Prescription Opioid Use Trajectories and Risk Factors Associated with Opioid-Related Hospitalizations in Older Adults

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Structured Abstract

Purpose: The project aims to assess high-risk prescription opioid use patterns and risk factors associated with opioid-related adverse events (ORAEs), including opioid misuse, opioid use disorder (OUD), and opioid overdose among older adults.

Scope: The project used a secondary data approach to examine the associations of trajectories of prescription opioid use, predisposing factors --- select clinical conditions and polypharmacy --- and prognostic factors --- injury, respiratory infection, and infection due to nonsterile opioid injection --- with risk for ORAEs.

Methods: A nested, case-control study was conducted in a cohort of 380,272 older --- aged ≥65 years --- patients with chronic noncancer pain (CNCP) who initiated prescription opioids, assembled from a 5% Medicare sample from 2011 to 2018.

Results: Of 3,103 ORAE cases and 3,103 matched controls selected from the cohort, four prescribed opioid dose trajectories during the 6 months before the incident ORAE diagnosis or matched date emerged: gradual dose discontinuation (23.5%), gradual dose increase (30.3%), consistent low dose (24.3%), and consistent moderate dose (22.0 %), with only few older patients (<5%) being prescribed a mean daily dose of ≥90 daily morphine milligram equivalents. The risk of ORAEs increased with increasing prescribed opioid dose and was associated with receipt of duplicated opioids, chronic opioid use, and co-use of opioids with other central nervous system medications. Mental health conditions, cardiovascular diseases, and kidney disease were significant predisposing factors of ORAEs. Newly diagnosed injury, respiratory infection, and infection due to nonsterile opioid injection after opioid initiation were significant prognostic factors associated with subsequent increased risk of ORAEs among older adults.

Key Words: trajectories of prescription opioid dose, predisposing factors, prognostic factors, opioid-related adverse events, older adults, and CNCP

Purpose

The objective of this study is to assess high-risk prescription opioid use patterns and risk factors associated with ORAEs that required inpatient or outpatient care among older adults with CNCP. To achieve the objective, the project team employed secondary data analyses of a 5% random sample of Medicare beneficiaries with their enrollment and claims records from 2011 to 2018 to study two specific aims as follows:

Aim 1: Examine trajectories of prescription opioid use and their association with ORAEs after opioid initiation among opioid-naïve Medicare older adults.

Aim 2: Examine the extent to which elderly-specific predisposing and prognostic factors are associated with risk for ORAEs after opioid initiation among opioid-naïve Medicare older adults.

Scope

Background

Older adults in the United States have experienced significant increases in ORAEs, including opioid misuse, opioid use disorder (OUD), and opioid overdose (OD), in the past 15 years, despite a decline in opioid prescribing. Prior research indicated that, between 2006 and 2016, adults aged ≥65 years had the largest increase of all age groups in incident diagnosis of OUD or OD (14.2-fold vs. 3.5-fold in adults aged 18-64 years).[1] This finding parallels an AHRQ study showing that OUD- and OD-related hospitalizations and emergency department visits in older adults increased by 34% and 74%, respectively, between 2010 and 2015.[2] These upward trends have continued throughout 2019, despite the increasing efforts to combat the national opioid epidemic.[3,4] Opioid misuse, defined as opioid use without a prescription or for reasons or in ways other than as prescribed, doubled from 484,000 persons (1.1%) in 2002 to 880,000 persons (2.0%) in 2014 among older adults.[5] The majority (98%) of opioid misuse episodes in older adults involve prescription opioids, with 2% involving nonprescribed opioids (i.e., diverted or illicit sources).[6] The increased trend in OUD, OD, and opioid misuse highlights an urgent need to understand the etiology of ORAEs, with a special emphasis on high-risk prescription opioid patterns and elderly-specific risk factors for identifying high-risk older adults and implementing interventions.

Prior studies that explored prescription opioid use patterns and their association with adverse opioid events are primarily among nonelderly[7-9] or mixed populations.[10-12] Only a few existing studies focused on elderly populations from a limited or nonrepresentative sample.[13-15] Thus, it remains unclear whether the employed metrics of high-risk prescription opioid use --- e.g., high daily dose --- from nonelderly populations can be applied to older adults who have a different threshold for adverse opioid outcomes due to declined renal/hepatic function, other comorbidities, and poly-pharmacy.[14,16] In addition, none of the prior studies was conducted during the new era of increasingly restricted

access to prescription opioids. Given the increasing transparency of prescription opioid access in Prescription Drug Monitoring Programs and other initiatives to reduce access to prescription opioids, early refills or multiple provider criteria may have decreasing utility in identifying high-risk users. Furthermore, the only existing elderly studies evaluated opioid use cross-sectionally limiting assessments of the progression of opioid use to adverse opioid outcomes.[13-15] Understanding prescription opioid use trajectories is important for the identification and intervention of high-risk groups. In Aim 1, the project focused on a longitudinal assessment of opioid utilization to identify trajectories from opioid initiation to high-risk use and manifestation of ORAEs in older adults.

