Original Research

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

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Abstract

Objectives: Little is known about the relationship between opioid (OPI) and gabapentinoid (GABA) use patterns and healthcare expenditures, and how this may impact pain management and risk of adverse outcomes. This study examined the association between patients' OPI and GABA use trajectories and direct medical expenditures in US Medicare.

Methods: This cross-sectional study included a 5% national sample (2011-2016) of fee-for-service beneficiaries with fibromyalgia, low back pain, neuropathy, and/or osteoarthritis newly initiating OPIs and/or GABAs. Using group-based multi-trajectory modeling, this study identified distinct OPI-GABA dose and duration patterns, based on standardized daily doses, within a year of initiating OPIs and/or GABAs. Concurrent direct medical expenditures within the same year were estimated using inverse probability of treatment weighted multivariable generalized linear regression, adjusting for socio-demographic and health status factors.

Results: Among 67,827 eligible beneficiaries (mean age±SD=63.6±14.8 years, female=65.8%, white=77.1%), 11 distinct trajectories were identified (three OPI-only, four GABA-only, and four concurrent OPI-GABA trajectories). In comparison, OPI-only early discontinuers ($13,830, 95%CI=$13,643–14,019), GABA-only early discontinuers and consistent low-dose and moderate-dose GABA only users were associated with 11%–23% lower health expenditures (adjusted mean expenditure: $10,607–$11,713), while consistent low-dose OPI-only users, consistent high-dose OPI-only users, consistent low-dose OPI-GABA users, consistent low-dose OPI and high-dose GABA users, and consistent high-dose OPI and moderate-dose GABA users were associated

with 14%–106% higher healthcare expenditures (adjusted mean expenditure: $15,721–$28,464).

Conclusions: OPI-GABA dose and duration patterns varied substantially among fee-for-service Medicare beneficiaries. Consistent OPI-only users and all concurrent OPI-GABA users were associated with higher healthcare expenditures compared to OPI-only discontinuers.

Introduction

The United States (U.S.) Food and Drug Administration (FDA) has approved gabapentinoids (GABAs), such as gabapentin and pregabalin, for partial seizures, postherpetic neuralgia, diabetic peripheral neuropathy (pregabalin only), fibromyalgia (pregabalin only), and restless legs syndrome in adults (gabapentin only).[1,2,3] Adult office-based ambulatory care visits in which a gabapentinoid was administered, ordered, continued, or supplied nearly quadrupled (9.1 to 34.9 per 1000 visits) from 2003 to 2016 in the US.[4] In 2016, the sales of pregabalin reached $4.4 billion, and the total number of gabapentin prescriptions reached 64 million in the U.S.[5]

Despite limited evidence for off-label use, GABAs have been extensively and increasingly used for various off-label pain conditions or in ways that are not federally approved.[4,6-8] In many of these chronic conditions such as fibromyalgia, neuropathy, osteoarthritis, and low back pain,[9-11] no curative therapy exists and the lifelong economic burdens for the management of these conditions are high. The annual direct medical costs are estimated to be $27,948 for fibromyalgia, $30,755 for diabetic peripheral neuropathy, $18,435 for osteoarthritis, and $8,386 for low back pain (in usual care settings) per capita.[12-15] The use of analgesics is a mainstay of disease management, and better pain management (e.g., use integrated therapy) may improve patients' quality of life and decrease health services use, thus reducing medical and other related costs (e.g., loss of work days and reduced productivity from pain).

In contrast, the substantial increases in GABA use raise safety concerns in the risk of misuse, abuse, dependence, and overdose of GABAs, especially among individuals with a history of substance use disorders or co-administration with opioids

(OPIs).[16-18] Over half (52%) of GABA users concurrently used OPIs in 2015.[19] Several recent studies showed that OPI-GABA use was associated with an increased risk of OPI-related deaths and other adverse outcomes (e.g., hospitalizations and mortality).[20-24] Therefore, concurrent OPI-GABA use may increase the occurrence of adverse health outcomes, resulting in increased healthcare expenditures.

Understanding the association between the patterns of use of OPIs-GABAs and healthcare expenditures may provide important information on the disease management of chronic pain conditions (e.g., osteoarthritis and low back pain). Given that the dynamic change in dose and duration of OPI-GABA use may reflect pain complexity and severity, the objectives of this study were to identify the distinct dose and duration patterns of OPI-GABA use of Medicare beneficiaries using group-based multi-trajectory modeling, and then to examine the associations of those patterns with concurrent and subsequent total direct medical expenditures. This study chose Medicare because of the high prevalence of prescription OPI and GABA use among its beneficiaries, its availability of national claims data, and its being one of the largest health payers in the US, accounting for over 20% of the overall healthcare spending (>$672 billion) in 2016.[29]

Methods

Data Source

This study used a 5% nationally representative sample of Medicare administrative claims data from 2011 to 2016 (~3.8 million unique beneficiaries).[25,26] Medicare is the U.S. governmental health insurance program provided for individuals aged ≥65 years and those aged <65 years with certain disability or end-stage renal disease (ESRD).[27] This study linked the Medicare data to the publicly available Area Health Resource File (AHRF).[28] The AHRF data include county-level information on healthcare providers (e.g., number of physicians; number of nurses), hospital and health facilities (e.g., number of hospitals; number of skilled nursing homes), and census-based demographic information (e.g., median household income; unemployment rate).[28]

Study Design and Cohort

This cross-sectional study included fee-for-service beneficiaries with fibromyalgia, low back pain, neuropathy, or osteoarthritis, identified from ≥1 inpatient or ≥2 other medical claims on different days using the International Classification of Diseases codes (see **eTable 1** for ICD-9-CM/ICD-10-CM codes).[29,30] This study restricted the analytical sample to the beneficiaries newly initiating OPIs or GABAs, defined as those with no OPI or GABA prescriptions within six months prior to the index date (i.e., date of the first prescription for either OPIs or GABAs, whichever occurred first) (**eFigure 1**). This study excluded beneficiaries who: (1) were non-US residents, had hospice service, ESRD, seizure or epilepsy, and any type of cancer during the study period (except non-melanoma skin cancer; **eTable 1**);[31] (2) did not have

continuous enrollment in Parts A, B, and D between six months prior to and 24 months post the index date; and (3) filled opioids for acute pain indications, which this study defined as (a) filling only one OPI prescription, (b) filling two OPI prescriptions on the same day, or (c) filling <15 day opioid supply during the index year (**eFigure 2**).[32] The University of Arizona Institutional Review Board approved this study.

