.x, 848.x, 848.4x, 84841, 84842, **Other pain:** 379.91, 380.2x, 381.81, 382.9, 388.70, 470, 522.4, 522.5, 525.9, 565.1,569.42, 604.90, 611.7x, 703.0, 706.2, 728.85, 786.52, 848.3, 848.8, 848.9, 873.63, 996.4	**Sprain:** S4350XA, S43409A, S4380XA, S43419A, S4380XA, S43429A, S4380XA, S4380XA, S43439A, S43499A, S46019A, S46119A, S46819A, S46919A, S53439A, S53449A, S53419A, S53429A, S53499A, S53409A, S56919A, S63509A, S66919A, S63519A, S63329A, S63529A, S63599A, S6390XA, S66919A, S638X9A, S63649A, S63659A, S63629A, S63639A, S638X9A, S73119A, S73129A, S73199A, S73109A, S76919A, S83429A, S83419A, S83509A, S8360XA, S838X9A, S86819A, S8390XA, S86919A, S93409A, S96919A, S93429A, S93419A, S93439A, S86019A, S93499A, S93609A, S96919A, S93629A, S93529A, S93519A, S93699A, , S336XXA, S338XXA, S339XXA, S233XXA, S238XXA, S335XXA, S239XXA, S031XXA, S034XXA, S135XXA, S2341XA, S23429A, S23420A, S23421A, S23428A, T1490, S39011A, S29019A, S039XXA **Other pain:** H5713, H6040, H60509, H60519, H60529, H60539, H60549, H60559, H6060, H608X1, H6090, H6980, H9209, J342, K044, K047, K089, K603, K604, K605, K6289, N451, N452, N453, N644, N63, N6451, N6452, N6453, N6459, L600, L723, M6240, M62383, S025XXA, S025XXB, T84498A, T84039A, T84029A, T84049A, T84059A, T84069A, T84099A, T84119A, T84129A, T84199A, T84498A
Mental Health conditions	**Mood** : '296' **Personality and adjustment disorders**: '301', 309 **Depression**: '311' **Anxiety** : '300' **ADHD** 31401,31400	**Mood disorders including bipolar, depression:** F30-F39 **Personality:**F60, F61, F62, F68 **Anxiety:** F40 F41 F42 F43 F44 F45 **Schizophrenia:** F20.x, F25.x

	Schizophrenia= 295 **Eating/sleeping disorders**= '32703','3074','3075','3071' **Substance Use disorders** **Alcohol dependence**: '2652',’2910’, ‘29181’, ‘29189’, ‘29182’, '2911','2912', '2913', '2915','2916','2917','2918','2919', '3030','303','30300','30301','30302','30303','3039','30390','30391','30392','30393','30500', ‘30501’ ,’30502’,’30503’, '3575', '4255', '5353', '5710','5711','5712','5713', '9800', '9801', '9802','9803', '9808','9809', ‘2914’, **Opioid dependence**: '30400', '30401','30402','30403','30470','30471','30472','30473', '30550', '30551','30552','30553','96500','96509','E9351',’E9352’,'3049' **Non opioid dependence**: ‘96501’, '30460','30461','30462', '30463','30480','30481','30482','30483', '30490','30491', '30492', '30493','30590','30591', '30592', '30593','30410','30411','30412','30413','30540','30541', '30542', '30543','30450','30451','30452', '30453', '30530','30531','30532', '30533','9696','30440','30441','30442','30443','30570','30571','30572','30573','30430','30431','30432','30433','30520','30521','30522','30523','30420','30421','30422','30423','30560','30561','30562','30563','30580’,’30581’,’30582’,’30583’,’E9350’	**Eating/sleep disorders**: F50, F51 **Substance use disorders** **Alcohol dependence:** F1010,F10120, F10121, F10129 F1014 F10150 F10151 F10159 F10180 F10181 F10182 F10188 F1019 F1020 F1021 F10220 F10221 F10229 F10230 F10231 F10232 F10239 F1024 F10250 F10251 F10259 F10280 F10281 F10282 F10288 F1029 F10920 F10921 F10929 F1094 F10950 F10951 F10959 F10980 F10981 F10982 F10988 F1099 **Opioid dependence:** F1110 F11120 F11121 F11122 F11129 F1114 F11150 F11151 F11159 F11181 F11182 F11188 F1119 F1120 F1121 F11220 F11221 F11222 F11229 F1123 F1124 F11250 F11251 F11259 F11281 F11282 F11288 F1129 F1190 F11920 F11921 F11922 F11929 F1193 F1194 F11950 F11951 F11959 F11981 F11982 F11988 F1199 **Non-opioid dependence:** F1210 F12120 F12121 F12122 F12129 F12150 F12151 F12159 F12180 F12188 F1219 F1220 F1221 F12220 F12221 F12222 F12229 F12250 F12251 F12259 F12280 F12288 F1229 F1290 F12920 F12921 F12922 F12929 F12950 F12951 F12959 F12980 F12988 F1299 F1310 F13120 F13121 F13129 F1314 F13150 F13151 F13159 F13180 F13181 F13182 F13188 F1319 F1320 F1321 F13220 F13221 F13229 F13230 F13231 F13232 F13239 F1324 F13250 F13251 F13259 F13280 F13281 F13282

