Effects of Pain, Insomnia, and Depression on Psychoactive Medication Supply in Older Adults With Osteoarthritis

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Background: Determinants of prescribing psychoactive medications for symptom management in older adults remain underexamined despite known risks and cautions concerning these medications.

Objective: To examine independent and combined effects of pain, concurrent insomnia and depression symptoms on psychoactive medications supplied to older adults with osteoarthritis (OA).

Research Design: Survey data on pain, insomnia, and depression obtained from OA patients screened for a randomized controlled trial were used to identify predictors of psychoactive medication supply [opioids, sedatives, tricyclic antidepressants (TCAs), and non-TCAs] over a 4-year period.

Subjects: Group Health Cooperative patients with a diagnosis of OA (N = 2976).

Measures: Survey data on pain (Graded Chronic Pain Scale), insomnia (Insomnia Severity Index), and depression (Patient Health Questionnaire-8); and medications supply assessed from electronic medical records.

Results: In negative binomial models, pain [incidence rate ratio (IRR), 2.8–3.5; $P < 0.001$], insomnia (IRR, 2.0; $P < 0.001$), and depression (IRR, 1.5; $P < 0.05$) each independently predicted opioid supply. Insomnia (IRR, 3.2; $P < 0.001$) and depression (IRR, 3.0; $P < 0.001$) each independently predicted sedative supply. Pain (IRR, 2.1; $P < 0.05$) and insomnia (IRR, 2.0; $P < 0.05$) independently predicted TCA supply, whereas only depression (IRR, 2.2; $P < 0.001$) independently predicted non-TCA supply. Combined effects of pain and insomnia/depression on these medications were additive and increased the rate of medication supply 1.5–7.5 times. Combined effects increased with insomnia or depression severity.

Conclusions: Concurrent insomnia and depressive symptoms predicted increased supply of opioids, sedatives, and antidepressants after accounting for pain, indicating the importance of sleep and mood disorders as factors increasing supply of these medications.

Key Words: osteoarthritis pain, insomnia, depression, medication supply, older adults

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Osteoarthritis (OA) affects half of adults aged 65 years and above and is among the leading causes of disability for adults.[1,2] Pain is prevalent in OA and is the main reason patients seek treatment. In addition to pain, patients with OA often report other concurrent conditions, most notably insomnia and depression.[3,4] Previous studies showed that patients with knee OA report problems with initiating sleep (31%), difficulty maintaining sleep at night (81%), and general sleep problems (77%).[5,6] Data from the Osteoarthritis Initiative showed that patients with multisite OA had higher odds (1.43–1.72) of developing depression compared with those without OA.[7] In addition, an increasing body of research has documented reciprocal relationships among chronic pain, insomnia, and depression in OA.[8,9] These concurrent symptoms not only add to the health burden for patients, but also increase the complexity of OA management.

Pharmacological treatment is an important approach for symptom management in older adults. The prevalence of prescribing psychoactive medications was high in older adults and their relative risk of being prescribed antidepressants and opioids has significantly increased from 1995 to 2010.[10,11] The potential harms of psychoactive medications have received more public health attention nowadays given increasing prescribing of psychoactive medications in older adults without clearly defined mental health disorders.[12,13] The increased prescribing of psychoactive medications also

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creates more safety concerns, given that the related risks are well-documented for older adults, such as fall injuries, hospitalization, and increased mortality.[14] This is an important concern particularly in older adults with OA receiving opioids for pain management as opioids were recently included as potentially inappropriate medication use in older adults.[15] Patients with OA or other chronic pain conditions were significantly more likely to use opioids and adjunctive psychoactive medications for treating insomnia and depressive symptoms.[16–18] Concurrent use of sedatives and opioids is a major contributing factor to the current epidemic of opioid overdose in the United States.[19] Wright et al[4] reported an increase in likelihood of opioid prescription for patients with OA and a history of depression.[20] Given the complex interplay between OA pain, insomnia, and depression,[21–24] it is unknown whether these concurrent symptoms have synergistic effects on psychoactive medication supply which creates even more risks in older adults with OA. It is also important to understand the respective contributions of these concurrent conditions to long-term psychoactive medication supply in this population.

The purposes of this study were to (1) describe pain, insomnia, and depressive symptom severity in older adults with OA; (2) describe the amounts supplied of 4 commonly prescribed psychoactive medication types to manage symptoms [opioids, sedatives, tricyclic antidepressants supply (TCAs), and non-TCAs]; (3) investigate the effects of pain, insomnia, and depression on the amount of psychoactive medications supplied and whether there is synergy among these symptoms on medications supplied; and (4) examine how pain, insomnia and depression jointly contribute to psychoactive medication supply in older adults with OA.