Understanding other elderly-specific factors associated with ORAEs is increasingly important, given the increasingly restricted access to prescription opioids. Ongoing research shows an increasing proportion of older patients who were newly diagnosed with OUD or OD had no opioid prescription in the year before the diagnosis[1] and received a prescribed opioid dose of less than 90-mg morphine equivalents daily or from fewer than three providers.[17] The project findings raise a question about what other factors may predispose older adults to opioid-related hospitalizations. The scarce literature on older adults reports several risk factors of chronic opioid use or opioid misuse, and

Figure 1: Potential Mechanisms of Risk Factors and Opioid-Related Adverse Event (ORAE) Among Older Adults
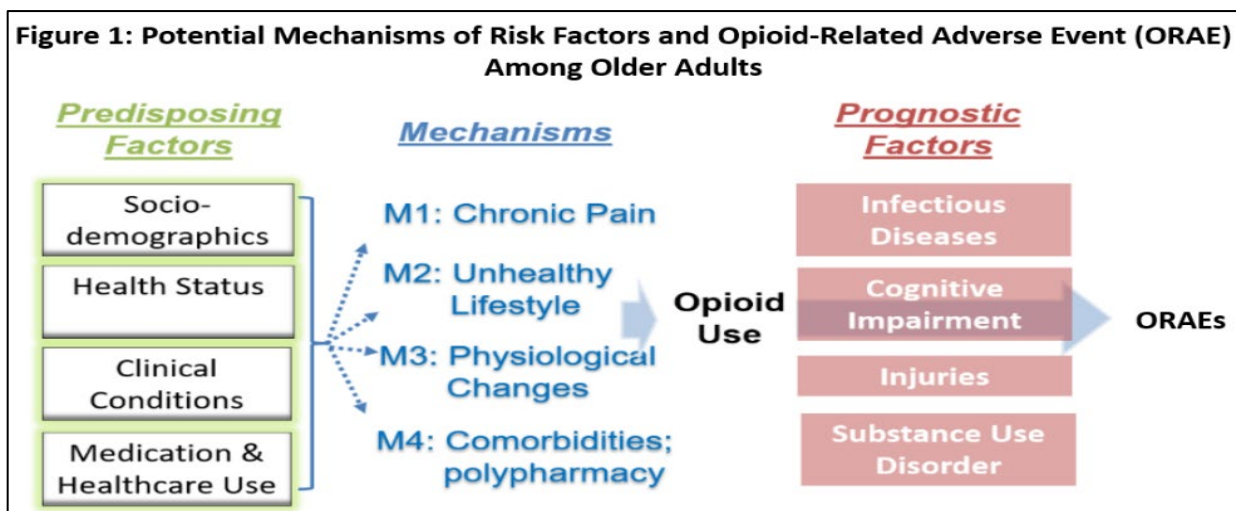
these include sociodemographic factors (younger old age [65-74], female, white, rural areas, low income, and low education), poor physical and mental health, history of substance use and abuse, and severe pain condition.[15,18] Yet, these potential factors along with many other predisposing and prognostic factors (**Figure 1**) that are prevalent in older adults treated for opioid dependence, and their associations with ORAEs, have not been explored in longitudinal research of older adult populations.

As shown in **Figure 1**, predisposing factors may increase the risk of ORAEs through one or more of the four hypothesized mechanisms, and prognostic factors that occur after opioid use are postulated as early warning signs that may be indicative of opioid overdose or misuse before the occurrence of ORAE encounters. For this project, the team prioritized two predisposing factors --- clinical conditions that may cause pain and medication use --- and three prognostic factors --- respiratory infection, infection due to nonsterile opioid injection, and injuries --- as they have not been examined in older adults.

The project team tested the role of these predisposing and prognostic factors in relation to the risk for ORAEs in older adults under Aim 2.