		F13288 F1329 F1390 F13920 F13921 F13929 F13930 F13931 F13932 F13939 F1394 F13950 F13951 F13959 F13980 F13981 F13982 F13988 F1399 F1410 F14120 F14121 F14122 F14129 F1414 F14150 F14151 F14159 F14180 F14181 F14182 F14188 F1419 F1420 F1421 F14220 F14221 F14222 F14229 F1423 F1424 F14250 F14251 F14259 F14280 F14281 F14282 F14288 F1429 F1490 F14920 F14921 F14922 F14929 F1494 F14950 F14951 F14959 F14980 F14981 F14982 F14988 F1499 F1510 F15120 F15121 F15122 F15129 F1514 F15150 F15151 F15159 F15180 F15181 F15182 F15188 F1519 F1520 F1521 F15220 F15221 F15222 F15229 F1523 F1524 F15250 F15251 F15259 F15280 F15281 F15282 F15288 F1529 F1590 F15920 F15921 F15922 F15929 F1593 F1594 F15950 F15951 F15959 F15980 F15981 F15982 F15988 F1599 F1610 F16120 F16121 F16122 F16129 F1614 F16150 F16151 F16159 F16180 F16183 F16188 F1619 F1620 F1621 F16220 F16221 F16229 F1624 F16250 F16251 F16259 F16280 F16283 F16288 F1629 F1690 F16920 F16921 F16929 F1694 F16950 F16951 F16959 F16980 F16983 F16988 F1699 F1910 F19120 F19121 F19122 F19129 F1914 F19150 F19151 F19159 F19180 F19181 F19182 F19188 F1919 F1920 F1921 F19220 F19221 F19222 F19229 F19230 F19231 F19232 F19239 F1924 F19250 F19251 F19259 F19280 F19281 F19282 F19288 F1929

		F1990 F19920 F19921 F19922 F19929 F19930 F19931 F19932 F19939 F1994 F19950 F19951 F19959 F19980 F19981 F19982 F19988 F1999

Appendix B. Relevant ICD-9-CM and ICD-10-CM codes for co-morbid conditions

Condition	ICD-9-CM	ICD-10-CM
Diabetes	'2500','2501','2502','2503', '2508','2509','2504','2505', '2506','2507'	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 E10.2 - E10.5, E10.7, E11.2 - E11.5, E11.7, E12.2 - E12.5, E12.7, E13.2 - E13.5, E13.7, E14.2 - E14.5, E14.7
Peptic ulcer disease	'531','532','533','534'	K25.x - K28.x
Cerebrovascular disease	'36234','430','431','432', '433','434','435','436','437','438'	G45.x, G46.x, H34.0, I60.x - I69.x
Peripheral Vascular disease	'0930','4373','440','441', '4431','4432','4438','4439','4471', '5571','5579','V434'	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Myocardial Infarction	'410','412'	I21, I22.x, I25.2
Congestive Heart Failure	'39891','40201','40211', '40291','40401','40403','40411', '40413','40491','40493', '4254','4255','4257','4258', '4259','428’	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 - I42.9, I43.x, I50.x, P29.0
Liver disease	'07022','07023','07032', '07033','07044','07054','0706', '0709','570','571','5733', '5734','5738','5739','V427',	B18.x, K70.0 - K70.3, K70.9, K71.3 - K71.5, K71.7, K73.x, K74.x, K76.0, K76.2 - K76.4, K76.8, K76.9, Z94.4, I85.0,