METHODS

Participants

The dataset used is from a National Institutes on Aging (NIA)-funded clinical trial that compared the efficacy of 3 behavioral group interventions for older adults with concurrent OA and insomnia.[25] The study was a collaboration between the University of Washington (UW) and Group Health Cooperative (GHC) (acquired by Kaiser Permanente in 2017), a Seattle-area integrated health care plan with over 600,000 enrollees. Before the clinical trial, from 2008 to 2010, a screening survey questionnaire was mailed to 8057 GHC members age 60+ who had an electronic medical record (EMR) OA diagnosis associated with a health care visit in the prior 3 years. A total of 3041 participants completed the questionnaire and gave permission to access their EMRs. This study used data from the screening survey and participants' GHC EMRs. The clinical trial was approved by the UW Human Subjects Division and the GHC Institutional Review Board. This secondary data analysis was reviewed by the UW Human Subjects Division and qualified for an exemption.

Inclusion criteria for receiving the screening survey were: age 60+, continuously enrolled in GHC 1 year before screening, receiving primary care services at one of 6 regional participating clinics, not in the "No Contact for Research File," and at least one visit noted in the EMR for OA in the prior 3 years. The parent study excluded participants if their EMR indicated a diagnosis of: (a) rheumatoid arthritis; (b) obstructive sleep apnea; (c) periodic leg movement disorder; (d) restless leg syndrome; (e) sleep-wake cycle disturbance; (f) rapid eye movement behavior disorder; (g) dementia or receiving cholinesterase inhibitors; (h) Parkinson disease or another neurodegenerative disease known to directly impact sleep; (i) cancer in the past year and receiving chemotherapy or radiation therapy in the past year; and/or (j) inpatient treatment for congestive heart failure within the previous 6 months.

Dataset Elements

Symptom Measures

Symptoms of pain, insomnia, and depression were measured by the Graded Chronic Pain Scale (GCPS), the Insomnia Severity Index (ISI) and Patient Health Questionnaire depression scale (PHQ-8), respectively. All 3 measures were chosen based on good internal consistency and validity in large studies. The GCPS assesses 2 dimensions of overall chronic pain severity: pain intensity and pain-related disability.[26] Subscale scores for pain intensity and disability are combined to calculate a chronic pain grade with 5 hierarchical categories, with grade 0 meaning no pain and grade IV meaning high disability-severely limiting pain.[27] Participants were asked to specifically report only arthritis pain on the GCPS, and to exclude other sources of pain. The ISI was designed to assess the nature, severity, and impact of insomnia and monitor treatment response in adults.[28] The ISI is a 7-item measure with scores ranging from 0 to 28, with a higher score indicating more severe insomnia. The PHQ-8 is an 8-item scale which has been shown to be a valid diagnostic and severity measure for depressive disorders in large clinical trials and is a reliable measure for depression in population-based studies.[29,30] Total scores range from 0 to 24, with higher scores representing more severe depression.

For this study, pain was coded as a binary variable: mild pain (GCPS = 1) and moderate to severe pain (2–4).[26] The insomnia variable was coded according to validated cut-points for this scale which were: no insomnia (≤ 7), subthreshold insomnia (8–14), and clinical insomnia (15–28).[28] The depression variable was coded according to validated cut-points for this scale as follows: no depression (≤ 4), subclinical depression (5–9), and current depression (10–24).[30] For terminological consistency, the term of subclinical insomnia was used throughout the paper to replace subthreshold insomnia.

Medication Supply

A programmer at GHC used the First Databank licensed by GHC, which uses the American Hospital Formulary Service (AHFS) code to classify drugs from the EMRs.[31] EMRs were used for 1 year immediately before the index date and 3 years after the index date, with index date defined as the date when the screening questionnaire was mailed to the participant. Medication supply was measured as days of supply for the following medication categories: (a) opioids; (b) sedatives; and (c) antidepressants, including TCAs and

non-TCAs. Please see the appendix, Supplemental Digital Content 1 (http://links.lww.com/MLR/B622) for specific medications included in each medication category.