Methods

Study Design For both Aims 1 and 2, the project team conducted a nested, case-control study in a cohort of older --- aged ≥65 years old --- Medicare beneficiaries with CNCP who initiated prescription opioids, assembled from a 5% random Medicare sample from January 1, 2011, to December 31, 2018. The project team used the nested, case-control study because it allowed for (1) including all identified ORAE cases --- i.e., the outcome of interest --- which are relatively rare among older adults compared with younger populations, and (2) studying the association between prescription opioid use --- i.e., exposure --- and risk for ORAEs by flexibly modeling the exposure at varying proximities to the event date.

As shown in **Figure 2**, the project team first select a cohort of older adults who were aged ≥65 years; were diagnosed with CNCP; had continuous Medicare enrollment; had no diagnosed ORAE outcome; and had no cancer, palliative care, or hospice care during the 12 months before the date of opioid initiation, the cohort entry date. Then, the project team followed patients from the cohort entry date until the earliest date of ORAE outcome, a cancer diagnosis, receipt of palliative or hospice care, death, Medicare disenrollment, or study end on 12/31/2018.

Figure 2: A nested case-control design

For Aim 1, the project team identified a cohort of 380,272 eligible patients who initiated an opioid prescription and who had no ORAE outcomes diagnosed during the 12 months before the cohort entry --- i.e., baseline with mean [SD] age, 76.2 [7.9] years; 65.4% female; and 81.4% white. Of the cohort, 6,176 patients developed ORAEs --- i.e., cases --- yielding an incidence rate of 7.17 per 1000 person-years. Of the 6,176 ORAE cases, 1,800 (29.1%) had the encounter within the first 6 months after prescription opioid initiation, and 1,273 (20.6%) had no prescription opioid filled in the 6 months preceding the ORAE diagnosis. This resulted in 3,103 cases with a 6-month follow-up preceding the ORAE, during which at least one opioid prescription was dispensed for dose trajectory analysis. Thus, the primary analysis for Aim 1 was restricted to the 3,103 cases that were matched to 3,103 controls selected by incidence density sampling. For cases and matched controls, the project team examined their trajectories of prescribed opioid dose and high-risk opioid use --- including opioid duplications, chronic opioid use of ≥90 consecutive days --- and concurrent use of opioids with central nervous system [CNS] medications, including
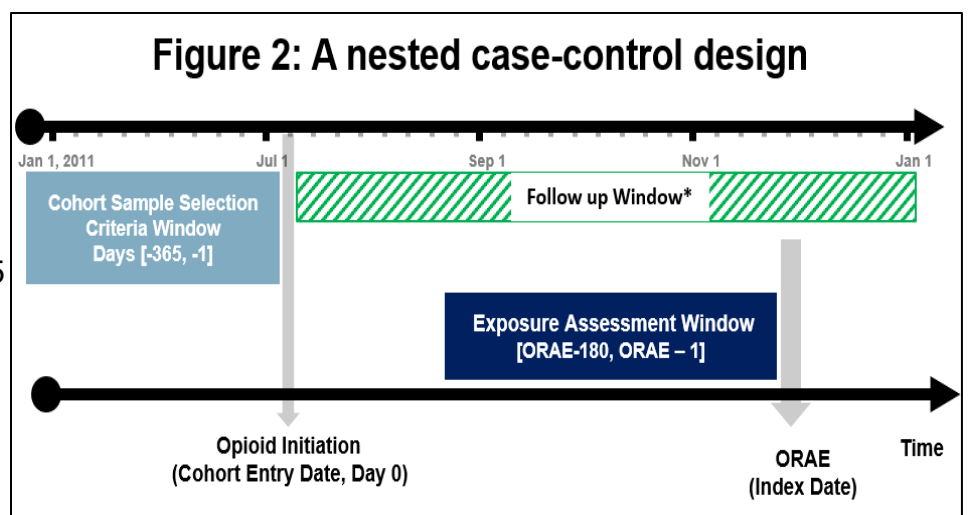
benzodiazepines, non-benzodiazepines, anticonvulsants, antidepressants, antipsychotics, and anxiolytics, in the 6 months before the event date for cases or matched date for controls at risk.

For Aim 2, the project team used the cohort built up under Aim 1 to further investigate three prognostic factors --- respiratory infection, infection due to nonsterile opioid injection, and injury --- and their risk for ORAEs. For each prognostic factor, the team created a separate cohort of Medicare opioid-naïve older patients with CNCP who had no ORAE outcome and had no prognostic condition of interest in the year before initiating a prescription opioid.