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

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

First, this study calculated the average daily SDD for OPIs using morphine milligram equivalent (MME) and for GABAs using minimum effective daily dose (i.e., 300mg for gabapentin and 150mg for pregabalin), based on dispensing date, quantity, unit strength, and days of supply. MME for each OPI prescription was calculated by the quantity dispensed multiplied by strength in milligrams, divided by days of supply, and further multiplied by a conversion factor provided by the Centers for Disease Control and Prevention (CDC).[33] Low-, moderate-, and high-dose opioid use was defined as an average daily dosage of <50 MME, 50-90 MME, and >90 MME, respectively.[34] For GABA use, SDD <2 (i.e., gabapentin <600 mg or pregabalin <300 mg), 2-3 (i.e., 600≤ gabapentin <900 mg or 300≤ pregabalin <450 mg), and ≥3 (i.e., gabapentin ≥900 mg or pregabalin ≥450 mg) were considered as low-, moderate-, and high-dose use. A daily

diary of OPI and GABA use was created for each patient by summing up the total SDD for OPIs and GABAs in one day, separately. For example, the total SDD for GABAs would be two, if a person had a 300 mg gabapentin prescription overlapping with a 150 mg pregabalin prescription on the same day.

Second, group-based multi-trajectory models were used to identify distinct utilization patterns of OPIs-GABAs by summarizing individuals with similar trajectories into subgroups.[35-40] This study modeled the average daily MME for OPIs and SDD for GABAs as a longitudinal, continuous outcome for each week of the year after initiating OPIs or GABAs, and the time variable as weeks since the index date (week 1-52). This study used the most flexible functional form of time, up to the fifth order polynomial function, in the model to allow dynamic trajectories to emerge from the data. Outputs of the group-based multi-trajectory modeling included the estimated probabilities of group membership for each individual, estimated trajectory curves over time, and proportion of each group trajectory. The final model was selected based on a combination of (1) the Bayesian information criterion (BIC), where the largest value indicates the best-fitting model, and (2) the Nagin's criteria to assess final model adequacy.[37,38,41] A well-performing trajectory model in accordance to Nagin's criteria includes average posterior probability of ≥0.7, odds of correct classification of ≥5.0, and narrow confidence intervals for estimated group membership probabilities.[41]

Outcomes: Concurrent Healthcare Expenditures

The primary outcome was the total annual direct medical costs during the year following the index date (i.e., concurrent medical expenditures of the year when the trajectories of OPIs-GABAs were measured). The direct medical costs were comprised

of the payment amounts for inpatient, outpatient, emergency department (ED), and skilled nursing facility utilizations, and prescriptions and pharmacy services covered by Medicare, other health plans, and the beneficiary's co-payments in the claims. The inpatient, ED, and skilled nursing facility expenditures included the costs of facility and professional health services received that were associated with an admission to that facility. The outpatient services included services provided in clinician offices, free-standing clinics, and hospital outpatient departments. The pharmacy costs included the costs of prescriptions and health services received in the pharmacy (excluding the pharmacy costs from inpatient stays). To make the costs identified in different years comparable to each other, all the expenditures were adjusted to the dollar in October, 2018, based on the consumer price index.[42] The secondary outcomes were separate total annual direct medical costs from inpatient, outpatient, ED, and skilled nursing facilities and pharmacy utilization.

Covariates

The covariate information was ascertained in the six months prior to the index date, including individual socio-demographic and health status factors and county-level factors. Covariates were measured before the initiation of OPIs and GABAs to assess the prediction accuracy of the variables and to avoid including predictor changes that might have been consequences of the use (or non-use) of OPIs and GABAs. Socio-demographics included age, sex, race/ethnicity (White, African American, Hispanic, and others), disability status, and receipt of low-income subsidy (LIS) or dual Medicaid eligibility (with both LIS and dual Medicaid eligibility, with either LIS or dual Medicaid eligibility, and without LIS or dual Medicaid eligibility). Health status factors included

Elixhauser comorbidity index (excluding metastatic cancers and solid tumors; range 0 to 27), serious mental health disorders, and anxiety disorders, identified by ICD-9-CM/ICD-10-CM codes (**eTable 1**),[43] inpatient, outpatient, skilled nursing facility, and pharmacy costs.[44] The county-level factors included the standardized number of hospitals, non-federally employed physicians, hospitals with a pain management program, and patient centers for physical medicine/rehabilitation per 10,000 population as a proxy for access to health care or certain specialties, population profile (metropolitan and non-metropolitan), annual median household income, and annual unemployment rate.

Statistical Analysis

First, this study described the characteristics of beneficiaries in each OPI-GABA trajectory group, with the mean and standard deviation (SD) for continuous variables, and frequency and percentage or median and interquartile range (IQR) as appropriate for categorical variables. Second, given that the identified trajectory groups were likely to be different in-patient characteristics and disease complexity, this study estimated the inverse probability of treatment weighting (IPTW) for each beneficiary using a multi-nominal logistic regression. Weighting subjects with IPTW creates a sample in which treatment assignment is independent of measured covariates.[45] This study weighted subjects with IPTW in the analyses to minimize confounding across trajectories. This study compared the characteristics across trajectories before and after weighting subjects with IPTW using the standardized mean difference (SMD), wherein SMD>0.1 was considered as having non-negligible differences.[45] Third, this study used the IPTW-weighted multivariable generalized linear model, with gamma distribution and log link, to estimate the total annual direct medical expenditures, adjusting for the covariates with

non-negligible differences after IPTW weighting. The cost ratios (CRs; also called “expenditure ratios”, interpreted as the mean expenditures in a given group divided by those in the reference group) with 95% conference intervals (CIs) were also reported.[46] Finally, this study conducted an additional secondary analysis to examine the association between distinct dual-trajectories of OPI-GABA use and annual direct medical expenditures during the subsequent year after the year of initiating OPIs or GABAs).