Participant Characteristics

Demographics were collected from the screening survey, including age, sex, race, marital status, employment status, and educational levels. Age and sex were verified from EMRs. Length of enrollment in GHC for each of the 4 years (1-y prestudy and 3-y post follow-up) and Charlson Comorbidity Index (CCI) scores were also calculated from participants' EMRs.[32]

Data Analysis

Participants with no enrollment in GHC after the index date were excluded (N = 6) because they did not have data on medication supply. Participants with missing data on more than 2 of the following variables were excluded: pain [39 missing (1.3%)], insomnia [20 (0.7%)], depression [107 (3.5%)], education [62 (2.0%)], marital status [67 (2.2%)], race [110 (3.6%)], and employment [122 (4.0%)] with a final sample of 2976 included in the final analysis. Multiple imputation technique was used with 5 imputations to accommodate the remaining missing information for variables mentioned above in the statistical analyses.[33] Demographics, symptoms of pain, insomnia, and depression, length of enrollment, CCI, and medication supply variables were used in the imputation models.

Two different analytic approaches were used to examine the data. The first, symptom approach, was to examine the independent effects of each symptom on medication supply and identify whether there was presence of synergy among the symptoms, controlling for demographics and CCI. In this approach, symptoms as continuous variables were included in regression models and interaction terms (pain×insomnia, pain×depression, insomnia×depression, and pain×insomnia×depression) were introduced one at a time. The second, group approach, was to further investigate independent and combined effects of 3 symptoms on medication supply using clinically defined groups that were formed based on the clinically relevant categorization of pain, insomnia, and depression severity. Given the high correlation between insomnia and depression, data analyses could not be completed due to small numbers of participants in certain categories, such as the category "mild pain and clinical insomnia and no depression" (n = 6). Therefore, 2 categorical variables of clinically defined groups were created based on the combination of symptom severities, with one variable representing the severity of pain and insomnia, and the other representing the severity of pain and depression. With this group approach, we could investigate independent effects of pain, insomnia and depression, and combined effects of pain and insomnia, and pain and depression. This allowed us to examine how the severity of insomnia and depression, in addition to pain, contribute to days of medication supply.

All data analyses were performed using Stata 14.0.[34] Descriptive statistics including mean, SD, percentage, and percentiles were used to describe participants' demographics, symptom distribution at baseline and medication supply from years 1 to 4. Because of the skewness of the outcome variables (shown in Table 2), analyses using negative binomial models were conducted to examine the independent and combined effects of pain+insomnia, and pain+depression on days of supply for medications 3 years post follow-up (years 2–4). The negative binomial model was appropriate, because the count data were over-dispersed, with the conditional variance exceeding the condition mean. Length of enrollment in GHC was included as an offset because some persons were lost to follow-up or were unenrolled for months where their medication supply information was unavailable (2975, 2935, 2849, and 2759 person-year for 4 years, respectively).

Two models of symptom predictors (a pain/insomnia model and a pain/depression model) were examined for each of the 4 medication categories in the group approach. In the pain/insomnia models, the mild pain/no insomnia category was treated as reference. Individual effects of pain were determined by comparing the category with pain but not insomnia symptoms (moderate to severe pain and no insomnia) to the reference category, and individual effects of insomnia were determined by comparing the categories with insomnia but mild pain (mild pain and subclinical to clinical insomnia) to the reference category. In the pain/depression models, the mild pain/no depression category was treated as reference. Individual effects of pain were determined by comparing the category with pain but no depression (moderate to severe pain and no depression) to the reference category, and individual effects of depression were determined by comparing the categories with depression but mild pain (mild pain and subclinical to current depression) to the reference category. Incidence rate of medication supply was defined as days of medication supply per person-year. Incidence rate ratios (IRRs) which means a ratio of 2 incidence rates of a medication supply per person-year in our study and 95% confidence intervals (CI) were reported; a P-value <0.05 was considered statistically significant.

RESULTS

Table 1 shows participant demographic characteristics and symptom distribution. Participants were, on average, 72 years old (range: 60–90 y, SD = 8.8) and largely Caucasian (90.9%), female (66.2%), married (60.7%), and highly educated (57.4% community college or higher). All participants reported at least mild pain. Approximately 47% reported moderate to severe pain, 55% at least subclinical insomnia, and 45% subclinical to current depression. About 34% and 29% of participants with moderate to severe pain also presented at least subclinical insomnia or at least subclinical depression, respectively.