	'4560','4561','4562','5722', '5723','5724','5728'	I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Hypertension	4019	I10, I16.9
Seizures	780.3, 345	R56.0, R56.8, G40, G41
Dementia	290, 331.0, 331.1, 331.2, 797	F00, F01, F02.0, F02.1, F03, F05.1, G30, G31.0, G31.1, R54
COPD/Chronic lung disease	'4168','4169','490','491', '492','493','494','495','496', '500','501','502','503', '504','505','5064','5081','5088'	I27.8, I27.9, J40.x - J47.x, J60.x - J67.x, J68.4, J70.1, J70.3
Chronic Kidney disease/renal disease	'40301','40311','40391','40402', '40403','40412','40413','40492', '40493','582', '5830','5831','5832', '5834','5836','5837','585','586', '5880','V420','V451','V56'	I12.0, I13.1, N03.2 - N03.7, N05.2 - N05.7, N18.x, N19.x, N25.0, Z49.0 - Z49.2, Z94.0, Z99.2
Hypothyroidism	244.1, 244.3, 244.8, 244.9	E01.8, E02, E03.2, E03.3, E03.5, E03.8, E03.9, E89.0
Substance use disorders (SUD)	SUD included as a comorbid condition for Aim 2 and 3	

Appendix C. Relevant codes for outcome events

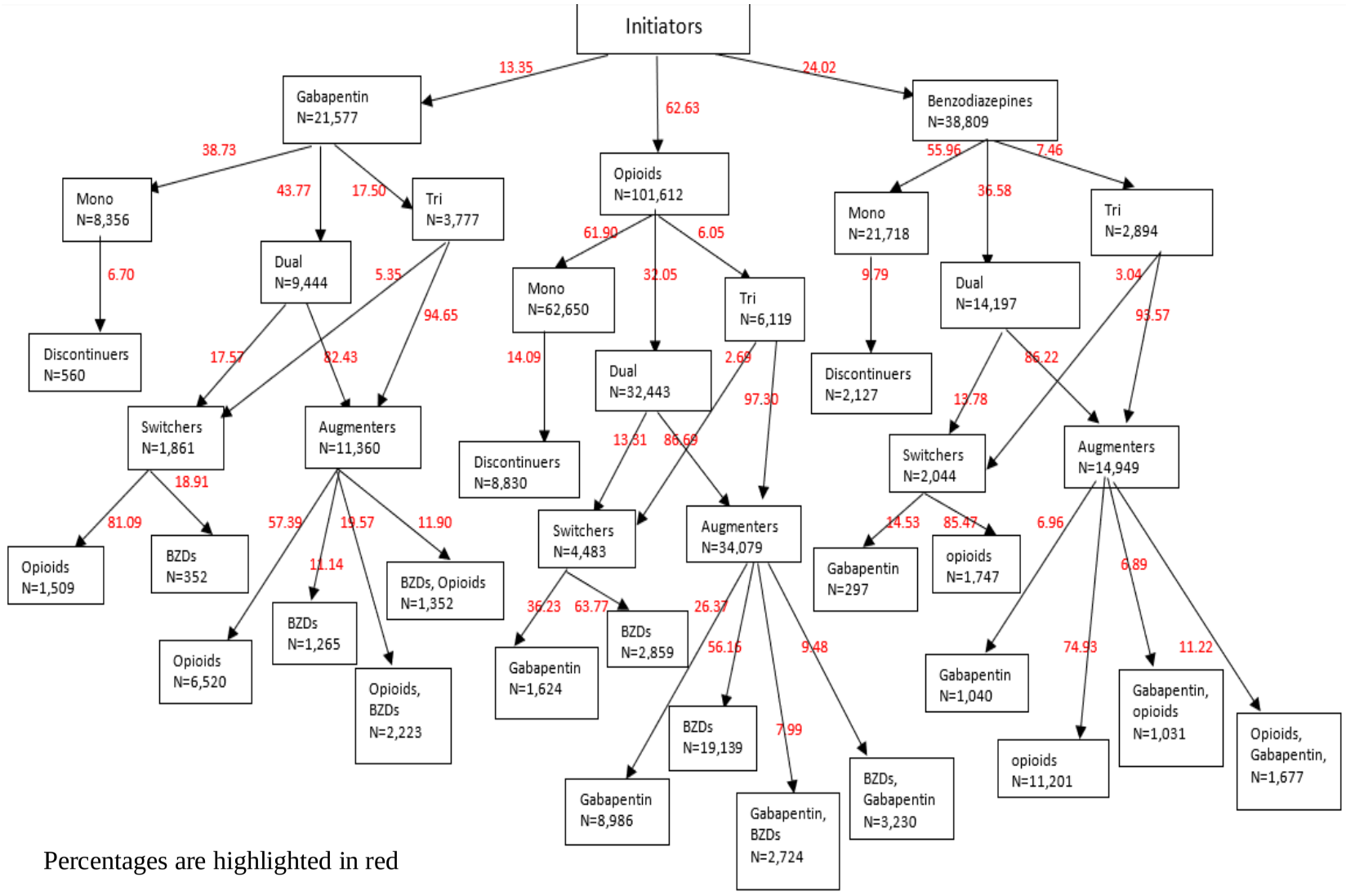
Diagnostic codes for identifying outcome measures		
Condition	**ICD-9-CM codes**	**ICD-10-CM codes**
Respiratory Depression	518.81, 518.82, 518.84, 518.5, 518.51, 518.52, 518.53, 518.54, 518.4x, 799.1, 786.03, 799.0, 799.01, 799.02	R06, J96.0 , J96.20, J951, J952,J810, R092
Opioid related overdose	965.0, 965.00, 965.02, 965.09, E850.1, E850.2, E935.1, E935.2	T40.0, T40.2, T40.3, T40.4, T40.6
Substance related overdose	965, 966, 967, 968, 969, 970, 971, 975, E850, E851, E852, E853, E854, E855, E935, E936,	T39, T40, T41, T42, T43, T44, T48