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

Results

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

Among 67,827 eligible beneficiaries initiating OPI or GABA prescriptions, the overall mean MME and SDD were 19.1 (SD= 38.7) for OPIs and 1.4 (SD= 2.1) for GABAs, respectively, within the year of initiating OPIs or GABAs (**eFigure 3)**. According to a combination of BIC values (largest BIC= -1,148,321) and Nagin's criteria, 11 distinct dual-trajectories were identified (**eTable 2**).

Among the 11 distinct OPI-GABA trajectories (**Figure 1**), three trajectories comprised OPI-only use (57.7% of the cohort), four trajectories comprised GABA-only use (27.3%), and the remaining four trajectories comprised OPI-GABA use (15.0%). Specifically, the 11 trajectory groups included: (1) OPI-only early discontinuers (Group A; 39.3% of the cohort), (2) consistent low-dose OPI-only users (Group B; 16.4%; MME ≤30), (3) consistent high-dose OPI-only users (Group C; 2.0%; MME ≥150), (4) GABA-only early discontinuers (Group D; 11.9%), (5) consistent low-dose GABA-only users (Group E; 9.5%; SDD <2 [i.e., gabapentin <600 mg or pregabalin <300 mg]), (6) consistent moderate-dose GABA-only users (Group F; 4.8%; 2≤ SDD ≤3 [i.e., 600 mg≤ gabapentin ≤900 mg or 300 mg≤ pregabalin ≤450 mg]), (7) consistent high-dose GABA-only users (Group G; 1.1%; SDD >5 [i.e., gabapentin >1500 mg or pregabalin >750 mg]), (8) early discontinuation of OPIs and consistent low-dose GABA users (Group H; 7.4%; SDD ≤1 [i.e., gabapentin ≤300 mg or pregabalin ≤150 mg]), (9) consistent low-dose OPI-GABA users (Group I; 3.8%; MME <40 and SDD <1.5 [i.e., gabapentin <450 or pregabalin <225]), (10) consistent low-dose OPI and high-dose GABA users (Group J; 2.8%; MME <30 and SDD ≥3 [i.e., gabapentin ≥900 mg or pregabalin ≥450 mg]), and

(11) consistent high-dose OPI and moderate-dose GABA users (Group K; 1.0%; MME >120 and 1.5< SDD ≤3 [i.e., 450< gabapentin ≤900 mg or 225< pregabalin ≤450 mg]).

Characteristics Overall and by Trajectory Group

Of the 67,827 eligible beneficiaries initiating OPI or GABA prescriptions in our sample, the majority had any low back pain (80.6%) or any osteoarthritis (70.3%) (**Table 1**). The mean age was 63.6 (SD= 14.8) years, 65.8% were female, and 77.1% were white. The average Elixhauser comorbidity index was 2.6 (SD= 2.2). The median outpatient and pharmacy costs within the six months prior to initiation of OPIs or GABAs were $306 (IQR= $1,242) and $565 (IQR= $1,569), respectively.

The identified 11 trajectory groups had significantly different characteristics before IPTW weighting (**Table 1**). For example, consistent high-dose OPI and moderate-dose GABA users were more likely to have any low back pain (95.1% vs. 80.6%) and any fibromyalgia (40.4% vs. 22.1%), to be younger (51.4 ± 12.0 years vs. 63.6 ± 14.8 years), male (46.2% vs. 34.2%), and white (86.9% vs. 77.1%), and to have a disability (83.3% vs. 43.5%), compared to the overall study cohort. Consistent high-dose OPI and moderate-dose GABA users also had lower outpatient (median [IQR]: $0 [$522] vs. $306 [$1,242]) and pharmacy (median [IQR]: $203 [$507] vs. $565 [$1,569]) costs within the six months prior to the initiation of OPIs or GABAs. After weighting subjects with IPTW, most of the characteristics were comparable across trajectory groups, except for the proportion of low back pain, age, and pharmacy costs. The minimum and maximum SMD across the 55 group comparisons (C_2^{11}; e.g., A vs. B, A vs. C, B vs. C) were presented in **eTable 3**.

Inverse Probability Treatment Weighted Multivariable Generalized Linear Models for Direct Medical Expenditures

The concurrent annual direct medical expenditures varied by trajectory group (**Table 2**). Using OPI-only early discontinuers as a reference group ($13,830, 95% CI= $13,643-$14,019), significantly higher expenditures were observed among consistent low-dose OPI-only users ($15,721, 95% CI= $15,395-$16,055; adjusted cost ratio [aCR]= 1.14, 95% CI= 1.11-1.17), consistent high-dose OPI-only users ($22,908, 95% CI= $21,421-$24,497; aCR= 1.66, 95% CI= 1.55-1.77), early discontinuation of OPIs and consistent low-dose GABA users ($18,309, 95% CI= $17,743-$18,893; aCR= 1.32, 95% CI= 1.28-1.37), consistent low-dose OPI-GABA users ($22,869, 95% CI= $21,841-$23,946; aCR= 1.65, 95% CI= 1.58-1.73), consistent low-dose OPI and high-dose GABA users ($20,281, 95% CI= $19,221-$21,411; aCR= 1.47, 95% CI= 1.39-1.55), and consistent high-dose OPI and moderate-dose GABA users ($28,464, 95% CI= $25,910-$31,271; aCR= 2.06, 95% CI= 1.87-2.26).