Table 2 describes days of supply for opioids, sedatives, TCAs, and non-TCAs from years 1 to 4. Among these medications, opioids had the highest percentage of receivers (35%–37%) and days of supply increased steadily across the 4 years. Days of supply per person-year (incidence rate) for opioids and non-TCAs also increased steadily across the 4 years but incidence rate of sedatives and TCAs did not change much. Table 3 presents crude incidence rate (days of supply per person-year) from years 2 to 4 for each medication

TABLE 1. Participant Demographics and Symptom Distribution (N = 2976)

Variables	N	Mean (SD)/ Number (%)
Age (y)	2976	72.2 (8.8)
Length of enrollment (mo)		
Y1	2976	12 (0.1)
Y2–Y4	2976	34.5 (5.7)
Sex	2976	
Female		1971 (66.2)
Male		1005 (33.8)
Education	2971	
Lower than college		1266 (42.6)
College		721 (24.3)
Graduate or professional		984 (33.1)
Marital status	2965	
Married/living as married		1799 (60.7)
Single/never married		120 (4.0)
Separated/divorced		477 (16.1)
Widowed		569 (19.2)
Employment	2911	
Employed		678 (23.3)
Unemployed		436 (15.0)
Retired		1797 (61.7)
Race	2922	
White		2655 (90.9)
Nonwhite		267 (9.1)
Charlson Comorbidity Index	2976	
0		1917 (64.4)
≥ 1		1059 (35.6)
Pain	2940	
Mild pain		1556 (52.9)
Moderate to severe pain		1384 (47.1)
Insomnia	2959	
No insomnia		1333 (45.1)
Subclinical insomnia		1119 (37.8)
Clinical insomnia		507 (17.1)
Depression	2927	
No depression		1603 (54.8)
Subclinical depression		711 (24.3)
Current depression		613 (20.9)
Pain and insomnia	2923	
Mild pain and no insomnia		931 (31.8)
Mild pain and subclinical insomnia		509 (17.4)
Mild pain and clinical insomnia		109 (3.7)
Moderate to severe pain and no insomnia		383 (13.1)
Moderate to severe pain and subclinical insomnia		598 (20.5)
Moderate to severe pain and clinical insomnia		393 (13.5)
Pain and depression	2891	
Mild pain and no depression		1055 (36.5)
Mild pain and subclinical depression		368 (12.7)
Mild pain and current depression		110 (3.8)
Moderate to severe pain and no depression		526 (18.2)
Moderate to severe pain and subclinical depression		442 (15.3)
Moderate to severe pain and current depression		390 (13.5)

Original dataset was used for descriptive statistics in this table.

TABLE 2. Descriptive Analysis for Medication Supply Across the 4 Years (N = 2976)

	Prestudy	Post Follow-up		
Medications	Y1 (2975 p-y)	Y2 (2935 p-y)	Y3 (2849 p-y)	Y4 (2759 p-y)
Opioids				
Receivers (%)*	37.2	37.4	35.9	35.1
Total supply (d)	66,515	71,008	73,940	76,595
Days of supply per p-y (IR)	22	24	26	28
Percentiles (d)				
75th	6	6	5	5
85th	19	22	24	20
95th	157	174	193	227
Sedatives				
Receivers (%)*	20.6	21.6	21.1	18.9
Total supply (d)	47,734	48,544	47,610	44,407
Days of supply per p-y (IR)	16	17	17	16
Percentiles (d)				
75th	0	0	0	0
85th	2	5	4	3
95th	114	112	107	97
Tricyclic antidepressants				
Receivers (%)*	7.6	7.3	6.9	6.7
Total supply (d)	42,430	41,913	41,029	39,308
Days of supply per p-y (IR)	14	14	14	14
Percentiles (d)				
75th	0	0	0	0
85th	0	0	0	0
95th	103	94	79	60
Non-TCA				
Receivers (%)*	20.5	21.7	21.6	22.0
Total supply (d)	148,061	153,175	154,284	157,758
Days of supply per p-y (IR)	50	52	54	57
Percentiles (d)				
75th	0	0	0	0
85th	164	180	180	189
95th	346	347	345	346

*The percentage of participants who received the corresponding medication prescription.

IR indicates incidence rate; p-y, person-year; TCA, tricyclic antidepressant.

across the clinically defined groups. Incidence rates of supply for each medication type were almost equivalent when participants presented similar symptom severity in 2 clinically defined groups (eg, 7.5 in participants with mild pain and no insomnia vs. 8.7 in those with mild pain and no depression). These incidence rates increased with symptom severity for all types of medications, particularly opioids and non-TCAs.