For each cohort, the team conducted a nested, case-control study in which incident ORAE cases were identified and matched to controls in a 1:4 ratio on age, sex, and time since opioid initiation. Prognostic factors were measured in the 6 months before the event date for cases or matched date for controls at risk.

Data Sources

For both Aims 1 and 2, the project team used a 5% random national sample of Medicare beneficiaries --- from 2011 to 2018 to constitute our study population. This population was chosen because they (1) represent older adults ≥ 65 years; (2) capture in- and outpatient encounters associated with opioid-related hospitalizations; and (3) provide a comprehensive account of prescription opioid and other prescription use.

This includes clinical encounter data --- Medicare Part D and Medicare Parts A and B --- with detail on procedures and diagnoses (coded using *the International Classification of Disease, 9th or 10th Revision, Clinical Modification, ICD-9-CM or ICD-10-CM*). Part D data include information on dispensed drug names, days' supply, dosage form, and fill dates. Beneficiary enrollment and demographics are also available.

Measures

ORAE: ORAE cases were identified as patients who had an inpatient or outpatient encounter with *ICD-9-CM or ICD-10-CM* diagnosis or E-codes for opioid misuse, dependence, or poisoning **(Table 1)**.[19,20] Those codes have been used by US government agencies to define ORAEs.[19,20] Consistent with prior studies,[1,21] when identifying patients with incident ORAE during follow-up, the project team only considered the first encounter with qualifying *ICD-10-CM* diagnosis codes. The team set the date of the first eligible ORAE as the index date, and the same date was assigned as the index date to the respective matched controls.

Table 1: ICD-9-CM, ICD-10-CM, or E-code to identify ORAEs

Opioid misuse or dependence (ICD-9): 305.50 (Opioid abuse – unspecified) 305.51 (Opioid abuse – continuous) 305.52 (Opioid abuse – episodic) 304.00 (Opioid type dependence – unspecified) 304.01 (Opioid type dependence – continuous) 304.02 (Opioid type dependence – episodic) 304.70 (Combinations of opioid type drug with any other – unspecified) 304.71 (Combinations of opioid type drug with any other – continuous) 304.72 (Combinations of opioid type drug with any other – episodic)
Opioid poisoning (ICD-9): 965.00 (Poisoning – opium (alkaloids), unspecified) 965.01 (Poisoning – heroin) 965.02 (Poisoning – methadone) 965.09 (Poisoning – opiates and related narcotics, other) E850.0 (Accidental poisoning by heroin) E850.1 (Accidental poisoning by methadone) E850.2 (Accidental poisoning by other opiates and related narcotics)
Corresponding ICD-10 codes for opioid misuse, opioid dependence, and opioid poisoning are listed at https://www.hcup-us.ahrq.gov/reports/statbriefs/sb258-Opioid-Hospitalizations-Rural-Metro-Hospitals-2016.jsp.

Measurement of prescription opioid use as the exposure for Aim 1: Prescription opioids approved for use in the US between 2011 and 2018 were captured from the Medicare Part D Prescription Event files based on the National Drug Code. These opioids included butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, nalbuphine, opium, oxycodone, oxymorphone, pentazocine, remifentanil, sufentanil, and tramadol. The project team excluded (1) injectable opioids because they are primarily used in inpatient settings, where prescription dispensing data are not available, and (2) buprenorphine sublingual tablets and buprenorphine-naloxone combinations, because they are indicated for the treatment of OUD or OD.

The dose of each prescription opioid filled during 6 months before the index date for cases and matched date for controls was converted to a morphine milligram equivalent (MME) dose based on a standard formula --- the quantity of opioids dispensed per day multiplied by the strength and the MME conversion factor.[22] The project team then calculated the mean daily MME dose in each month by adding the MMEs of all days with prescribed opioids dispensed during the month and then dividing by 30 days. Sensitivity analysis was conducted with the mean daily MME dose calculated at bi-weekly intervals.

The team used a group-based trajectory model to identify clusters of patients who followed a similar longitudinal pattern for prescribed opioid dose during the 6 months preceding an incident ORAE encounter for cases and matched controls.

Prognostic factors: The project team examined all inpatient or outpatient medical encounters with a primary diagnosis code of respiratory infections, infections due to nonsterile opioid injection, cognitive impairment, and injuries (**Table 2**) during the 6 months before the index date as the primary analysis. To identify patients with prognostic conditions, the team relied on relevant claims-based algorithms, which have shown high validity; ICD-9 codes were converted to ICD-10 codes.