The concurrent expenditures related to inpatient, emergency department, outpatient, pharmacy and skilled nursing use for the 11 trajectories are presented in **Tables 3 and 4**. Compared to the OPI-only discontinuers, consistent low-dose OPI-only users, consistent low-dose GABA-only users, and all OPI-GABA only users were associated with higher inpatient costs ($22,070 for the reference group v.s. $25,371-$29,057) and emergency department costs ($8,386 vs. $9,913-$11,987); consistent high-dose OPI-only users were also associated with higher ED expenditures ($12,053, 95% CI=$10,797-$13,456), but not higher for inpatient related expenditure. For outpatient-related expenditures, all OPI-GABA users were associated with higher costs

($3,730-$4,408) whereas GABA-only early discontinuers and consistent low-dose and moderate-dose GABA only users were associated with lower costs, compared to OPI-only early discontinuers. For pharmacy-related expenditures, all consistent users of OPI-only, GABA-only and OPI-GABA were associated with higher costs ($3,291-$12,192) compared to OPI-only early discontinuers ($2,618, 95%CI=$2,588-$2,618). For skilled nursing home-related expenditures, only consistent high-dose GABA-only users, early discontinuation of OPIs and consistent low-dose GABA users and consistent low-dose OPI-GABA users were associated with higher costs compared to OPI-only early discontinuers.

Additional secondary analyses examining the association between OPI and GABA trajectories and annual total direct medical expenditures in the subsequent year yielded similar findings as the primary analyses (**eTable 4**). Consistent high-dose OPI-only users and all consistent OPI, GABA or concurrent users had significantly higher subsequent direct medical expenditures compared to OPI-only early discontinuers. The cost differences across trajectory groups were mainly driven by the differences in inpatient, ED, and pharmacy costs (**eTables 5-6**).

Discussion

This study identified 11 distinct trajectories of OPI-GABA use in the year after initiating OPIs or GABAs among fee-for-service Medicare beneficiaries with fibromyalgia, low back pain, neuropathy, or osteoarthritis. This high variability in the dose and duration patterns may be attributed to a combination of patient factors (e.g., type of pain conditions, pain chronicity and severity, and medication preferences), prescriber factors (e.g., prescribing preferences; actual or perceived level of patient risk), and payer factors (e.g., formulary tiers; co-pays). We found that 85% of the cohort were OPI-only or GABA-only users. Compared to OPI-only early discontinuers, trajectories characterized by consistent OPI-only users and all consistent OPI-GABA users were associated with significantly higher annual total direct medical expenditures during the year of initiating OPIs and/or GABAs, while GABA-only early discontinuers and consistent low-dose and moderate-dose GABA-only user were associated with lower total medical expenditures.

To our knowledge, this is the first study examining medical expenditures associated with trajectories of OPI-GABA use. Previous observational studies have only examined the association between OPI-GABA use and adverse outcomes (e.g., OPI-related deaths) using arbitrary single value measures (e.g., any overlapping OPI and GABA use in the 120 days before OPI-related deaths).[20-23] Using an arbitrary single value may mask distinct heterogeneities in the dose and duration of medication use patterns over time. Alternatively, group-based multi-trajectory models have strengths to (1) account for dynamic medication use over time and identify subgroups with similar changes over time, (2) simultaneously examine dose and duration thresholds and other

patterns most relevant to outcomes, and (3) develop intuitive graphical results of trajectories.[37,41]

Consistent OPI-only users and consistent OPI-GABA users had significantly higher costs compared to the reference group. The cost components that comprise the total direct medical expenditures for those trajectory groups were slightly different, but generally inpatient, ED, and pharmacy costs were the major drivers of increased direct medical expenditures for all consistent OPI-GABA users (regardless of dose) as they had relatively higher proportion of ED visits and inpatient, ED, and pharmacy expenditures. Over half of consistent OPI-GABA users had at least one ED visit within the year of initiating OPIs and GABAs. A possible explanation for the higher overall healthcare expenditures among the consistent OPI-only and OPI-GABA users is that due to their potentially more severe pain they had more intensified (e.g., long-term OPI use) or more physical therapy or integrated pain treatment needed than the other trajectory groups, and thus they had a higher risk of visiting the ED due to pain exacerbations or even possibly due to drug-related adverse events.

According to the 2019 Updated American Geriatrics Society Beers Criteria® for potentially inappropriate medication use in older adults, it is recommended to avoid OPI-GABA use, except when (1) transitioning from OPI therapy to GABA, or (2) using GABAs to reduce OPI dose.[47] Recently, given more restrictions on OPI prescribing, health providers have been increasingly co-prescribing OPIs-GABAs in clinical practice, to reduce the OPI dose and duration of use.[48,49] In our related work, compared to consistent high-dose OPI-only users, lower risk of drug overdose were observed among consistent low-dose OPI-GABA users and consistent low-dose OPI and high-dose

GABA users (consistent high-dose OPI-only users, consistent low-dose OPI-GABA, and consistent low-dose OPI and high-dose GABA users were likely to be switchable in analgesic use).[24] These findings agreed with the Beers Criteria® recommendation in terms of co-administration of OPI-GABA to reduce OPI dose. However, the current study indicated that, from the cost perspective, OPI-GABA use was not associated with lower healthcare expenditures, compared to high-dose OPI-only users. A possible explanation is that high-dose OPI-only users may achieve better pain management effects and thus have a decreased likelihood of inpatient and outpatient visits, while they may have a higher risk of adverse health outcomes and pharmacy expenditures, compared to OPI-GABA users.

Understanding healthcare expenditures associated with different OPI-GABA trajectories may better guide the management of patients with fibromyalgia, neuropathy, osteoarthritis, and low back pain. The most desirable treatment choice would be the one with improved health outcomes, reduced risks, and low costs. However, tradeoffs are often necessary, because avoiding risks, especially sentinel events, is more desirable than reducing costs. For example, for those beneficiaries who have multiple chronic conditions with polypharmacy use (making them more susceptible to drug-related adverse events), co-administration of OPI-GABA may be necessary and a better treatment option, but continuous monitoring for the risks is suggested. Similarly, for patients in the trajectories with similar risk of overdose, cost saving or reducing unnecessary medical expenditures can be considered, especially from the payer's perspective. Therefore, the benefit (lower likelihood of inpatient and outpatient visits associated with high-dose OPI-only use) and risk (higher risk of drug overdose and

pharmacy costs associated with high-dose OPI-only use) profiles should both be taken into consideration when deciding the treatment strategy of OPI and GABA use.