Table 4 shows the results from the analyses in the first analytic approach using continuous symptom variables. Either the 2-way and 3-way interaction terms were statistically insignificant or the statistically significant coefficients were <1 suggesting the absence of synergy. Table 4 presents the crude and adjusted independent effects of each symptom on medication supply without interaction terms. Pain was associated with greatly increased incidence rate of opioid (IRR, 1.54; 95% CI, 1.39–1.70) and TCA supply (IRR, 1.25; 95% CI, 1.05–1.50) after adjusting insomnia, depression and covariates. It means 1-point increase on GCPS scale was associated with 1.5 times more days of opioid supply per person-year. Insomnia was associated with increased incidence rate of opioid (IRR, 1.03; 95% CI, 1.00–1.06), sedative (IRR, 1.06; 95% CI, 1.03–1.09), supply and decreased non-TCA supply

TABLE 3. Crude Incidence Rate (Days of Supply Per Person-year) of Medication Supply Across Clinically Defined Groups From Years 2 to 4

Clinically Defined Groups	Number	Crude Incidence Rate (95% Confidence Interval)			
		Opioids	Sedatives	TCA	Non-TCA
Pain and insomnia					
Mild pain and no insomnia	931	7.5 (7.4–7.6)	7.1 (7.0–7.2)	8.8 (8.7–8.9)	40.6 (40.3–40.8)
Mild pain and subclinical to clinical insomnia	618	14.1 (14.0–14.3)	22.1 (21.8–22.3)	12.9 (12.7–13.0)	48.6 (48.2–48.9)
Moderate to severe pain and no insomnia	383	30.8 (30.5–31.2)	11.8 (11.6–12.0)	13.4 (13.2–13.6)	51.2 (50.8–51.6)
Moderate to severe pain and subclinical insomnia	598	39.0 (38.7–39.3)	19.7 (19.5–19.9)	18.0 (17.8–18.2)	67.1 (66.7–67.5)
Moderate to severe pain and clinical insomnia	393	65.0 (64.5–65.4)	30.6 (30.2–30.9)	24.9 (24.6–25.2)	85.2 (84.6–85.7)
Pain and depression					
Mild pain and no depression	1055	8.7 (8.6–8.8)	8.3 (8.2–8.4)	10.7 (10.6–10.9)	30.9 (30.7–31.1)
Mild pain and subclinical to current depression	478	13.4 (13.3–13.6)	23.4 (23.1–23.6)	10.1 (9.9–10.2)	73.2 (72.8–73.7)
Moderate to severe pain and no depression	526	28.5 (28.3–28.8)	13.7 (13.5–13.9)	11.7 (11.6–11.9)	34.0 (33.7–34.4)
Moderate to severe pain and subclinical depression	442	34.7 (34.4–35.0)	16.4 (16.2–16.6)	15.7 (15.5–15.9)	83.4 (82.9–83.9)
Moderate to severe pain and current depression	390	73.3 (72.8–73.8)	33.7 (33.3–34.0)	31.5 (31.1–31.8)	95.9 (95.3–96.5)

TCA indicates tricyclic antidepressant.

(IRR, 0.98; 95% CI, 0.96–1.00) after adjusting pain, depression, and covariates. Depression was associated with increased incidence rate of opioid (IRR, 1.04; 95% CI, 1.01–1.07), sedative (IRR, 1.05; 95% CI, 1.02–1.09) and non-TCA supply (IRR, 1.10; 95% CI, 1.08–1.13) after adjusting insomnia, depression, and covariates.

Table 5 shows the results from the analyses in the second analytic approach using clinically defined groups, which are the independent effects of pain, insomnia and depression, and combined effects of pain+insomnia, and pain +depression severity on supply of the 4 medication types without adjustment (crude IRRs) and after controlling for covariates (adjusted IRRs). We focused on presenting results on adjusted effects.

Opioids

In the pain/insomnia models, adjusted independent effects of pain (IRR, 3.5; 95% CI, 2.5–4.9) and insomnia (IRR, 2.0; 95% CI, 1.4–2.7) on opioid supply were significant. Combined effects of pain and insomnia were significant and increased with insomnia severity. Participants with moderate to severe pain and clinical insomnia had about 7 times the rate of opioid supply in the reference group (IRR, 6.6; 95% CI, 4.9–9.0). In the pain/depression models, both pain (IRR, 2.8; 95% CI, 2.1–3.8) and depression (IRR, 1.5; 95% CI, 1.1–2.2) showed a significant effect on opioid supply after adjustment. Combined effects of pain and depression increased with depression severity, and participants with moderate to severe pain and current depression had the highest rate of opioid supply—about 8 times the rate in the reference group (IRR, 7.5; 95% CI, 5.6–10.1).