	E937, E938, E939, E940, E945, E950.0-E950.5, E980.0-E980.5	
Adverse drug-related event	Adverse drug reaction 965.0x,995.20, 995.27, 995.29 966.3, 977.8, 977.9, E936.3 Catatonia 293 Altered mental state 294.0,780.97,780.93,331,780.02 293.0, 293.1,292, 296.9 Euphoria 296.9 Insomnia 780.5 Sedation/Somnolence 780.5,327.1 Ataxia 781.2, 781.3 Blurred vision 367.8, 367.9, 368.8, 368.9 Extrapyramidal symptoms 333,781.0 Nystagmus 379.5 Palpitations 785.1 Slurred speech 784.5 Tachycardia 785.0 Respiratory depression 786.0, 518.81 Weakness/Syncope 780.2, 728.87	Adverse drug reaction T39.8 ,T40 ,T42 Catatonia F06.1 Altered mental state F04, R41,F05,F06.3,F09, F39 Euphoria F39 Insomnia G47 Sedation/Somnolence G47.1,R40.0 Ataxia R26,R27.0 Blurred vision H52.6,H52.7,H53.8,H53.9 Extrapyramidal symptoms G24,G25.1,G25.4, G25.6,G25.7, R25 Nystagmus H55 Palpitations R00.2 Slurred speech R47.81 Tachycardia R00.0 Respiratory depression R06, J96.0 Weakness/Syncope R55, M62.82

Appendix D. Variables included in Disease Risk Score

Clinical conditions	chronic lung disease, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, connective tissue disease, cerebrovascular disease, peptic ulcer disease, liver disease, hypertension, hypothyroidism, seizure disorders, dementia, substance use disorders
Previous Health Care Utilization	Number of inpatient and outpatient visits
Pharmacologic factors	Opioids, benzodiazepines, Gabapentin, Muscle relaxants, Pregabalin, Non-benzodiazepine sedatives

Appendix E. Flow chart for Aim 1



Percentages are highlighted in red

Appendix F. Sensitivity analyses: Association between concurrent use category and adverse outcomes among opioid naïve Medicare disabled beneficiaries

		Respiratory depression	Opioid related overdose	Substance related overdose	Adverse drug event
Sub-group	**Concurrent use category**				
Acute Pain	GABA+OP +BZD	1.16 (0.76-1.75)	**8.94 (2.30-12.47)**	2.43 (0.95-6.21)	**1.41 (1.03-1.94)**
	GABA+BZD	--------	-------	1.38 (0.71-2.68)	1.04 (0.86-1.27)
	GABA+OP	0.86 (0.67-1.10)	1.72 (0.58-5.13)	1.45 (0.71-2.94)	1.12 (0.95-1.32)
	OP only	reference	reference	-------	--------
	GABA only	------	------	reference	reference
Chronic Pain	GABA+OP +BZD	1.13 (0.78-1.63)	**2.89 (1.04-6.08)**	1.85 (0.86-4.01)	1.06 (0.80-1.41)
	GABA+BZD	-------	-------	1.56 (0.85-2.94)	**1.50 (1.24-1.80)**
	GABA+OP	0.81 (0.65-1.01)	1.05 (0.80-2.75)	1.13 (0.62-2.08)	0.98 (0.85-1.13)
	OP only	reference	reference	-------	---------
	GABA only	-------	------	reference	reference
Mental Health conditions	GABA+OP +BZD	1.42 (0.92-2.19)	**4.78 (1.49-10.03)**	1.83 (0.82-4.11)	1.28 (0.92-1.78)
	GABA+BZD	---------	----------	1.41 (0.79-2.50)	**1.40 (1.16-1.69)**
	GABA+OP	0.80 (0.58-1.08)	1.19 (0.39-3.62)	0.66 (0.31-1.40)	1.08 (0.97-1.34)
	OP only	reference	reference	-------	---------
	GABA only	-------	------	reference	reference

Significant findings are highlighted in bold

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