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

Conclusions

There exists distinct OPI-GABA dose and duration patterns among fee-for-service Medicare beneficiaries, and each trajectory of OPI-GABA use was associated with different healthcare expenditures. Consistent OPI-only users and all OPI-GABA users (regardless of dose and duration) were associated with significantly higher total medical expenditures. The benefit-risk profiles should be taken into consideration when deciding the treatment strategy for chronic pain conditions in clinical practice.

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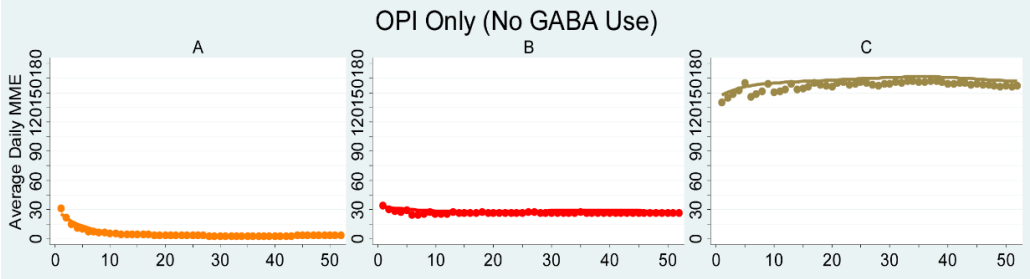
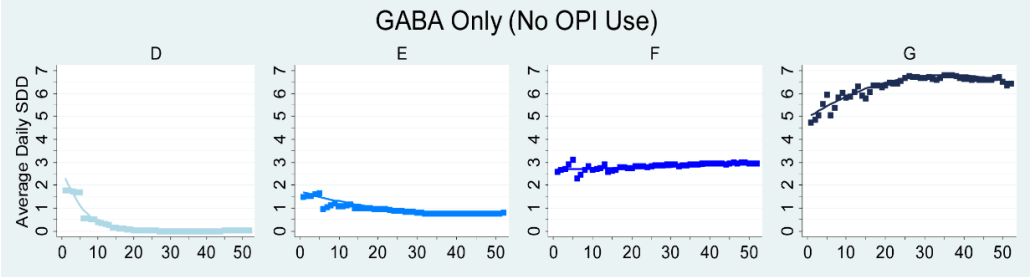
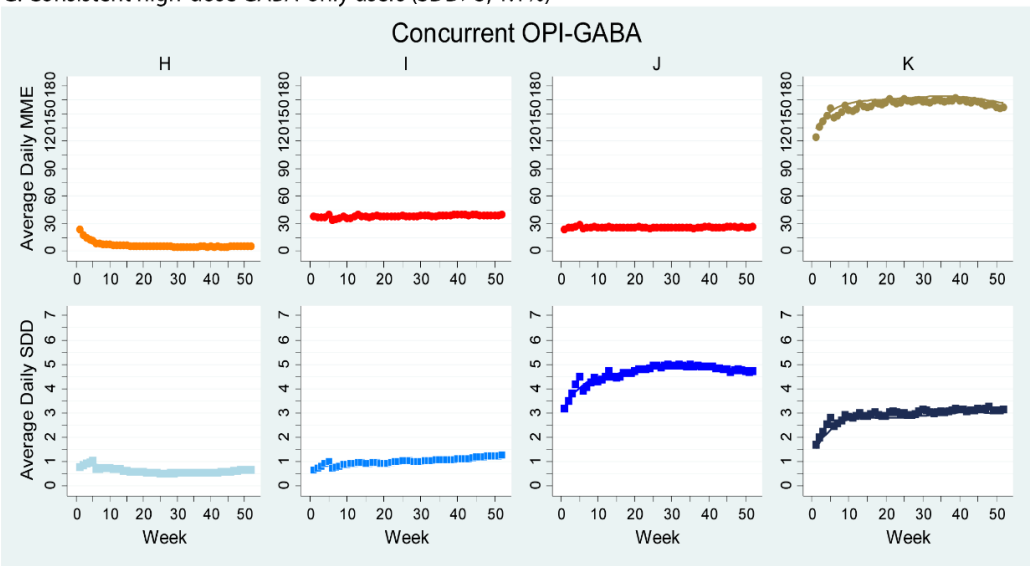


A: OPI-only early discontinuers (39.3%)
B: Consistent low-dose OPI-only users (MME≤30; 16.4%)
C: Consistent high-dose OPI-only users (MME≥150; 2.0%)



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



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

Figure 1. Dual-Trajectories of Opioid and Gabapentinoid Utilization Patterns among Medicare Beneficiaries

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

Table 1. Characteristics of Medicare Beneficiaries Initiating Opioids or Gabapentinoids and by Trajectory Group

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

Table 1. (Continued)

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

Abbreviations: **GABA**, gabapentinoid; **IPTW**, inverse probability of treatment weighting; **IQR**, interquartile range; **LIS**, low-income subsidy; **MME**, morphine milligram equivalent; **No**, number; **OPI**, opioid; **SD**, standard deviation; **SDD**, standardized daily dose; **SMD**, standardized mean difference

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

[b] Average SMD of 55 SMDs from group comparisons (C_2^{11}; e.g., group A vs B, group A vs C, and group A vs D). The maximum and minimum SMD were presented in eTable 3

[c] Included payment amount of Medicare, other primary health plans other than Medicare, and co-pays of beneficiary ($)

[d] Per 10,000 population

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

Table 2. Total Annual Concurrent Direct Medical Expenditures across Identified Trajectory Groups among Medicare Beneficiaries Initiating Opioids or Gabapentinoids

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

[a] Adjusted for age, disability, low back pain, and pharmacy costs

Abbreviations: **CI**, confidence interval; **CR**, cost ratio; **GABA**, gabapentinoid; **OPI**, opioid; * indicates significantly higher or lower compared to the reference group