Sedatives

In the pain/insomnia models, adjusted independent effects on sedative supply were not significant for pain but they were significant for insomnia (IRR, 3.2; 95% CI, 2.1–4.7). Combined effects of pain and insomnia were significant and increased with insomnia severity. The rate of sedative supply in participants with moderate to severe pain was about 4 times the rate in participants with mild pain and no insomnia (IRR, 4.2; 95% CI, 2.8–6.5). In pain/depression models, both pain (IRR, 1.7; 95% CI, 1.1–2.6) and depression (IRR, 3.0; 95% CI, 2.1–4.4) were associated with increased rate of sedative supply after adjusting covariates. Combined effects of pain and depression were significant and increased with depression severity. Participants with moderate to severe pain and current depression had ~4 times the rate of supply in the reference group (IRR, 4.2; 95% CI, 2.8–6.1).

TCAs

In the pain/insomnia models, both pain and insomnia showed a significant and equivalent independent effects on TCA supply (IRR, 2.1; 95% CI, 1.2–3.6; IRR, 2.1; 95% CI, 1.1–3.8, respectively) without adjustment. Combined effects of pain and insomnia were significant and greatly increased with insomnia severity. The rate of TCA supply in participants with moderate to severe pain and clinical insomnia was about 5 times the rate in the reference group (IRR, 4.7; 95% CI, 2.7–8.1). In the pain/depression models, independent effects were insignificant on TCA supply for both pain and depression regardless of adjustment. However, combined effects of pain and depression were significant and greatly increased with depression severity. Days of TCA supply in participants with moderate to severe pain and current depression were about 4 times as many days of TCA supply in participants with mild pain and no depression (IRR, 3.9; 95% CI, 2.4–6.2).

Non-TCAs

In the pain/insomnia models, neither pain nor insomnia were associated with non-TCA supply regardless of adjustment. However, combined effects of pain and insomnia were significant and they increased with insomnia severity. Participants with moderate to severe pain and clinical insomnia had about 2 times the rate of non-TCA supply compared with those with mild pain and no insomnia (IRR, 1.8, IRR, 1.4–2.3). In the pain/depression models, adjusted independent effects on non-TCA supply were significant only for depression (IRR, 2.2; 95% CI, 1.7–2.8). Combined effects of pain and depression were significant, and increased with

TABLE 4. Independent Effects of Pain, Insomnia, and Depression on Medication Supply From Years 2 to 4 (Days of Supply)

Symptoms	Opioids IRR (95% CI) Crude	Opioids IRR (95% CI) Adjusted	Sedatives IRR (95% CI) Crude	Sedatives IRR (95% CI) Adjusted	TCA IRR (95% CI) Crude	TCA IRR (95% CI) Adjusted	Non-TCA IRR (95% CI) Crude	Non-TCA IRR (95% CI) Adjusted
Pain	1.63 (1.47–1.80)***	1.54 (1.39–1.70)***	1.08 (0.95–1.23)	1.08 (0.94–1.23)	1.20 (1.04–1.39)*	1.25 (1.05–1.50)*	1.09 (1.02–1.18)*	1.04 (0.96–1.13)
Insomnia	1.02 (0.99–1.05)	1.03 (1.00–1.06)*	1.06 (1.03–1.09)***	1.06 (1.03–1.09)***	1.01 (0.97–1.05)	1.03 (0.98–1.07)	0.97 (0.95–0.99)**	0.98 (0.96–1.00)*
Depression	1.06 (1.03–1.09)***	1.04 (1.01–1.07)**	1.05 (1.02–1.09)**	1.05 (1.02–1.09)**	1.04 (1.00–1.09)*	1.05 (1.00–1.10)	1.11 (1.09–1.14)***	1.10 (1.08–1.13)***

Crude IRRs did not adjust covariates but only length of enrollment in Group Health; adjusted IRRs adjusted for demographics, Charlson Comorbidity Index, and length of enrollment in Group Health.
CI indicates confidence interval; IRR, incidence rate ratio; TCA, tricyclic antidepressant.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

TABLE 5. Independent and Combined Effects of Pain+Insomnia and Pain+Depression on Medication Supply From Years 2 to 4 (Days of Supply)