Table 2: Summary of measures for prognostic factors

Factors	Claims-based algorithm for identifying prognostic condition	Validity
Respiratory Infections	pneumonia (480–486, 487.0), bronchitis (466.0,490.x, 491.x, V81.3), bronchiolitis (466.1x), emphysema (492.x), bronchiectasis (494.x), and chronic airway obstruction, not elsewhere classified (496)	Sensitivity (76-97.8%); Specificity (96.9-99.0%); PPV (92.0-96.2%)[23-25]
Infections due to nonsterile opioid injection	HIV (0.42.x and V08), Hepatitis C (070.41, 070.44, 070.51, 070.54, 070.70, 070.71, V02.62), skin/soft tissue (035, 040.0. 569.61, 681.x, 682.x, 785.4, 728.86), endocarditis (421.x), Bone/joint (711.0x, 730.0x, 730.1x, 730.2x). 320), and bacteremia (041.2, 038.2, 790.7)	Sensitivity (80-100%); Specificity (97-100%); PPV (82-100%)[26-28]
Injuries	Injuries (800-959, excluding 895-897, 905-909, 930-939)	Agreement (82-87%)[29]

Predisposing factors: The team prioritized two predisposing factors: clinical conditions and medication use. Clinical conditions defined using ICD-9 or ICD-10 diagnosis codes included select comorbid conditions that may cause pain, including mental health disorders, diabetes, cardiovascular diseases, hypertension, pulmonary condition, kidney disease, gastrointestinal tract disorder, and liver disease. The select comorbid conditions were identified based on ICD codes defined in the Clinical Classifications Software (CCS) of the Healthcare Cost and Utilization Project. We listed the ICD codes for clinical conditions in our articles.[30,31] Medication use of interest measured using Medicare Part D prescription data included polypharmacy, which is defined as having ≥5 different medications, excluding opioids.

Covariates for adjustment: Important covariates included demographic characteristics such as age, sex, race, and ethnicity --- classified as White, Black, and other, including Hispanic, Asian, Pacific Islander, and Native American individuals; low-income subsidy status --- yes vs no; US region --- Northeast, Midwest, South, and West; diagnosis of alcohol or tobacco use disorder; types of chronic pain conditions, including musculoskeletal, neuropathic, and idiopathic pain; and overall healthcare use, including any inpatient admission, any ED visit, and any skilled nursing facility stay.

For Aims 1 and 2, the team examined the association between exposure measured in the 6 months before the index date and subsequent risk for ORAE in the project sample of cases and controls; the project team adjusted for the covariates along with potential prognostic and predisposing factors, measured between 12 and 6 months before the index date (i.e., ORAE onset) for cases and matched date for controls.

Project Limitations

1. This project allows for establishing an association but not causation. Residual confounding caused by unknown or unmeasured confounders is possible.

2. Illicit opioid use, a growing concern in the opioid epidemic, was not captured in our data.

3. The analysis of prescription dispensing data confirms receipt of medications and not medication use.

4. Medicare administrative claims data lack information on pain severity, which is the key factor associated with selection into opioid treatment.

5. The validity of ORAE is unclear and warrants additional research.

6. The project team was unable to determine whether the prognostic factors, such as injury, were caused by opioid misuse or other reasons, such as uncontrolled pain.

7. Not all fatal prognostic factors --- e.g., injuries --- would be present in inpatient or outpatient care, and we included only injuries that received medical attention. Thus, the project team could not rule out the possibility of exposure misclassification --- i.e., patients were misclassified as having no injury, because their events did not present in medical settings.

8. The findings can only be generalized to Medicare fee-for-service beneficiaries with CNCP.

9. With data derived from 2011 to 2018, the project findings may not be reflective of clinical practices after 2018, during which patterns of opioid prescribing and its relevance to ORAEs may have changed.

Results

Aim 1: Examine trajectories of prescription opioid use and their association with ORAEs after opioid initiation among opioid-naïve Medicare older adults.