Table 3. Total Annual Concurrent Expenditures Related to Inpatient, Emergency Department, and Outpatient Use across Identified Trajectory Groups among Medicare Beneficiaries Initiating Opioids or Gabapentinoids

Trajectories	No. beneficiaries	Inpatient			Emergency Department			Outpatient		
		%[a]	Mean[b]	(95% CI)	%[a]	Mean[b]	(95% CI)	%[a]	Mean[b]	(95% CI)
OPI only										
A. OPI-only early discontinuers	26,673	16.2	22,070	(21,504, 22,650)	46.1	8,386	(8,206, 8,571)	72.8	3,498	(3,439, 3,559)
B. Consistent low-dose OPI-only users	11,125	13.4	25,371*	(24,314, 26,475)	42.4	9,931*	(9,582, 10,293)	69.1	3,602	(3,506, 3,700)
C. Consistent high-dose OPI-only users	1,339	11.8	23,444	(20,514, 26,794)	43.0	12,053*	(10,797, 13,456)	59.3	3,353	(3,067, 3,666)
GABA only										
D. GABA-only early discontinuers	8,052	10.2	22,895	(21,557, 24,317)	42.6	8,192	(7,839, 8,562)	67.9	2,813*	(2,724, 2,906)
E. Consistent low-dose GABA-only users	6,410	10.7	25,637*	(23,969, 27,422)	43.5	9,222*	(8,769, 9,699)	71.1	3,030*	(2,924, 3,140)
F. Consistent moderate-dose GABA-only users	3,223	10.9	24,078	(21,751, 26,654)	43.7	7,877	(7,321, 8,475)	73.2	2,998*	(2,851, 3,153)
G. Consistent high-dose GABA-only users	763	12.2	22,969	(18,928, 27,873)	45.4	7,859	(6,771, 9,122)	70.3	3,612	(3,247, 4,018)
OPI-GABA										
H. Early discontinuation of OPIs and consistent low-dose GABA users	4,999	19.6	25,510*	(24,176, 26,918)	52.2	10,191*	(9,708, 10,698)	74.8	3,926*	(3,776, 4,082)
I. Consistent low-dose OPI-GABA users	2,600	19.5	28,286*	(26,172, 30,571)	54.0	10,696*	(9,955, 11,493)	71.5	4,408*	(4,161, 4,668)
J. Consistent low-dose OPI and high-dose GABA users	1,905	16.3	29,057*	(26,265, 32,146)	50.2	9,142*	(8,358, 10,000)	76.2	3,730*	(3,491, 3,985)
K. Consistent high-dose OPI and moderate-dose GABA users	738	15.5	26,907	(22,968, 31,523)	50.8	11,987	(10,401, 13,816)	66.4	4,961	(4,407, 5,584)

[a] The percentage is the proportion of people with the corresponding healthcare service in each group; [b] Adjusted for age, disability, low back pain, and pharmacy cost at baseline

Abbreviations: **CI**, confidence interval; **GABA**, gabapentinoid; **No**, number; **OPI**, opioid; * indicates significantly higher or lower compared to the reference group

Table 4. Total Annual Concurrent Expenditures Related to Pharmacy and Skilled Nursing Expenditures across Identified Trajectory Groups among Medicare Beneficiaries Initiating Opioids or Gabapentinoids

Trajectories	No. beneficiaries	Pharmacy			Skilled nursing		
		%[b]	Mean[a]	(95% CI)	%[b]	Mean[a]	(95% CI)
OPI only							
A. OPI-only early discontinuers	26,673	100	2,618	(2,588, 2,648)	6.8	21,155	(20,229, 22,123)
B. Consistent low-dose OPI-only users	11,125	100	4,341*	(4,265, 4,419)	6.4	19,819	(18,586, 21,135)
C. Consistent high-dose OPI-only users	1,339	100	10,311*	(9,744, 10,911)	3.9	24,168	(19,523, 29,919)
GABA only							
D. GABA-only early discontinuers	8,052	100	2,526	(2,473, 2,580)	4.1	20,270	(18,351, 22,391)
E. Consistent low-dose GABA-only users	6,410	100	3,291*	(3,214, 3,370)	6.0	20,954	(18,911, 23,218)
F. Consistent moderate-dose GABA-only users	3,223	100	3,978*	(3,846, 4,114)	4.3	20,278	(17,112, 24,029)
G. Consistent high-dose GABA-only users	763	100	5,139*	(4,793, 5,510)	2.6	27,029*	(18,677, 39,116)
OPI-GABA							
H. Early discontinuation of OPIs and consistent low-dose GABA users	4,999	100	3,419*	(3,330, 3,511)	7.8	24,023*	(21,882, 26,373)
I. Consistent low-dose OPI-GABA users	2,600	100	6,021*	(5,792, 6,259)	6.5	24,113*	(21,341, 27,245)
J. Consistent low-dose OPI and high-dose GABA users	1,905	100	7,104*	(6,787, 7,436)	6.0	16,970*	(14,448, 19,933)
K. Consistent high-dose OPI and moderate-dose GABA users	738	100	12,192*	(11,263,13,197)	3.3	15,213	(11,065, 20,914)

[a] The percentage is the proportion of people with the corresponding healthcare service in each group; [b] Adjusted for age, disability, low back pain, and pharmacy cost at baseline

Abbreviations: **CI**, confidence interval; **GABA**, gabapentinoid; **No**, number; **OPI**, opioid; * indicates significantly higher or lower compared to the reference group

Online Supplemental Materials

eTable 1. ICD-9-CM and ICD-10-CM Codes of Diseases and Conditions Used in the Study

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

eTable 1. (Continued)

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

eTable 2. Nagin's Diagnostic Criteria for Group-Based Multi-Trajectory Models of Opioid and Gabapentinoid Use among Medicare Beneficiaries[a]

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

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

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

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

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

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

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

eTable 3. Minimum and Maximum Standardized Mean Difference across Trajectory Group Comparisons

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

Abbreviations: **LIS**, low-income subsidy; **No**, number; **SD**, standard deviation; **SMD**; standardized mean difference; **Unwt**, unweighted; **Wt**, weighted