Clinically Defined Groups	Opioids IRR (95% CI) Crude	Opioids IRR (95% CI) Adjusted	Sedatives IRR (95% CI) Crude	Sedatives IRR (95% CI) Adjusted	TCA IRR (95% CI) Crude	TCA IRR (95% CI) Adjusted	Non-TCA IRR (95% CI) Crude	Non-TCA IRR (95% CI) Adjusted
Pain and insomnia[†]								
Mild pain and subclinical to clinical insomnia[‡]	1.8 (1.2–2.6)**	2.0 (1.4–2.7)***	3.1 (2.1–4.6)***	3.2 (2.1–4.7)***	1.4 (0.9–2.4)	2.0 (1.2–3.6)*	1.2 (1.0–1.6)	1.1 (0.8–1.4)
Moderate to severe pain and no insomnia[§]	4.0 (2.8–5.8)***	3.5 (2.5–4.9)***	1.8 (1.0–3.0)*	1.7 (1.0–2.9)	1.5 (0.9–2.6)	2.1 (1.1–3.8)*	1.3 (1.0–1.7)	1.1 (0.8–1.4)
Moderate to severe pain and subclinical insomnia	5.1 (3.7–7.0)***	5.0 (3.7–6.8)***	2.9 (1.9–4.3)***	3.0 (1.9–4.5)***	2.1 (1.3–3.3)**	2.5 (1.5–4.2)**	1.7 (1.3–2.1)***	1.4 (1.1–1.8)*
Moderate to severe pain and clinical insomnia	8.3 (6.1–11.4)***	6.6 (4.9–9.0)***	4.5 (3.0–6.7)***	4.2 (2.8–6.5)***	3.1 (2.0–4.9)***	4.7 (2.7–8.1)***	2.2 (1.7–2.7)***	1.8 (1.4–2.3)***
Pain and depression[‖]								
Mild pain and subclinical to current depression[¶]	1.5 (1.0–2.2)*	1.5 (1.1–2.2)*	2.9 (2.0–4.2)***	3.0 (2.1–4.4)***	0.9 (0.5–1.6)	1.1 (0.6–1.9)	2.3 (1.8–2.9)***	2.2 (1.7–2.8)***
Moderate to severe pain and no depression[#]	3.0 (2.2–4.3)***	2.8 (2.1–3.8)***	1.7 (1.1–2.6)*	1.7 (1.1–2.6)*	1.2 (0.7–1.9)	1.4 (0.8–2.6)	1.1 (0.8–1.4)	1.0 (0.7–1.3)
Moderate to severe pain and subclinical depression	4.0 (2.8–5.6)***	3.4 (2.5–4.8)***	2.1 (1.4–3.2)***	2.2 (1.5–3.4)***	1.5 (0.9–2.4)	1.8 (1.0–3.3)*	2.6 (2.1–3.3)***	2.3 (1.8–3.0)***
Moderate to severe pain and current depression	8.8 (6.6–11.9)***	7.5 (5.6–10.1)***	4.4 (3.1–6.2)***	4.2 (2.8–6.1)***	3.2 (2.1–4.7)*	3.9 (2.4–6.2)***	3.2 (2.6–4.0)***	2.7 (2.1–3.5)***

Crude IRRs did not adjust covoriates but only length of enrollment in Group Health; adjusted IRRs adjusted for demographics, Charlson Comorbidity Index, and length of enrollment in Group Health.
[†]Reference group is "mild pain and no insomnia."
[‡]Indepdenent effects of insomnia.
[§]Independent effects of pain in pain/insomnia model.
[‖]Reference group is "mild pain and no depression."
[¶]Independent effects of depression.
[#]Independent effects of pain in pain/depression model.
CI indicates confidence interval; IRR, incidence rate ratio; TCA, tricyclic antidepressant.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

depression severity. Participants with moderate to severe pain and current depression had about 3 times the rate of non-TCA supply compared with those with mild pain and no depression (IRR, 2.7; 95% CI, 2.1–3.5).

DISCUSSION

This study examined independent and combined effects of pain, insomnia, and depression on psychoactive medications supplied to older adults with OA. To our knowledge, this is the first attempt to examine effects of concurrent insomnia and depression jointly with pain on psychoactive medications supplied to persons with OA. About half of the participants presented with at least one of the 3 symptoms, and around 34% and 29% suffered from insomnia or depression, respectively, in addition to moderate to severe pain. This indicates the importance of addressing these concurrent symptoms in primary care older adults with OA, which was also highlighted in previous research.[35] Our study also sheds lights on polypharmacy in this population, as participants with only pain, insomnia or depression are still likely to have concurrent use of 2 or more psychoactive medications.