Principal Findings

Among 3,103 cases and 3,103 controls, four prescribed opioid dose trajectories during the 6 months before the incident ORAE diagnosis or matched date emerged: gradual dose discontinuation from ≤3 to 0 daily MME, 1,456 (23.5%); gradual dose increase from 0 to >3 daily MME, 1,878 (30.3%); consistent low dose between 3 and 5 daily MME, 1,510 (24.3%); and consistent moderate dose >20 daily MME, 1,362 (22.0%). Few older patients (<5%) were prescribed a mean daily dose of ≥90 daily MME during 6 months before diagnosis or matched date.[30]

Conditional logistic regression analyses showed that, compared with patients who had gradual dose discontinuation, those patients with gradual dose increase had an adjusted odds ratio [aOR]=3.4 (95% confidence interval [CI]: 2.8-4.0; P<0.001); consistent low dose had an aOR=3.8 (95% CI: 3.2-4.6; P<0.001); and consistent moderate dose had an aOR=8.5 (95% CI: 6.8-10.7; P<0.001). These patients had a higher risk of ORAE after adjustment for covariates (**Table 3**).[30]

Table 3. Unadjusted and adjusted association between trajectories of prescription opioid dose and risk for opioid-related adverse events

Variables	Cases vs. matched controls			
	Unadjusted OR (95% CI)	P Value	Adjusted[2] OR (95% CI)	P Value
Opioid dose trajectory group				
Gradual dose discontinuation group	1.00 Reference		1.00 Reference	
Gradual dose increase group	3.09 (2.63-3.64)	<0.001	3.36 (2.83-4.00)	<0.001
Consistent low-dose group	3.82 (3.22-4.54)	<0.001	3.81 (3.17-4.58)	<0.001
Consistent moderate-dose group	8.28 (6.86-9.99)	<0.001	8.53 (6.79-10.70)	<0.001

Variables	Cases vs. matched controls			
	Unadjusted OR (95% CI)	P Value	Adjusted[2] OR (95% CI)	P Value
Race/ethnicity				
White	1.00 Reference		1.00 Reference	
Black	0.84 (0.70-1.00)	0.050	0.88 (0.70-1.10)	0.273
Other[1]	0.83 (0.71-0.98)	0.026	0.97 (0.79-1.19)	0.765
Low-income subsidy status (Yes vs no as the reference)	1.06 (0.95-1.18)	0.287	0.89 (0.77-1.03)	0.117
Region				
South	1.00 Reference		1.00 Reference	
Northeast	1.12 (0.96-1.30)	0.144	1.15 (0.96-1.38)	0.121
Midwest	0.93 (0.82-1.06)	0.300	0.97 (0.83-1.13)	0.670
West	1.21 (1.06-1.39)	0.006	1.24 (1.05-1.47)	0.002
Tobacco or alcohol use disorder (Yes vs no)	1.74 (1.46-2.08)	<0.001	1.48 (1.30-1.68)	0.030

| | Cases vs. matched controls | | | |
Variables	Unadjusted OR (95% CI)	P Value	Adjusted[2] OR (95% CI)	P Value
Chronic pain diagnosis[3]				
Musculoskeletal pain (Yes vs no)	1.69 (1.47-1.94)	<0.001	1.21 (1.02-1.43)	0.035
Neuropathic pain (Yes vs no)	1.84 (1.65-2.05)	<0.001	1.48 (1.30-1.68)	<0.001
Idiopathic pain (Yes vs no)	2.44 (2.13-2.80)	<0.001	1.58 (1.34-1.87)	<0.001
Clinical conditions				
Mental health conditions (Yes vs no)	1.51 (1.35-1.69)	<0.001	1.19 (1.03-1.36)	0.014
Diabetes (Yes vs no)	1.04 (0.94-1.15)	0.451	0.88 (0.77-1.01)	0.067
Cardiovascular disease (Yes vs no)	1.39 (1.26-1.54)	<0.001	1.16 (1.02-1.33)	0.028
Hypertension (Yes vs no)	1.15 (1.02-1.30)	0.026	1.00 (0.85-1.17)	0.973
Pulmonary condition (Yes vs no)	1.33 (1.20-1.47)	<0.001	1.08 (0.93-1.26)	0.294
Kidney disease (Yes vs no)	1.28 (1.14-1.45)	<0.001	1.31 (1.12-1.52)	<0.001
Gastrointestinal disorder (Yes vs no)	1.35 (1.20-1.51)	<0.001	1.10 (0.95-1.28)	0.185
Respiratory infections (Yes vs no)	1.40 (1.25-1.56)	<0.001	1.17 (1.00-1.37)	0.056
Injuries (Yes vs no)	1.42 (1.26-1.61)	<0.001	1.03 (0.87-1.22)	0.741