[a] Represented the minimum and maximum SMD across the 55 SMDs from group comparisons (the number of 2-combinations from given 11 elements: $C_2^{11} = 55$; e.g., group A vs B, group A vs C, group A vs D).

eTable 4. Subsequent Annual Healthcare Expenditures across Identified Trajectory Groups among Medicare Beneficiaries

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

[a] Adjusted for age, disability, low back pain, and pharmacy costs

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

eTable 5. Total Subsequent Annual Inpatient, Emergency Department, and Outpatient Expenditures across Identified Trajectory Groups among Medicare Beneficiaries Initiating Opioids or Gabapentinoids

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

eTable 5. (Continued)

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

[a] The percentage is the proportion of people with the corresponding healthcare service in each group; [b] Adjusted for age, disability, low back pain, and pharmacy costs at baseline

Abbreviations: **CI**, confidence interval; **GABA**, gabapentinoid; **No**, number; **OPI**, opioid

eTable 6. Total Subsequent Annual Pharmacy and Skilled Nursing Expenditures across Identified Trajectory Groups among Medicare Beneficiaries Initiating Opioids or Gabapentinoids

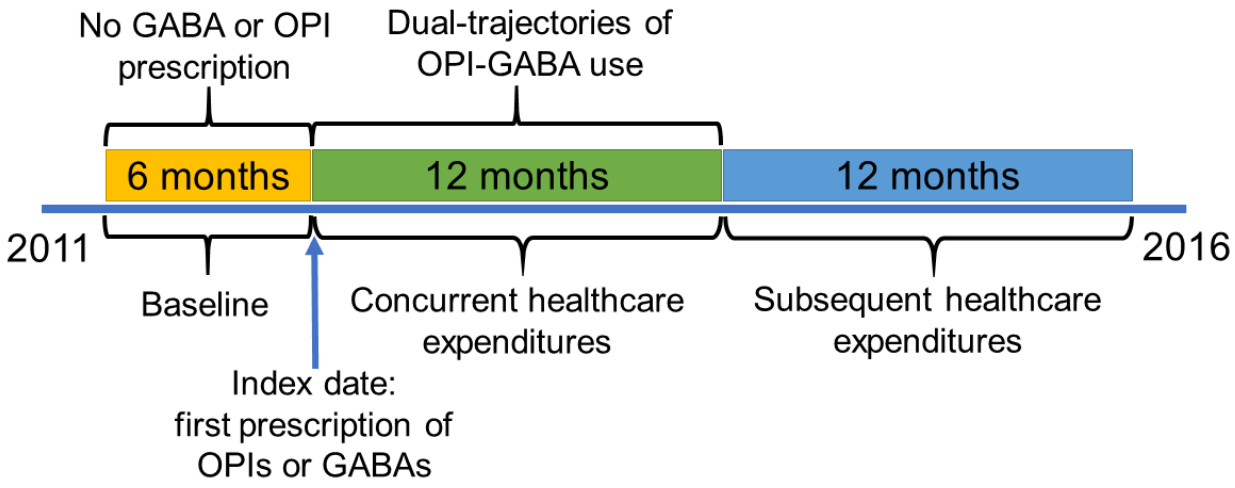
Trajectories	No. beneficiaries	Pharmacy			Skilled nursing		
		%[a]	Mean[b]	(95% CI)	%[a]	Mean[b]	(95% CI)
OPI only							
A. OPI-only early discontinuers	26,673	97.3	2,893	(2,855, 2,931)	5.7	22,595	(21,538, 23,704)
B. Consistent low-dose OPI-only users	11,125	98.4	4,550	(4,460, 4,641)	5.9	20,558	(19,229,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

eTable 6 (Continued)

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

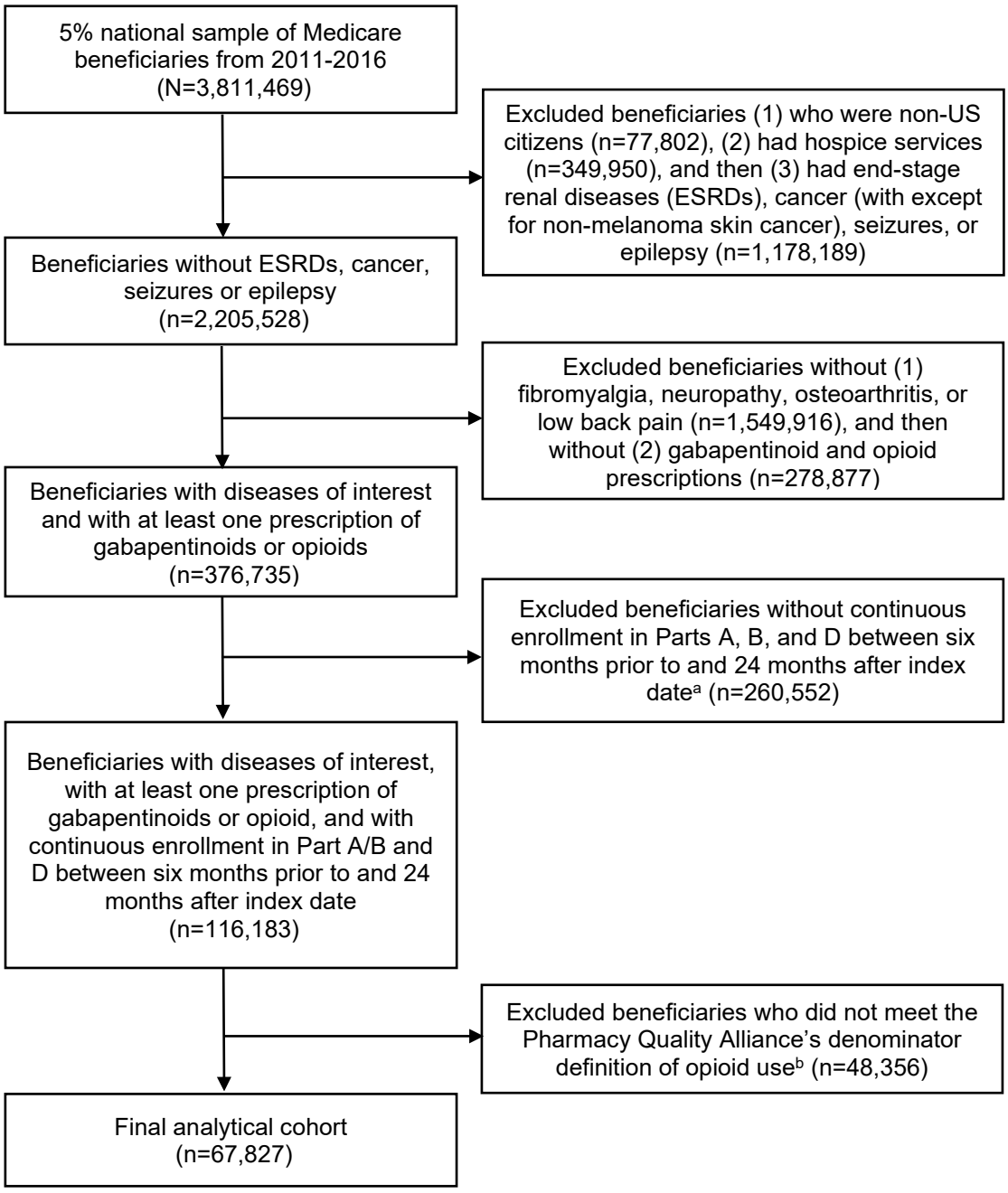
[a] The percentage is the proportion of people with the corresponding healthcare service in each group; [b] Adjusted for age, disability, low back pain, and pharmacy costs at baseline