We evaluated the independent effects of pain, insomnia and depression on psychoactive medication supply using 2 different analytic approaches with first using continuous symptom variables (symptom analyses) and the second using clinically defined groups (group analyses). Results from the symptom analyses showed the absence of synergistic effects among pain, insomnia and depression, indicating their combined effects are additive. This finding provides a good implication for patient treatment safety as these concurrent symptoms do not interact with each other to create greater effects on psychoactive medication supply than their additives. Findings from the 2 approaches showed consistent patterns (ie, increased medication supply with increased symptom severity), with a few exceptions. For example, pain was associated with sedative supply after adjustment in the pain/depression models from the group analyses, but this association was not significant in the symptom analyses. This may be explained by the group analyses not eliminating effects of insomnia in participants with moderate to severe to severe pain and no depression. However, the group analyses complement the symptom analyses by providing meaningful and interpretable information for comparing the magnitude of pain, insomnia, and depression effects on medication supply between different clinically defined groups.

Our study showed that pain, insomnia, and depression were associated with opioid supply after adjusting other concurrent symptoms and covariates. Participants with subclinical or greater insomnia received about 2 times the days of opioid supply compared with those without insomnia or pain. Similarly, participants with subclinical or greater depression received about 1.5 times the days of opioid supply compared with those without depression or pain. This finding is supported by research that opioids have been reported to have nonanalgesic effects that could be used for treating minor sleep problems.[36] Patients with depression and other mood disorders were found to receive 51% of the total opioid prescriptions distributed in the United States each year which suggests the need for caution in prescribing opioids in this population.[37] We found that opioid supply increased markedly with insomnia and depression severity when moderate to severe pain was present. Previous studies have also found that patients with mental disorders and sleep disorders are more likely to use opioids when pain is present but not specific to symptom severity levels.[38] These findings call clinicians' attention to OA patients with concurrent insomnia and depression, as they are more likely to use opioids. This is of concern given inadequate evidence regarding the long-term efficacy and safety of opioids for pain management.[39–41] Clinicians should further review and evaluate the treatment prescriptions for older adults with severe insomnia and depression to avoid opioid overuse and reduce multiple medication adverse effects.

Insomnia and depression showed equivalent independent effects on sedative supply. Participants with either insomnia or depression had about 3 times the rate of sedative supply compared with those without the symptom. Older adults with insomnia are likely to have concurrent depressive symptom and co-prescription of antidepressant and sedative drugs is common in these patients. Although pain showed inconsistent effects on sedative supply, participants with pain received significantly greater supply of sedatives when their insomnia or depressive symptoms were severe.

Our study suggests that participants with pain or insomnia only received significantly more tricyclic antidepressants, whereas participants with depression only were prescribed more nontricyclics. When participants had concurrent pain and insomnia or concurrent pain and depression, they received more days of supply for both tricyclics and nontricyclics. These findings are consistent with current literature to the effect that TCAs and non-TCAs are being prescribed to treat some chronic pain conditions, because the analgesic effects of these agents appear to be independent of their antidepressant effects and since TCAs are more efficacious in treating severe depression.[42–44] However, both TCAs and non-TCAs should be used with caution as there are limited data supporting the use of antidepressants for pain management in OA.[45,46] It should be noted that participants with pain or insomnia only are more likely to use TCAs, which should be prescribed carefully as they have greater side effects compared with non-TCAs.[47]

This study had several limitations. Medication supply may have been underestimated, because the EMRs included only prescription medications and not over-the-counter medications or medications filled outside the GHC pharmacy system. This study was carried out in a single health plan in Washington State, so generalizability to other populations is not known. As antidepressants were classified into TCAs and non-TCAs in this study, conclusions may not be made to certain specific classes of antidepressants, such as Serotonin and norepinephrine reuptake inhibitors.

In summary, our study revealed that the OA pain, concurrent insomnia, and depression are highly prevalent in older adults with OA. Pain, insomnia, and depression independently contributed to opioid supply. Insomnia and depression independently contributed to sedative supply. Pain or insomnia independently predicted TCA supply, whereas depression individually predicted non-TCA supply. Combined effects of these symptoms on opioid, sedative, TCA, and non-TCA were additive and increased with insomnia or depression severity

when moderate to severe pain was present. These results indicate that clinicians should give particular attention to the appropriateness of psychoactive prescriptions and related risks in older adults who have concurrent insomnia or depression along with OA pain.

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