Variables	Cases vs. matched controls			
	Unadjusted OR (95% CI)	P Value	Adjusted[2] OR (95% CI)	P Value
Infections from nonsterile opioid injection (Yes vs no)	1.21 (1.02-1.45)	0.032	0.91 (0.73-1.12)	0.360
Medication utilization				
Polypharmacy (Yes vs no)	1.34 (1.22-1.67)	<0.001	0.96 (0.78-1.17)	0.660
Healthcare utilization				
Any hospital stay (Yes vs no)	1.35 (1.19-1.54)	<0.001	0.94 (0.77-1.13)	0.488
Any ED visit (Yes vs no)	1.33 (1.19-1.54)	<0.001	1.03 (0.88-1.20)	0.672
Any SNF stay (Yes vs no)	1.49 (1.21-1.83)	<0.001	1.00 (0.76-1.31)	0.995

Abbreviations: OR, Odds Ratio; ED, emergency department; SNF, skilled nursing facility.
[1] Included Hispanic, Asian, Pacific Islander, and Native American individuals.
[2] Adjusted for race/ethnicity, low-income subsidy status, region, tobacco or alcohol use disorder, chronic pain diagnoses, clinical conditions, medication utilization, healthcare utilization, and the year of the index date.

The project team also quantified the prevalence of three other measures of high-risk prescription opioid use as well as a composite of any of the measures assessed during the 6-month before incident ORAE diagnosis and matched controls. The prevalence of these --- opioid duplications, 39.1% vs 15.5%; chronic opioid use, 22.4% vs 9.0%; and concurrent use of opioids and CNS-active drugs, 45.5% vs 28.9% --- were higher in the cases than in controls. Multivariate regression analyses showed that for all three composite measures, older adults with versus without high-risk prescription opioid use had a significantly higher risk of developing ORAEs (**Table 4**).

Table 4: **High-risk use of prescription opioids and risk of opioid-related adverse events and matched controls**

High-risk use of prescription opioids	% of cases (N=767)	% of matched£ controls (n=767)	Crude RR (95% CI)	Adjusted RR+ (95% CI)
Opioid duplications (≥2 or more opioids on the same day)	39.1	15.5	3.4 (2.6, 4.4)	3.3 (2.5, 4.4)
Chronic opioid use (≥90 days)	22.4	9.0	2.8 (2.1, 3.8)	2.7 (2.0, 3.7)
Concurrent use of opioids and other CNS drugs for ≥7 days¥	45.5	28.9	2.1 (1.7, 2.6)	1.9 (1.5, 2.5)
Composite of any	63.8	37.9	2.8 (2.3, 3.5)	2.7 (2.2, 3.5)

Abbreviations: CNS, central nervous system; RR, relative risk.
¥CNS drugs included antipsychotics, benzodiazepine, non-benzodiazepine or hypnotics, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors
£matched on age and duration of follow-up
+adjusted for demographics (sex, race, low-income subsidy, and region), alcohol or tobacco use, chronic pain diagnosis (musculoskeletal, neuropathic, and idiopathic pain), clinical diagnoses (mental health disorders, diabetes, cardiovascular diseases, pulmonary conditions, kidney disease, gastrointestinal disorders, respiratory infections, injuries, infections due to nonsterile opioid injection), polypharmacy, and healthcare utilization (any inpatient stay, emergency room visit, skilled nursing home stay, and inpatient surgery).

Conclusions for Aim 1:

- Four prescribed opioid dose trajectories during 6 months before the incident ORAE diagnosis or matched date emerged: gradual dose discontinuation, from ≤3 to 0 daily MME, gradual dose increase, from 0 to >3 daily MME, consistent low dose between 3 and 5 daily MME, and consistent moderate dose >20 daily MME.

- Few older patients --- <5% --- were prescribed a mean daily dose of ≥90 daily MME during 6 months before diagnosis or matched date.

- The risk of ORAEs increased with increasing prescribed opioid dose, suggesting that many older adults might be susceptible to a prescribed opioid dose as low as 3 mg MME. Alternatively, these patients might have used illicit opioids or other substances to supplement prescribed low-dose opioids to achieve pain control before ORAE events.

- The receipt of duplicated opioids, chronic opioid use, or concurrent use of opioids with other CNS drugs was associated with an increased risk of ORAEs.

Aim 2: Examine the extent to which elderly-specific predisposing and prognostic factors are associated with risk for ORAEs after opioid initiation among opioid-naïve Medicare older adults.