Abbreviations: **CI**, confidence interval; **GABA**, gabapentinoid; **No**, number; **OPI**, opioid



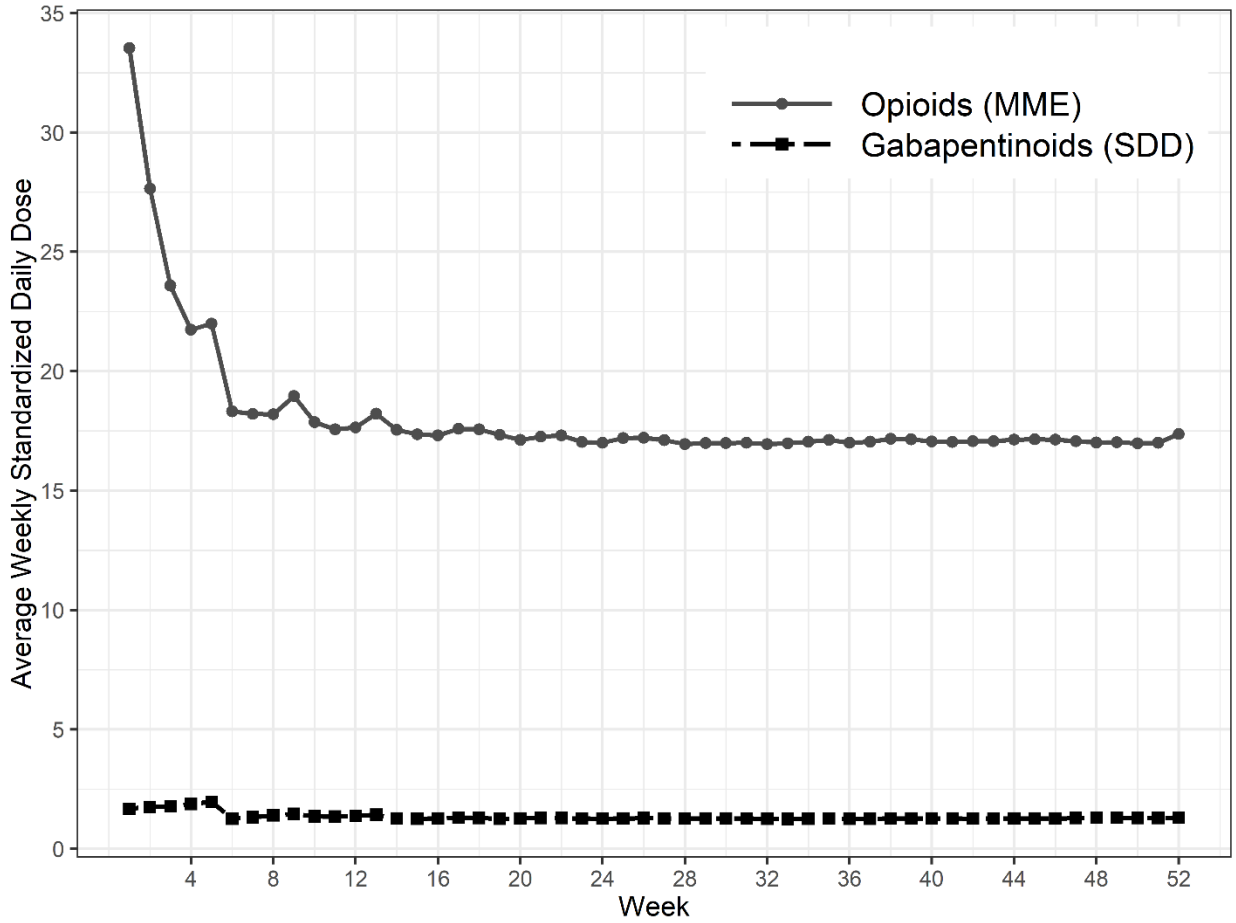
eFigure 1. Study Design Diagram

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



eFigure 2. Sample Size Flowchart

[a] Defined as the earliest prescription date of gabapentinoids or opioids, depending on which occurred first
[b] Two or more prescription claims for opioids filled on at least two separate days, for which the sum of the days supply is ≥15 during the year after initiating opioids or gabapentinoids



eFigure 3. Average Weekly Standardized Daily Dose for Opioid and Gabapentinoid Prescriptions among Medicare Beneficiaries

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