Principal findings for predisposing factors (clinical conditions and polypharmacy) and risk for ORAEs: The project team found that older patients with mental health conditions (aOR=1.2; 95% CI: 1.3-1.4; P<.14 vs no such condition), with cardiovascular disease (aOR=1.2; 95% CI: 1.2-1.3; P<0.028 vs no such condition), and with kidney disease (aOR=1.3; 95% CI: 1.1-1.5; P<.1 vs no such condition) had a significantly high risk of ORAEs. In terms of medication use, the team found a nonsignificant association between polypharmacy and risk for ORAEs (aOR=.96; 95% CI: 0.78-1.2; P=0.660) (**Table 4**).

Principal findings for prognostic factors and risk for ORAEs: The project team found that older patients who had an injury (aOR=3.4, 95% CI: 3.1-3.8; P<0.001 vs versus those who did not), respiratory infection (aOR=2.1, 95% CI: 1.9-2.4; P<.001 vs versus those who did not), and infection due to nonsterile opioid injection (aOR=2.0, 95% CI: 1.7-2.3; P<0.001 vs versus those who did not) after opioid initiation but within 6 months before index date had significant risks for ORAEs after accounting for confounders (**Table 5**).

The project team conducted an additional sensitivity analysis that matched cases with four controls using an advanced method --- a disease risk score approach --- and assessed injuries after opioid initiation and before the index date. The additional analysis showed a consistent result, with a higher risk of ORAEs observed in patients with vs without injury.[31]

Table 5: Associations between Prognostic Factors and Risk for ORAEs in Older Adults with Chronic Noncancer Pain

Prognostic Factors	Sample size (n)	Cases vs matched controls¶ Odds Ratio (95% Confidence Interval)	
		Unadjusted	Adjusted*
Injuries (vs no)	14,004	3.64 (3.32, 3.99)	3.44 (3.10, 3.81)
Respiratory infection (vs no)	16,626	2.41 (2.18, .267)	2.11 (1.88, 2.38)
infection due to nonsterile opioid injection (vs no)	22,088	2.35 (2.08, 2.65)	1.97 (1.71, 2.26)

¶ Controls were matched by age, sex, and time since cohort entry.
*Adjusted for baseline predisposing factors including race, residential regions, low-income subsidy, region, tobacco or alcohol use, type of chronic pain, mental health disorders, diabetes, cardiovascular diseases, pulmonary conditions, kidney disease, gastrointestinal disorders, and healthcare and medication utilization.

Conclusions for Aim 2:

- Mental health conditions, cardiovascular diseases, and kidney disease after prescription opioid therapy were significant predisposing factors of ORAEs.

- Newly diagnosed injury, respiratory infection, and infection due to nonsterile opioid injection after opioid initiation were associated with subsequent increased risk of ORAEs.

Project Implications: In this sample of older patients who are Medicare beneficiaries with CNCP, findings from Aims 1 and 2 may have the following implications:

- The CDC-recommended 90 mg/day MME high-risk opioid dose threshold may not sufficiently detect older patients at risk for ORAEs, given that only 5% of ORAE cases received prescribed opioid doses at or above this threshold, as observed in this project.

- We recommend that additional studies that collect illicit opioid use among older adults are needed to clarify the safe dose threshold of prescribed opioids for older adults, particularly during the new era of increasingly restricted access to prescription opioids.

- Older adults with receipt of opioid duplications, chronic opioid use, and concurrent use of opioids and CNS medications were at increased risk for ORAEs and should be closely monitored.

- After initiating opioids for older adults with CNCP, clinicians also should pay close attention to those with mental health conditions, cardiovascular diseases, and kidney disease, as they were demonstrated to be significant predisposing factors of ORAEs.

- Project findings demonstrated that newly diagnosed injury, respiratory infection, and infection due to nonsterile opioid injection after opioid initiation are significant prognostic factors for ORAEs. Regular monitoring of these events after initiating prescription opioids may help identify older opioid users at risk for ORAEs.

List of Publications and Products

1. Wei YJ, Chen C, Schmidt S, Lewis OL(g), Winterstein AG. Trajectories of Prescription Opioid Dose and Risk of Opioid-Related Adverse Events Among Older Adults—A Nested Case-Control Study. *PLOS Medicine*. 2022 Mar; 19(3): e1003947. doi: 10.1371/journal.pmed.1003947

2. Wei YJ, Chen C, Cheng TY, Schmidt S, Fillingim RB, Winterstein AG. Association of Injury After Prescription Opioid Initiation with Risk of Opioid-Related Adverse Events Among Older Medicare Beneficiaries in The United States—A Nested Case-Control Study. *PLOS Medicine*. 2022 September 22.

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